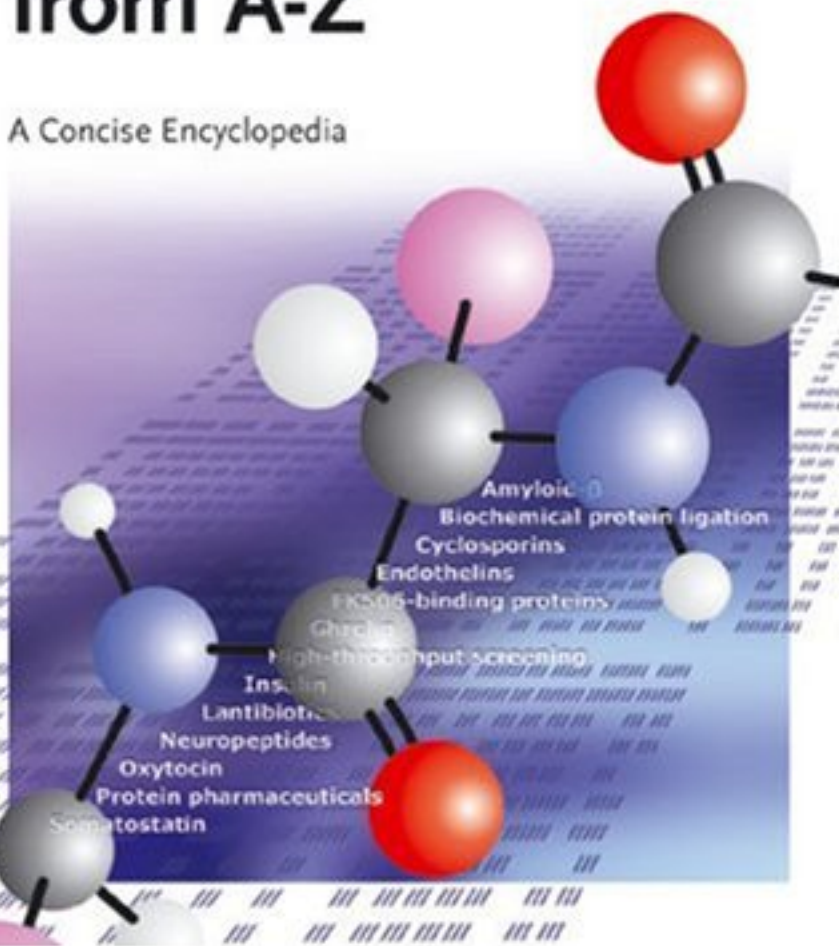


Hans-Dieter Jakubke and
Norbert Sewald

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A Concise Encyclopedia



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Preface

The versatility of peptides with respect to structure, biological activity, and potential application has led to a renaissance of peptides, also in a pharmaceutical context and a growing interest in the chemistry and biology of peptides. Recent progress in peptide research is documented by numerous scientific contributions, both in the primary literature and patents. Peptides exert impact not only onto chemistry and biochemistry, but also influence biology, pharmacology, medicinal chemistry, biotechnology, and gene technology. The ubiquitous and trans-disciplinary relevance of peptides for the life sciences calls for reference works in a handy, compact volume providing an informative overview of all types of aspects of peptides, either as natural products or synthetic compounds.

The overwhelmingly positive review and feedback for the glossary of our previously published monograph "*Peptides: Chemistry and Biology*" fostered the idea to produce this specific concise encyclopedia. We faced the difficult task of selecting and processing the vast knowledge in the peptide field and presenting it within one volume. This approach cannot be free of subjective decisions, but we hope to have collected the most relevant issues. Care has been taken to compile a concise, clearly presented scientific definition of the keywords among more than 2000 entries. A task such as this, of course, can never be completed and should not replace a textbook. Rather, this compendium is meant to provide a useful first reference tool, an "information mine" with key information and up-to-date references on a specific peptide topic. Besides covering important biologically active peptides, the book also provides basic information on general and specific topics of modern peptide research.

This encyclopedia will be useful to scholars, professors, lecturers, laboratory technicians, science teachers and students that are interested in certain aspects of peptides – occasionally or permanently. Readers belonging to the disciplines chemistry, biosciences, physics, pharmacy, biology, medicine or even beyond the academic community will profit from using the encyclopedia either when searching for specific issues or by just browsing through the topics.

We appreciate contributions by our colleagues Gunter Fischer (Max Planck Research Unit for Enzymology of Protein Folding, Halle/S., Germany), John D. Wade (University of Melbourne, Australia), Siegmund Reißmann (Friedrich Schiller University, Jena, Germany), Frank Bordusa (Martin Luther University, Halle-Wittenberg, Germany) on topics related to their research fields. Helpful discussions with Paul Cordopatis (University of Patras, Greece), Gerd Gäde (University of Cape Town, South Africa), Ferenc

Hudecz (Eötvös Loránd University, Budapest, Hungary), John H. Jones (Balliol College, Oxford, U.K.), Luis Moroder (Max-Planck Institute of Biochemistry, Martinsried, Germany), Robin E. Offord (University of Geneva, Switzerland), and Dirk Ullmann (Evotec, Hamburg, Germany) are gratefully acknowledged. We express our special thanks to the Protein Research Foundation (Osaka, Japan) for providing the biweekly journal *Peptide Information* to one of us (H.-D. J.) over many years, which has been a very useful source for conceiving the latest developments in peptide research.

The editorial team at Wiley-VCH took care that the manuscript was converted into this book in a rather short period of time without complications.

Bielefeld
and
Dresden-Langebrück

Norbert Sewald

Hans-Dieter Jakubke

How to use this book

Entries

Entries are listed in alphabetical order. The main entry title is printed in bold type, followed by synonyms in bold italics. Numbers, Greek letters and configurational numbers/letters at the beginning of the name are ignored when allocating in alphabetical order, e.g. O-Acyl isopeptide method is listed under A, α_2 -macroglobulin is listed under M, while 8-quinolyl ester is listed under Q.

Abbreviations

The standard abbreviations and symbols in peptide science are mainly used according to the previously published recommendations in Journal of Peptide Science (J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 1-12) and many of them have been included as entries in the appropriate alphabetical positions. The three-letter code is used for peptides with up to ten amino acid residues. For larger peptide sequences the one-letter symbols are used. In the latter case, a C-terminal amide is symbolized by “a”.

Other abbreviations

abbr.	abbreviation
$[\alpha]$	optical rotation
b	bovine
b.p.	boiling point
<i>c</i>	concentration
°C	degrees Celsius/degrees centigrade
Da	dalton
3D	three dimensional
<i>ee</i>	enantiomeric excess
<i>E. coli</i>	<i>Escherichia coli</i>
h	human

IC	inhibitory concentration
i.c.v.	intracerebroventricular(ly)
i.p.	parenteral(ly)
i.t.	intrathecal(ly)
i.v.	intravenous(ly)
kb	kilo base pair
kDa	kilodalton
K_M	Michaelis constant
LD ₅₀	lethal dose 50%
m.p.	melting point
M	molar
M_r	relative molecular mass
N	refractive index
o	sheep (<i>ovinus</i>)
p	porcine
pI	isoelectric point
r	rat
® , TM	trade mark
<i>rac.</i>	racemic
<i>syn.</i>	synonym

Cross References

Cross references to other keywords are indicated by → .

References

Key references are given at the end of most entries to suggest further reading in the form of recent review articles, important original publications or even the first publication to communicate the discovery. They are meant to illustrate recent developments or important aspects of the keyword.

Trademarks, Patents

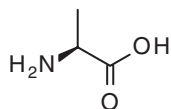
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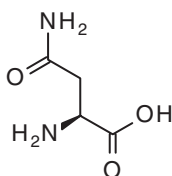
Further Reading

A comprehensive bibliography on peptide research until the end of the last century was published by John H. Jones (*J. Peptide Sci.* **2000**, 6, 201). The same author has published a useful commentary on the confusing nomenclature and bibliography of serial publications which use the term 'peptide' in their titles (*J. Peptide Sci.* **2006**, 12, 503). The Houben-Weyl volumes E22a to E22e "*Synthesis of Peptides and Peptidomimetics*" (Thieme, Stuttgart, **2002**), edited by Murray Goodman (Editor-in-Chief), Arthor Felix, Luis Moroder and Claudio Toniolo, represents the most up-to-date and exhaustive general treatise in the field of peptide synthesis. In addition, the *Handbook of Biologically Active Peptides* (Elsevier, San Diego, **2006**), edited by Abba J. Kastin, presents a tremendous body of knowledge in the field of biologically active peptides.

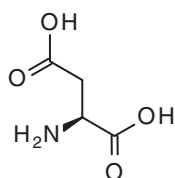
Structures and Symbols (Three-Letter and One-Letter Code) for the Proteinogenic Amino Acids



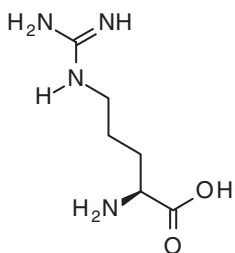
Alanine (Ala) A



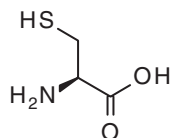
Asparagine (Asn) N



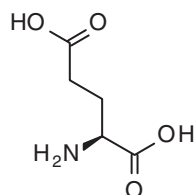
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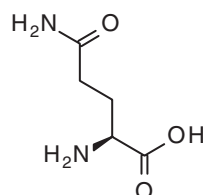
Arginine (Arg) R



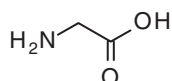
Cysteine (Cys) C



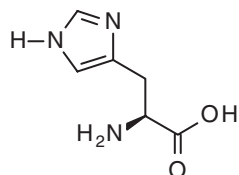
Glutamate (Glu) E



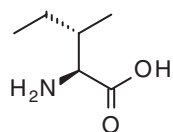
Glutamine (Gln) Q



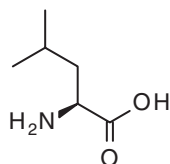
Glycine (Gly) G



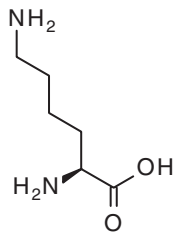
Histidine (His) H



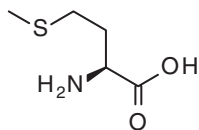
Isoleucine (Ile) I



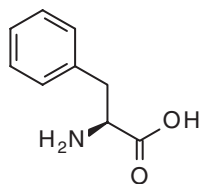
Leucine (Leu) L



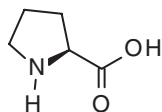
Lysine (Lys) K



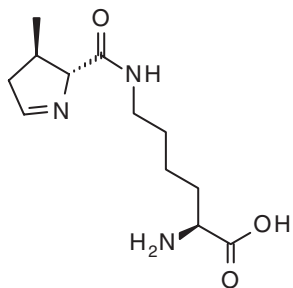
Methionine (Met) M



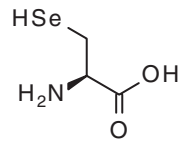
Phenylalanine (Phe) F



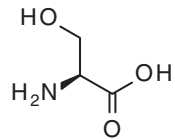
Proline (Pro) P



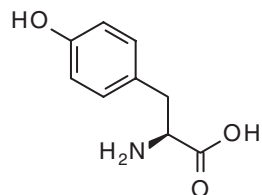
Pyrrolysine (Pyl) O



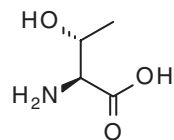
Selenocysteine (Sec) U



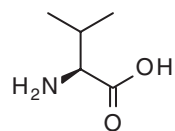
Serine (Ser) S



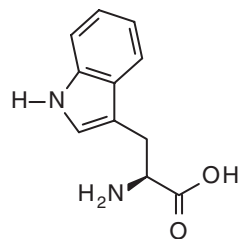
Tyrosine (Tyr) Y



Threonine (Thr) T



Valine (Val) V



Tryptophan (Trp) W

A

aa, amino acid.

AA, antamanide.

Aad, α -aminoadipic acid.

β -Aad, β -aminoadipic acid.

AAP, antimicrobial animal peptides.

Aart, a designed Cys2-His2 \rightarrow zinc finger protein (190 aa, M_r 21.4 kDa). It was designed and constructed based on the application of zinc-finger domains of predetermined specificity to bind a 22-base-pair duplex DNA. The aart protein was expressed in *E. coli* as a C-terminal fusion to maltose-binding protein (MBP). The fusion protein contained a factor Xa protease cleavage site for the MBP tag. Aart complexed with its DNA target was crystallized followed by X-ray analysis. Aart binds its DNA target with picomolar affinity. The 1.96 Å structure of Aart was described in 2006 [B. Dreier et al., *J. Biol. Chem.* **2001**, 276, 29466; J. W. Crotty et al., *Acta Crystallogr.* **2005**, F61, 573; D. J. Segal et al., *J. Mol. Biol.* **2006**, 363, 405].

AatRS, amino acyl tRNA synthetase.

A β , amyloid- β .

Ab, antibody.

A₂bu, 2,4-diaminobutyric acid.

Abderhalden, Emil (1877–1950), professor of physiology (1908–1910) at Berlin, of biochemistry (1911–1945) at Halle/S. (Germany), and of physiological chemistry (1946/47) at Zurich (Switzerland). From 1931–1950 Prof. Abderhalden was Presi-

dent of the German Academy of Natural Scientists Leopoldina in Halle/S. In 1902, Abderhalden had joined \rightarrow Emil Fischer's group and worked on protein hydrolysates and proteolytic enzymes which led, in 1904, to *Habilitation*. Further scientific activities were mainly directed towards the chemistry of proteins and physiological chemistry of metabolism [J. Gabathuler (Ed.), *Emil Abderhalden, Sein Leben und Werk*, Ribaux, St. Gallen, **1991**].

Abrin, a highly toxic protein isolated and crystallized from the red seeds of *Abrus precatorius*. It consists of an A-chain ($M_r \sim 30$ kDa) and a B-chain ($M_r \sim 35$ kDa), joined by disulfide bridges. The A-chain is a highly specific *N*-glucosidase acting as ribosome-inactivating protein (RIP), whereas the B-chain is a glycoprotein responsible for anchoring at the cell surface. One of the carbohydrate chains forms a bridge between two neighboring molecules, whereas another sugar chain covers the surface of the B-chain. A disulfide-cleaving system of the cell releases the A-chain, which enters the cell by endocytosis. RIP cleaves a single adenine residue from the rRNA, resulting in inhibition of protein synthesis followed by cell death. Similar action and structure are possessed by \rightarrow ricin. The A-chain coupled with a monoclonal antibody directed against a tumor antigen is used in drug targeting [J. Y. Lin et al., *J. Formosan Med. Assoc.* **1969**, 68, 32; J. Y. Lin et al., *Nature* **1970**, 227, 292; A. J. Cumber et al., *Methods Enzymol.* **1985**, 112, 207; T. H. Tahirov et al., *J. Mol. Biol.* **1995**, 250, 354].

Abu, α -aminobutyric acid.

Abz, aminobenzoic acid.

Abzyme, *catalytic antibody*, a monoclonal antibody with catalytic activity. An antibody raised against a transition-state analogue of a particular reaction can catalyze that reaction. The first abzyme to be generated was capable of catalyzing the hydrolysis of esters. Abzymes have been described that catalyze, e.g., acyl transfer, C–C bond cleavage, β -elimination, and C–C bond formation. From X-ray analyses it could be concluded that antibodies bind peptides of various length in elongated grooves using hydrogen bonding, van der Waals forces, and ionic contacts for recognition. Abzymes are also an interesting choice for \rightarrow abzyme-catalyzed peptide synthesis [L. Pauling, *Am. Sci.* **1948**, 36, 51; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, **1969**; R. A. Lerner et al., *Science* **1991**, 252, 659; D. Hilvert et al. in: *Bioorganic Chemistry: Peptides and Proteins*, S. M. Hecht (Ed.), Oxford University Press, Oxford, **1998**].

Abzyme-catalyzed synthesis, the application of catalytic antibodies as catalysts for formation of the peptide bond. If an abzyme could bind a substrate already in the transition-state conformation, it might act as an enzyme catalyzing the reaction to which the transition-state conformation is predisposed. Analogues of the transition state were used as haptens to induce abzymes (catalytic antibodies) with the correct arrangement of catalytic groups. At present, the main disadvantage of the abzyme approach is the requirement of a large number of abzyme catalysts to accommodate the wide specificity pattern of amino acids in coupling reactions. However, these first interesting results in this field provide an impetus for producing

further generations of abzymes capable of catalyzing the ligation of longer, unprotected fragments, combined with a general strategy for the development of sequence-specific abzyme ligases [R. Hirschmann et al., *Science* **1994**, 265, 234; J. R. Jacobson, P.G. Schultz, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 5888; D. W. Smithrud et al., *J. Am. Chem. Soc.* **1997**, 119, 278; S. N. Savinov et al., *Bioorg. Med. Chem. Lett.* **2003**, 13, 1321].

Ac, acetyl.

ACE, angiotensin-converting enzyme.

ACE 2, angiotensin-converting enzyme 2.

ACE inhibitors, pharmaceuticals for the treatment of hypertension, congestive heart failure, and myocardial infarction. Different types of synthetic ACE inhibitor have been designed. Synthetic ACE inhibitors are grouped by their ligand for the active site of the \rightarrow angiotensin converting enzyme (ACE). The major representative of this group is \rightarrow captopril bearing a sulfhydryl moiety, whereas \rightarrow enalapril and lisinopril have a carboxyl moiety, and fosinopril a phosphorous group. The beneficial effects of this group of ACE inhibitors in hypertension and heart failure result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE causes a decrease in plasma angiotensin II (\rightarrow angiotensins) level, which leads to decreased vasopressor activity and to a small decrease in aldosterone secretion. However, these synthetic ACE inhibitors are known to have strong adverse side effects, such as cough, skin rashes, and angioedema. Attempts to use \rightarrow angiotensin-converting enzyme 2 and its proteolysis product angiotensin-(1–7) for the regulation of blood pressure are under investigation. Naturally occurring \rightarrow ACE inhibitory peptides have been reported to

have potential as antihypertensive components in functional foods or nutraceuticals. However, the development of ACE inhibitors was greatly influenced by natural products, e.g., by special members of the \rightarrow bradykinin-potentiating peptides. The 9-peptide *teprotide*, <Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH (BPP_{9a}, SQ20, 881) was the most active ACE inhibitor *in vivo*, whereas the 5-peptide <Glu-Lys-Trp-Ala-Pro-OH (BPP_{5a}, SQ20, 475) showed *in vitro* the highest activity. The proposed binding of BPP_{5a} to the active site of ACE led to the rational design of the first marketed, orally active ACE inhibitor \rightarrow captopril [M. A. Ondetti et al., *Biochemistry* **1971**, *10*, 4033; M. A. Ondetti et al., *Science* **1977**, *196*, 441; D. W. Cushman et al., *Biochemistry* **1977**, *16*, 5484; M. L. Cohen, *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 307; G. Lawton et al., in: *Advances in Drug Research*, B. Testa (Ed.), Volume 23, p. 161, Academic Press, New York, **1992**; T. F. T. Antonius, G. A. Macgregor, *J. Hypertens.* **1995**, *13*, S11].

ACE inhibitory peptides, naturally occurring peptides derived, for example, from the venoms of the Brazilian pit viper *Bothrops jararaca* and other snakes, known as \rightarrow bradykinin-potentiating peptides, have significantly influenced the development of synthetic \rightarrow ACE inhibitors based on rational drug design. Surprisingly, peptides from the enzymatic partial hydrolysis of proteins, such as milk, maize, gelatin, soybean, wheatgerm, serum, hemoglobin, porcine and chicken muscle have a potential as antihypertensive compounds in functional foods and nutraceuticals. It is interesting to note that some of these peptides not only show ACE inhibitory activity *in vitro*, but also exhibit *in-vivo* antihypertensive activity in spontaneously hypertensive rats [H. Kato, T. Suzuki, *Experientia* **1969**, *25*, 694; *Biochemistry* **1971**, *10*, 972;

L. Vercruysee et al., *J. Agric. Food Chem.* **2005**, *53*, 8106].

Acetaldehyde/chloranil test, a monitoring method for the control of complete coupling reaction in \rightarrow solid-phase peptide synthesis [T. Voikovskiy, *Peptide Res.* **1995**, *8*, 236].

Acetamidomethyl group (Acm), a type of thiol protecting group with an *N*-acyl *N*,*S*-acetal moiety, compatible with both Boc and Fmoc chemistry. The Acm group is completely stable towards acidolysis, and is cleaved with mercury(II) salts at pH 4, thallium(III) trifluoroacetate, or iodine. Oxidizing agents such as iodine simultaneously induce disulfide formation. Structural analogues of the Acm group are the chloroacetamidomethyl group, the isobutyrylamidomethyl group, and the \rightarrow trimethylacetamidomethyl group.

Achatin, a 4-peptide isolated from the ganglia of the African giant land snail *Achatina fulica*. The neuroexcitatory peptide *achatin I* (H-Gly-D-Phe-Ala-Asp-OH) contains a D-amino acid (\rightarrow dermorphin, \rightarrow deltorphins, \rightarrow fulicin) in position 2, whereas *achatin-II* with the L-isomer in the same position shows neither physiological nor pharmacological activities. Because of Na⁺, *achatin I* induced a voltage-dependent inward current on the giant neuron. It has been assumed that D-Phe in *achatin-I* is a prerequisite for forming a 15-membered ring with a unique turn conformation structure, which may be the active conformation suitable for interactions with the receptor. The characterization of a cDNA encoding a precursor polypeptide of *achatin-I* have been described [Y. Kamatani et al., *Biochem. Biophys. Res. Commun.* **1989**, *160*, 1015; T. Ishida et al., *FEBS Lett.* **1992**, *307*, 253; H. Satake et al., *Eur. J. Biochem.* **1999**, *261*, 130].

AchR, acetylcholine receptor.

Acm, acetamidomethyl.

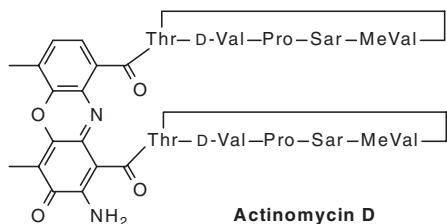
ACP, acyl carrier protein.

ACTH, acronym of adrenocorticotrophic hormone, → corticotropin.

Actin, a contractile protein occurring in many eukaryotic cell types. Actin and → myosin are the major components of the muscle. Both proteins account for 60–70% and 20–25% of the total muscle protein, respectively. Actin and its filaments are the major components of the cytoskeleton in eukaryotic cells. Besides thrombomyosin and → troponin, actin is the major constituent of thin filaments. The fibrous *F-actin* forms the core of the thin filament and is formed under physiological conditions by polymerization of the globular *G-actin* ($M_r \sim 42$ kDa; 375 aa). The regulation of the polymerization/depolymerization of F-actin is essential for cytokinesis, cell mobility, and the control of cell shape and polarity. The monomeric G-actin consists of two domains, each of which is divided into two subdomains. G-actin normally binds one molecule of ATP, which is hydrolyzed during polymerization to F-actin, and the resulting ADP remains bound to the F-actin monomer unit. ATP and ADP bind in a cleft between the two domains. The F-actin helix (diameter 100 Å) has 2.17 actin monomers per left-handed helix turn (13 subunits in six turns) and a rise per turn of 60 Å. The monomeric unit of each F actin is capable of binding a single myosin S 1 fragment [R. A. Milligan et al., *Nature* **1990**, 348, 217; P. Sheterline, J. C. Sparrow, *Protein Profiles* **1994**, 1, 1; P. Sheterline et al., *Actin*, Oxford University Press, New York, **1998**; J.-W. Chu, G. A. Voth, *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13111].

Actinohivin (AH), a sugar-binding anti-human immunodeficiency virus protein produced by an actinomycete *Longispora al-bida* gen. nov, sp. nov. AH consists of 114 aa and is composed of highly conserved three-tandem repeats. Each repeat unit is built of 38 aa containing a Gln-Xaa-Trp motif at the C-terminus. It has been reported that AH inhibits the infection of susceptible cells by various strains of T-lymphocyte (T)-tropic and macrophage (M)-tropic HIV types 1 and 2, and both T- and M-tropic syncytium formation via AH binding to the high-mannose-type saccharide chains of HIV gp120. The three tandem-repeat structure of AH is essential for potent anti-syncytium formation activity and gp120-binding [H. Chiba et al., *J. Antibiot.* **2001**, 54, 818; *Biochem. Biophys. Res. Commun.* **2004**, 316, 203; A. Takahashi et al., *Arch. Biochem. Biophys.* **2005**, 437, 233].

Actinomycins, peptide antibiotics produced by various strains of *Streptomyces*. Actinomycins are orange-red bacteriostatic and cytostatic, but highly toxic, chromopeptides. The chromophore *actinocin*, 2-amino-4, 6-dimethyl-3-oxo-phenoxazine-1,9-dicarboxylic acid, is linked to two five-membered peptide lactones by the amino groups of two threonine residues. The various naturally occurring and synthetic actinomycins differ mostly in the amino acid sequence of the lactone moieties. *Actinomycin D* is one of the well-known actinomycins with known 3D structure. Actinomycin D is a useful antineoplastic agent that binds tightly to ds-DNA, and in this manner strongly inhibits both transcription and DNA replication. It presumably interferes as an intercalating agent with the passage of RNA polymerase and DNA polymerase, respectively. Actinomycin D is used as a cytostatic in the treatment of the rare types of cancer, e.g.,



Wilms' carcinoma, chorion carcinoma, and Hodgkin's disease [A. B. Mauger, *Topics Antibiot. Chem.* **1980**, 5, 223].

Active ester, R-CO-XR', an amino acid or peptide ester bearing an electron-withdrawing substituent XR' that promotes the nucleophilic attack of the amino component during the formation of a peptide bond. The acylating power of an ester moiety increases with the ability of its leaving group ^-XR to depart, which in turn is related to the strength of the acid HXR'. A very large number of different types of active esters have been described, but only some of these, e.g., thiophenyl-, pentafluorophenyl- and 4-nitrophenyl esters, have been used much. New types of active ester are mechanistically based on intramolecular base catalysis. Efforts to minimize racemization have led to studies of neighboring effects (anchimeric assistance) which led to the development of active esters capable of discriminating effectively between aminolysis and racemization first indicated by 8-quinolyl ester and *N*-hydroxypiperidiny ester. The same situation applies to other active esters of high practical importance, such as derivatives of *N*-hydroxysuccinimide (HOSu), 1-hydroxybenzotriazole ((HOBt), and the 7-aza analogue of HOBt, commonly referred to as 1-hydroxy-7-azabenzotriazole (HOAt; the correct name is 1-hydroxy-1,2,3-triazolo[5,4-b] pyridine) [H.-D. Jakubke et al., *Chem. Ber.* **1967**, 106, 2367;

M. Bodanszky, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York **1979**, 105].

Activins, members of the transforming growth factor- β protein family, originally discovered in the follicular fluid from ovaries and in leukemic cells. They stimulate the release of \rightarrow follitropin. *Activin A* is a homodimer of the β -chains of \rightarrow inhibin-A, whereas *activin B* consists of the β -chains of inhibin-A and inhibin-B. Activin is involved in the regulation of a couple of biological events, ranging from early development to pituitary function. It has numerous functions in both normal and neoplastic cells. Several different cells synthesize activin and have a specific binding site for this protein. It has been described that the activin-binding protein in rat ovary is \rightarrow follistatin. Another activin-binding protein in biological fluids is \rightarrow α_2 -macroglobulin. cDNAs coding for an activin receptor were cloned in order to obtain more information on the cellular mechanisms of activin actions. The resulting cDNAs code for a receptor protein consisting of 494 aa comprising a ligand-binding extracellular domain, a single membrane-spanning domain, and an intracellular kinase domain with predicted Ser/Thr specificity. Recently, regulated production of activin A and activin B throughout the cycle of seminiferous epithelium in the rat have been described [T. Nakamura et al., *Science* **1990**, 247, 836; L. S. Mathews, W. W. Vale, *Cell* **1991**, 65, 973; P. G. Knight et al., *J. Endocrinol.* **1996**, 148, 267; Y. Okuma et al., *J. Endocrinol.* **2006**, 190, 331].

Activity-dependent neurotrophic peptides (ADNP), peptides derived from the neuroprotective protein, named *activity-dependent neuroprotective factor* (ADNF). ADNF ($M_r \sim 14$ kDa; pI 8.3) is a glia-derived

protein and is neuroprotective at femtomolar concentrations. Besides ADNF, even the related peptide fragment ADNP-14, VLGGGSALLR¹⁰SIPA, protects neurons from multiple neurotoxins. From structure–activity studies it follows that ADNP-9, SALLRSIPA, shows greater potency and a broader effective concentration range (10^{-16} – 10^{-13} M) compared with ADNF and ADNP-14 in preventing cell death with tetrodotoxin treatment of cerebral cortical cultures [D. E. Brenneman, I. Gozes, *J. Clin. Invest.* **1996**, *97*, 2299; D. E. Brenneman et al., *Pharmacol. Exp. Ther.* **1998**, *285*, 619].

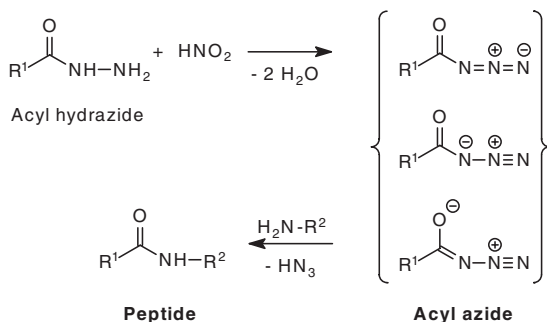
Aculeacins, antifungal peptides affecting glucan synthesis. Aculeacins A to G are produced by *Aspergillus aculeantus*. The peptides A through D, F, and G show good *in-vitro* activity against *C. albicans* and *Saccharomyces cerevisiae*, but reduced the growth of only a few filamentous fungi [K. Mizuno et al., *J. Antibiot.* **1977**, *30*, 297].

Acyl azide method, one of the oldest coupling methods in peptide synthesis, introduced by Theodor → Curtius in 1902. Starting compounds are amino acid or peptide hydrazides ($R\text{-CO-NH-NH}_2$), easily accessible from the corresponding esters by hydrazinolysis, which are transformed into azides ($R\text{-CO-N}_3$) by *N*-

nitrosation at -10°C . The azide is extracted from the aqueous layer with ethyl acetate, washed, dried and reacted with the amino component. The azide method is still important, especially for segment condensations, because of its low tendency towards racemization [J. Meienhofer, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York, **1979**, 197].

Acyl enzyme, an intermediate in the catalytic mechanism of serine proteases, such as trypsin and chymotrypsin. After the serine protease has bound a peptide substrate to form the Michaelis complex, Ser¹⁹⁵ (in the case of chymotrypsin) nucleophilically attacks the peptide bond in the rate-determining step, forming a transition-state complex, known as a tetrahedral intermediate. The latter decomposes to the acyl enzyme, an extremely unstable intermediate, that bears the acyl moiety at the hydroxy group of Ser¹⁹⁵. The acyl enzyme intermediate is deacylated by water during proteolysis, or the attacking nucleophile is an amino component in case of kinetically controlled → enzymatic peptide synthesis.

O-Acyl isopeptide method, an approach to the efficient synthesis of peptides containing → difficult sequences via the O–N

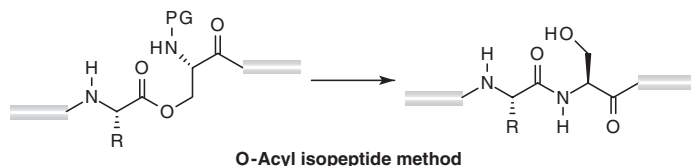


intramolecular acyl migration reaction of *O*-acyl isopeptides. Such intermediates have also been termed \rightarrow click peptides or \rightarrow switch peptides. The sequence-specific formation of stable β -strands that aggregate and consequently prevent further deprotection or acylation reactions in SPPS is a major problem in peptide synthesis. Depending on the amino acid sequence present in the target peptide, the synthetic accessibility may be hampered or even rendered impossible. Such \rightarrow difficult sequences require special consideration when planning a synthesis. Besides the introduction of \rightarrow backbone amide protecting groups or serine/threonine derived \rightarrow pseudo-prolines building blocks, the application of the *O*-acyl isopeptide method provides appropriate measures for obtaining difficult sequences. It relies on an *O*-*N*-intramolecular acyl migration at serine or threonine residues in strategic positions. During the peptide synthesis, a serine or threonine residue protected at N^α is incorporated, involving the β -hydroxy functionality and giving rise to a depsipeptide bond (*O*-acyl isopeptide). Such a single isopeptide moiety prevents the undesired formation of secondary structures. The method allowed, e.g., the synthesis of the Alzheimer's disease-related \rightarrow amyloid β peptide (1-42) [$A\beta$ (1-42)]. The water soluble $A\beta$ (1-42) isopeptide precursor with Gly²⁵-Ser²⁶ replacement by the corresponding β -depsipeptide undergoes, upon Ser²⁶ N^α deprotection, an *O*-*N* acyl migration forming the target $A\beta$ (1-42). Because of this property, the names \rightarrow click peptide and \rightarrow

switch peptide have been coined. As there is a protecting group at the N^α of the isopeptide bond, the *O*-*N* acyl migration can not only be triggered by acidolytic cleavage of the N^α -Boc group, but also, e.g., by the photolysis of photolabile N^α -protecting groups. Such compounds will certainly facilitate the investigation of, e.g., β -sheet formation. Besides $A\beta$ (1-42), other difficult sequences such as the Jung-Redemann 10-peptide and 26-peptide, H-(VT)₁₀NH₂ and the 37-peptide of the FEP28 WW-domain have been synthesized [Y. Sohma et al., *Biopolymers* **2007**, 88, 253; M. Mutter et al., *Angew. Chem. Int. Ed.* **2004**, 43, 4172; L. Carpino et al., *Tetrahedron Lett.* **2004**, 45, 7519].

***O*-Acylisourea**, a reactive intermediate of the \rightarrow carbodiimide method.

Acyl halides, derivatives of amino acids in which the hydroxy group in the carboxyl group is replaced by a halogen atom. Acyl halides are reactive compounds suitable as acylating agents. First, Fmoc-protected amino acid chlorides have been used as stable derivatives for rapid peptide coupling reaction without the danger of racemization. However, their general application is somewhat limited, as not all Fmoc-protected amino acid derivatives are accessible. In contrast, Fmoc-protected amino acid fluorides do not suffer from such limitations. Further advantages of fluorides relative to the chlorides include their greater stability towards water, including moisture in the air, and their relative lack of conversion to the corresponding oxazolones on treatment with tertiary



organic bases. The Fmoc-protected amino acid fluorides are suited both for solution peptide synthesis and for SPPS [L. A. Carpino et al., *J. Org. Chem.* **1986**, *51*, 3732; L. A. Carpino et al., *Acc. Chem. Res.* **1996**, *29*, 268; L. A. Carpino et al., *Tetrahedron Lett.* **1998**, *39*, 241].

Acyltransfer, the transfer of an acyl group R-CO- between two molecules in the course of a reaction as takes place, for example, in a serine protease-catalyzed cleavage of a peptide bond (\rightarrow acyl enzyme).

AD, Alzheimer's disease.

Ada, adamantyl.

Adaptins, accessory proteins thought to bind the membrane-spanning receptors for those specific proteins that the coated vesicle clathrin sequester.

Adhesion molecules, proteins responsible for interactions between cells and their environment, especially, the extracellular matrix and other cells. Several different molecules act as cell adhesion receptors such as \rightarrow integrins, intercellular adhesion molecules (ICAM), leukocyte LFA-1, Mac-1 and p150/95 molecules, the fibronectin receptor complex (\rightarrow fibronectin), tenascin, and the position-specific (PS) antigens of *Drosophila*.

Adipokinetic hormones (AKH), peptide hormones belonging to the \rightarrow AKH/RPCH peptide hormone family. As early in the 1960s, it was observed that extracts of the corpus cardiacum (CC) from either the American cockroach or the migratory (*Locusta migratoria*) and desert locust show metabolic effects such as elevation of the blood sugar trehalose or of the blood lipids (adipokinetic or hyperlipemic effect). In 1976, the complete sequence of the locust's AKH, today denoted as *Locmi-AKH-I*, pGlu-Leu-Asn-Phe-Thr-Pro-Asn-

Trp-Gly-Thr-NH₂, was elucidated. Insecta contain up to three AKH peptides (isoforms) as demonstrated by the other two peptides produced by the African migratory locust: *Locmi-AKH-II*, pGlu-Leu-Asn-Phe-Ser-Ala-Gly-Trp-NN₂, and *Locmi-AKH-III*, pGlu-Leu-Asn-Phe-Thr-Pro-Trp-Trp-NH₂.

The mobilization of substrates for high-energetic phases is the major function of AKH in insects. AKH are involved in the regulation of the level of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cells. However, AKH peptides play also a multifunctional role and exert pleiotropic actions. For example, in certain insects (firebug, cricket) AKH show an effect on the locomotory activity, and are also involved in the immune response of locusts. Beside the members listed above, a huge number of AKHs such as Phymo-AKH (from *Phymateus morbillosus*), Emppe-AKH (from *Empusa pennata*), Manto-CC (*Mantophasmatodea*), and others (Psein-AKH, Grybi-AKH) are known. Recently, a novel member in a water boatman (*Heteroptera*, *Corixidae*), named Corpu-AKH, and its bioanalogue in a saucer bug (*Heteroptera*, *Naucoridae*), code-name Anaim-AKH, have been described. Interestingly, a glycosylated AKH, denoted Carma-HrTH (hypertrehalosemic hormone)-I, synthesized in the CC of the stick insect, is characterized by a unique modification. The hexose moiety is thought to be linked by C-glycosylation to the C-2 atom of the indole ring of tryptophan. On the other hand, Trifa-CC isolated of an extracts of CC from the protea beetle, *Trichostetha fascicularis*, is the first report of a phosphorylated invertebrate neuropeptide [J. V. Stone et al., *Nature* **1976**, *263*, 207; L. Schoofs et al., *Peptides* **1997**, *18*, 145; M. J. Lee et al., *Regul. Pept.* **1997** *69*, 69; G. Gäde, *Annu. Rev. Entomol.* **2004**, *49*,

93; G. Gäde et al., *Biochem. Biophys. Res. Commun.* **2005**, 330, 598; G. Gäde et al., *Biochem. J.* **2006**, 393, 705; G. Gäde et al., *Peptides* **2007**, 28, 594].

Adiponectin, adipocyte complement-related protein of 30 kDa (ACRP30), *adipoQ*, adipose most abundant gene transcript 1 (*apM1*), gelatin-binding protein of 28 kDa (*GBP28*), an adipose-tissue-derived protein with important effects in glucose and lipid homeostasis. The molecular structure of adiponectin is characterized by an N-terminal collagen-like domain and a C-terminal globular domain with similarities to the complement factor C1q. It assembles into homotrimers, and higher-order oligomeric structures resulting by interactions between the collagen-like domains. The production and/or secretion of adiponectin is regulated by various mechanisms; e.g., it is increased by both IGF-1 and insulin in white adipose tissue. The synthesis and secretion of adiponectin are decreased by TNF- α , β -adrenergic agonists, glucocorticoids, and cAMP. With AdipoR1 and AdipoR2 two receptors for adiponectin have been cloned. AdipoR1 occurs primarily in skeletal muscle, whereas AdipoR2 is primarily produced in hepatic tissues. It may act also directly on bone, since receptors are found in osteoblasts and these cells also secrete adiponectin [L. Shapiro, P. E. Scherer, *Curr. Biol.* **1998**, 12, 335; A. H. Berg et al., *Trends Endocrinol. Metab.* **2002**, 13, 84; H. S. Berner et al., *Bone* **2004**, 35, 842; U. Meier, A. M. Gressner, *Clin. Chem.* **2004**, 50, 1511].

Adoc, 1-adamantylloxycarbonyl.

Adrenocorticotrophic hormone (ACTH), \rightarrow corticotropin.

Adrenocorticotropin, \rightarrow corticotropin.

Adrenomedullin (AM), YRQSMNNFQG¹⁰ LRSFGCRFGT²⁰CTVQKLAHQI³⁰YQFTD KDKDN⁴⁰VAPRSKISQ⁵⁰GYa (disulfide bond: C¹⁶–C²¹), a vasoactive 52-peptide amide which is a member of the \rightarrow calcitonin/calcitonin gene-related peptide family and shares 24% sequence homology with \rightarrow calcitonin gene-related peptide (CGRP). AM was first discovered in human pheochromocytoma tissue in 1993, and later found in the normal adrenal medullae, kidneys, lungs, and blood vessels. AM has been reported to be synthesized and secreted by various types of cell, such as vascular endothelial and smooth muscle cells, cardiomyocytes, macrophages, fibroblasts, neurons, glial cells, and retinal pigment epithelial cells. In humans, its gene is situated in a single locus on chromosome 11p15.4. The amino acid sequence is highly conserved across species. The gene contains four exons separated by three introns and codes for a longer preprohormone of 185 aa, which is processed post-translationally, originating AM and *proadrenomedullin N-terminal 20-peptide (PAMP)*. Both peptides participate in many physiological functions, including vasodilatation, bronchodilatation, neurotransmission, regulation of hormone secretion, brain functions, renal homeostasis, and antimicrobial activities. Apart from vasodepressive effects in mammals, caused by decreasing peripheral vascular resistance, AM shows diuretic and bronchodilatory effects and plays a regulatory role on aldosterone and ACTH (\rightarrow corticotropin) release. In renal failure, hypertension, heart failure, pregnancy loss, and septic shock plasma, the AM level has been found to be increased. The biological actions of AM are mediated through the calcitonin receptor-like receptor (CRLR) complexed with \rightarrow receptor activity-modifying proteins (RAMPs),

especially via both CRLR/RAMP2 and CRLR/RAMP3 receptors, respectively (\rightarrow calcitonin/calcitonin gene-related peptide family). Plasma AM concentration is increased in patients with cardiovascular diseases. It has been shown that the source of increased AM levels in cardiac failure is the heart. AM has hypotensive, diuretic and natriuretic properties that are in common with \rightarrow natriuretic peptides; however, the role of AM in cardiac pathologies is less clear. Sequence analysis of the *Fugu rubripes* genome led to the identification of three AM orthologues characterized by a 31 aa C-terminal domain sharing 50, 38, and 35% sequence identity with hAM in the mature area. The sequence N-terminal to the cystine ring varies greatly among species. Recently, it has been reported that AM and PAMP might be potent inducers of angiogenesis which is required for the maintained growth of solid tumors [K. Kitamura et al., *Biochem. Biophys. Res. Commun.* **1993**, 192, 553; C. J. Charles et al., *Am. J. Hypertens.* **1999**, 12, 166; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, 11, 167; M. Jougasaki, J. C. Burnett, Jr., *Life Sci.* **2000**, 66, 855; T. Eto et al., *Regul. Pept.* **2003**, 112, 61; M. T. Rademaker et al., *Regul. Pept.* **2003**, 112, 51; C. L. Chang et al., *Peptides* **2004**, 25, 1633; A. Martinez, *Cancer Lett.* **2006**, 236, 157].

Adrenorphin, \rightarrow metorphamide.

Advanced glycation end products (AGEs), a heterogeneous group of non-enzymatically glycated and oxidized proteins or lipids. AGEs are present and accumulated in many different cell types, and affect extracellular and intracellular structure and function. Microvascular and macrovascular complications are caused through the formation of crosslinks between molecules in the basement membrane of the extracellular matrix. AGCs are prevalent in the

diabetic vasculature, and contribute to the development of atherosclerosis. The concentrations of AGEs are altered in the body, particularly in relation to changes occurring with age. AGEs contribute to amyloidosis in \rightarrow Alzheimer's disease, and AGEs formation is also stimulated by oxidative stress, e.g., in uremia. A decrease in renal function increases circulating AGE concentrations by reduced clearance [M. P. Vitek et al., *Proc. Natl. Acad. Sci. USA* **1994**, 91, 4766; R. Singh et al. *Diabetologia* **2001**, 44, 129; J. M. Bohlender et al., *Am. J. Renal Physiol.* **2005**, 289, F645; A. Goldin et al., *Circulation* **2006**, 114, 597].

Aequorin, a calcium-sensitive photoprotein originally obtained from the jellyfish *Aequorea victoria*. This bioluminescent jellyfish produces a greenish luminescence from the margin of its umbrella using aequorin and a chromophore-bearing \rightarrow green fluorescent protein (GFP). Aequorin is a Ca^{2+} -binding protein ($M_r \sim 21$ kDa), and undergoes an intramolecular reaction on binding Ca^{2+} , yielding a blue fluorescent protein in the singlet excited state, transferring its energy by resonance to GFP. Aequorin consists of four helix-loop-helix "EF-hand" domains, of which three can bind Ca^{2+} . It also contains coelenterazine as its chromophoric ligand. The addition of Ca^{2+} causes decomposition of the protein complex into apoaequorin, coelenteramide and CO_2 , accompanied by the emission of light. Regeneration of apoaequorin into active aequorin takes place in the absence of Ca^{2+} by incubation with coelenterazine, oxygen, and a thiol agent. Aequorin is widely used as a probe to monitor intracellular levels of Ca^{2+} . The crystal structure of recombinant aequorin at 2.3 Å resolution shows a globular molecule containing a hydrophobic core cavity accommodating the ligand

coelenterazine-2-hydroperoxide [O. Shimomura et al., *J. Cell. Comp. Physiol.* **1962**, 59, 223; H. Morise et al., *Biochemistry* **1974**, 13, 2656; M. Brini et al., *J. Biol. Chem.* **1995**, 270, 9896; J. F. Head et al., *Nature* **2000**, 405, 291].

Aeruginosins, a main class of → cyanobacterial peptides characterized by a derivative of hydroxyphenyl lactic acid (Hpla) at the N-terminus, 2-carboxy-6-hydroxyoctahydroindole (Choi) and the arginine derivative agmatine at the C-terminus. The aeruginosins 98-A and B from the blue-green alga *Microcystis aeruginosa* act as trypsin inhibitors [M. Murakami et al., *Tetrahedron Lett.* **1995**, 36, 2785].

Aet, aminoethyl.

Affinity chromatography, a special variant of adsorption chromatography in which the adsorbent is biospecific. A molecule, known as the ligand, that specifically binds, for example to the protein of interest, is covalently attached to an inert porous matrix, e.g., agarose gel, glass beads, cellulose, polyacrylamide, crosslinked dextrans. The impure protein solution is passed through this stationary phase and the desired protein with selective affinity to the ligand is retained, while other proteins and substances are immediately eluted. The bound substance can then be recovered in highly purified form by changing the elution conditions such that the desired protein is released from the stationary phase. Specific interactions between, e.g., antibodies and antigens, enzymes and their inhibitors, nucleic acids of complementary sequences, lectins and polysaccharides, receptors and hormones, avidin and biotin can be utilized [P. Cuatrecasas et al., *Proc. Natl. Acad. Sci. USA* **1968**, 61, 636].

Ag, antigen.

AG3, AYSSGAPPMP¹⁰PF, an inorganic-binding peptide (→ silver-binding peptides) that specifically and selectively binds to silver. AG3 was immobilized on the surface of protonated poly(ethylene terephthalate) (PET) film which was prepared for biomimetic synthesis of silver particles *in vitro*. Silver crystallites have been formatted on the surface of the AG3-PET film showing various shapes 1 to 4 μm in size [Z. Xu et al., *J. Inorg. Biochem.* **2005**, 99, 1692].

AGaloc, tetra-O-acetyl-β-D-galactopyranosyloxycarbonyl.

AGE, advanced glycation end product.

Agloc, tetra-O-acetyl-D-glucopyranosyloxycarbonyl.

Agonist, a term given for analogues of native peptide hormones that trigger the hormone signal in the same manner.

Agouti protein, a 131 aa protein encoded by the murine agouti gene and expressed in the skin. During hair growth, agouti acts to regulate coat coloration, and abnormal expression of the agouti protein causes the yellow phenotype. The agouti protein is a paracrine signaling molecule that regulates coat coloration via competitive antagonism of α-MSH (→ melanocortin peptides) binding to its receptor (→ melanocortin receptors, MCR). The antagonistic action of agouti protein prevents the α-MSH-mediated increase in intracellular cAMP that results in the cell switching from the production of black pigment, eumelanin, to yellow pigment, pheomelanin. Pharmacologically, agouti is a high-affinity, competitive antagonist of the melanocortin peptides at melanocortin receptors MC1R, MC3R, MC4R, and the adrenocortical ACTH (→ corticotropin) receptor, MC2R, respectively [D. Lu et al., *Nature* 1994, 371,

799; D. M. Dinulescu, R. D. Cone, *J. Biol. Chem.* **2000**, 275, 6695].

Agouti-related protein (AGRP), a 132 aa protein first identified by database searches for molecules with homology to \rightarrow agouti protein in 1997. AGRP is expressed predominantly in the adrenal gland, hypothalamus, and at low levels in the lung, testis, and kidney. AGRP has been physiologically implicated in the regulation of food intake, body weight, and energy homeostasis. It is acting as a brain melanocortin-4 (MC4R) and melanocortin-3 (MC3R) receptor (\rightarrow melanocortin receptor) antagonist. It has been reported that AGRP has additional targets in the hypothalamus and/or physiologically functions through a mechanism in addition to competitive antagonism of α -MSH at the brain melanocortin receptors. AGRP is a orexigenic (appetite-stimulating) peptide that promotes food intake and is coexpressed with another potent orexigenic neuropeptide, \rightarrow neuropeptide Y. The human AGRP gene is relatively short, spanning 1.1 kb on chromosome 16q22. Most investigations on the *in-vivo* function of AGRP have used C-terminal AGRP peptide sequences that mimic the effect of the full-length protein. Human AGRP-(87–132): CVRLHESCLG¹⁰QQVPCDPCA²⁰TCYCRFFNAF³⁰CYCRKLG⁴⁰TAMNPCSRT (disulfide bonds: C¹–C¹⁶/C⁸–C²²/C¹⁵–C³³/C¹⁹–C⁴³/C²³–C³¹), a synthetic 46-peptide was capable of binding the melanocortin receptors MC3R, MC4R, and MC5R, thus, inhibiting binding of α -MSH. NMR structure analysis of AGRP-(87–132) revealed an inhibitor cysteine-knot structure which makes possible contact with the MC3R and MC4R with two loops which are present in this structure. The appetite-boosting AGRP-(87–132) may be both an important

tool for elucidating the mechanism of obesity, and a potentially interesting drug target in combating obesity and related co-morbidities [M. M. Ollman et al., *Science* **1997**, 278, 135; J. R. Shutter et al., *Genes Dev.* **1997**, 17, 75; R. D. Rosenfeld et al., *Biochemistry* **1998**, 37, 16041; E. J. Bures et al., *Biochemistry* **1998**, 37, 12172; C. Haskell-Luevano, E. K. Monck, *Regul. Pept.* **2001**, 99, 1].

AGRP, agouti-related protein.

Ahx, 2-aminohexanoic acid (norleucine).

ϵ Ahx, 6-aminohexanoic acid.

AHZ, β -alanyl-histidinato zinc.

Aib, α -aminoisobutyric acid (α -methyl-alanine).

AIDS, acquired immunodeficiency syndrome.

alle, allo-isoleucine (2*S*,3*R* in the L-series).

Aimoto thioester approach, a polypeptide synthesis method characterized by converting an *S*-alkyl thioester moiety in the presence of a silver salt into an active ester derived from HOBT or HODhbt, followed by segment condensation of partially protected segments [S. Aimoto, *Biopolymers* **1999**, 51, 247].

Akabori Conference, called in honor of Shiro Akabori, a series of conferences with Japanese and German peptide chemists held every two years, alternating between the two countries, founded by Erich Wunsch and Shumpei Sakakibara.

Akabori method, an approach to C-terminal amino acid end group analysis of peptides using hydrazine. By treatment of the peptide under investigation with anhydrous hydrazine for 90–100 h at 90°C in the presence of an acidic ion-exchange resin, only the C-terminal amino acid residue

is released as free amino acid, whereas all other amino acids are converted into hydrazides. The resulting C-terminal free amino acid can be identified chromatographically [S. Akabori et al., *Bull. Chem. Soc. Japan* **1956**, 29, 507].

Akabori, Shiro (1900–1992), professor of organic chemistry at Osaka University (1939–1966), known as the father of peptide chemistry in Japan, with outstanding international achievements in peptide research, inter alia → Akabori method. From 1960 onwards, and even after his retirement in 1966, Professor Akabori continuously served the scientific community for over 20 years as president of the Protein Research Foundation Japan.

AKH, adipokinetic hormone.

AKH/RPCH peptide hormone family, *adipokinetic hormone/red pigment-concentrating hormone family*, peptide hormones produced in the neurosecretory organs of crustacean and insects, and named after the first fully characterized members and their most prominent functions. These include the aggregation of pigment in the epidermal cells of crustaceans by the → red pigment-concentrating hormone (Pando-RPCH), whereas the → adipokinetic hormones (AKH) in insects regulate the levels of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cell. The resulting substrates can subsequently be used during intense muscular work, e.g., flight, swimming, or running. At present, only Pando-RPCH have been found in a relatively large number of crustaceans, whereas about 40 analogues (isoforms), including Panbo-RPCH, have been isolated from all major orders of insects. The members of this peptide hormone family consist of 8 to 10 amino acid residues

bearing both a blocked *N*-terminus (pyroglutamate residue) and C-terminus (amide) respectively. They are characterized by aromatic amino acids at position four (Phe or Tyr) and eight (Trp). Besides the well-known members of this family, some AKH/RPCH peptides are produced in the brain and not in the retrocerebral corpora cardiaca (CC), for example in the migratory locust and the African malarial mosquito. In addition to the modified termini of the peptides, additional post-translational modifications comprise C-glycosylations at Trp and phosphorylation at Thr residues [G. Gäde, *Z. Naturforsch.* **1996**, 51, 333; G. Gäde, H. G. Marco, in: *Studies in Natural Product Chemistry (Bioactive Natural Products)*, Atta-ur-Rahmann (Ed.), Vol. 33, pp. 69–139, Elsevier Science Publishers, The Netherlands, **2005**].

Al, allyl

Ala, alanine

Alanine (Ala, A), α -aminopropionic acid, $\text{H}_3\text{C}-\text{CH}(\text{NH}_2)-\text{COOH}$, $\text{C}_3\text{H}_7\text{NO}_2$, M_r 89.09 Da, a proteinogenic amino acid.

Alanine scan, systematic substitution of each amino acid residue of a native peptide by a simple amino acid such as alanine. A first step in structure–activity relationship studies.

β -Ala, β -alanine

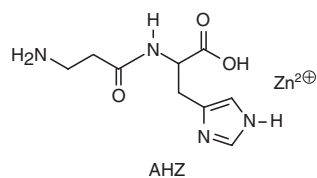
β -Alanine (β -Ala), β -aminopropionic acid, a naturally occurring non-proteinogenic amino acid occurring, e.g., in → carnosine, → anserine, and coenzyme A.

Alamethicin, a member of the → peptaibols produced by the fungus *Trichoderma viride*. This is one of the most extensively investigated member of the long peptaibol antibiotics. Alamethicin consists of a natural microheterogeneous peptaibol mixture

of which 23 members have been sequenced up to 2004. All alamethicins are 19-peptides blocked at the *N*-terminus by an acetyl moiety, and at the *C*-terminus by the 1,2-aminoalcohol *L*-phenylalaninol (Fol). The acidic alamethicins bear a Glu¹⁸ residue, whereas this building block is replaced by Gln¹⁸ in the neutral alame-thicins. The alamethicins are classified into two groups. The major group is called F50 and is composed of neutral peptides (Gln¹⁸), whereas the minor group, termed F30, consists of acidic peptides (Glu¹⁸). Only the F30/6 analogue bears two acidic amino acids (Glu⁷, Glu¹⁸), while in all other alamethicins Gln⁷ is conserved. The alame-thicins are rich (7–10 aa) on the strongly helicogenic, non-coded α -aminoisobutyric acid (Aib), and contain two well-spaced proline residues in positions 2 and 14. A major component of the natural alame-thicin mixture is the F50/5 analogue with the following sequence: Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib¹⁰-Gly-Leu-Aib-Pro-Val-Aib-Aib-Glu-Gln-Phe-ol, the total synthesis of which in solution by an easily tunable segment condensation approach was described in 2004. Besides this approach, more than 20 other synthesis variants of alamethicin have been reported. Alamethicin is amphiphilic, but of high overall hydrophobicity. It is known to generate voltage-dependent pores in biological membranes, and to insert spontaneously into lipid bilayers. Some more or less convincing models have been postulated. From the crystal structure it could be revealed that alamethicin is preferentially α -helical, with a bend in the helix axis at Pro¹⁴. This structure is in agreement with an early model for the mode of action, in which a certain number (6–12) of molecules form aggregates, like the staves of a barrel. However, there are also other models for channel formation. One model, based on a voltage-

dependent flip-flop of α -helix dipoles, postulates that the membrane-inserted helices attract each other when oriented in anti-parallel fashion. In contrast to the flip-flop model, another model assumes that the gating charge transfer is involved in the opening-closing mechanisms. The mechanisms of membrane permeability by alamethicin remain the subject of debate [R. Nagaray, P. Balaram, *Acc. Chem. Res.* **1981**, *14*, 356; E. Benedetti et al., *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 7951; R. O. Fox, F. M. Richards, *Nature* **1982**, *300*, 325; H. Brückner, H. Graf, *Experientia* **1983**, *39*, 528; G. Boheim et al., *Biophys. Struct. Mech.* **1983**, *9*, 181; D. T. Edmonds, *Eur. Biophys. J.* **1985**, *13*, 31; H. Wenschuh et al., *J. Org. Chem.* **1995**, *60*, 405; M. S. P. Sansom, *Mol. Biol.* **1991**, *55*, 139; J. Kirschbaum et al., *J. Peptide Sci.* **2003**, *9*, 799; C. Peggion et al., *Biopolymers (Pept. Sci.)* **2004**, *76*, 485].

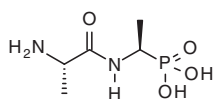
β -Alanyl-histidinato zinc (AHZ), a zinc-chelated dipeptide for the exogenous administration of zinc. The zinc delivery potential of AHZ is more effective on bone metabolism than zinc sulfate. In-vitro studies have established that AHZ causes complete inhibition of the decrease of bone calcium in a bone tissue culture system, as well as in the formation of osteoclast-like cells in mouse marrow culture [M. Yamaguchi, *Gen. Pharmacol.* **1995**, *26*, 1179].



β -Alanyl-histidinato zinc

Alaphosphin, *L*-alanyl-*L*-1-aminoethylphosphonic acid, a \rightarrow phosphopeptide acting as an antibacterial agent. It selectively inhibited peptidoglycan biosynthesis in both

Gram-negative and Gram-positive bacteria. Alaphosphin was selected from a range of phosphonopeptides for studies in humans on the basis of its antibacterial activity, pharmacokinetics, and stability against intestinal and kidney proteases. *In vitro*, it proved active against the majority of about 50 strains of *Serratia marcescens* [J. G. Allen et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 684; F. R. Atherton et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 696; W. H. Traub, *Chemotherapy* **1980**, *26*, 103].



Alaphosphin

Albomycins, natural siderophores and antibiotics first isolated from *Streptomyces griseus* and named grisein in 1947. Some years later, another microbial iron-transport compound, named albomycin, was isolated from *Streptomyces subtropicus* which had the same structure as grisein. In 1982, the structure of the albomycins was firmly established. The linear tripeptide built of *N*⁵-acetyl-*N*⁵-hydroxy-L-ornithine is the hexadentate, octahedral ligand for ferric ion responsible for intracellular transport of iron. The albomycins are used for treatment of iron metabolism disorders [G. Benz et al., *Angew. Chem. Int. Ed.* **1982**, *21*, 527; G. Benz, *Liebigs Ann. Chem.* **1984**, 1408].

Albumins, a group of water-soluble proteins occurring in body liquids, animal tissues and in some plant seeds. They are rich in both Glu and Asp (20–25%) as well as Leu and Ile (up to 16%). Albumins have a low molecular mass, are easily crystallizable, and their isoelectric points are in the weakly acid range. High concentrations of neutral salts are necessary for “salting

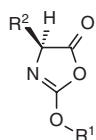
out.” Albumins have been used as a model protein for diverse biophysical, biochemical, and physico-chemical studies. *Serum albumins* ($M_r \sim 67.5$ kDa) are the most abundant of these proteins in blood plasma. These proteins have been one of the most investigated proteins for many years, and show interesting properties of binding a variety of hydrophobic ligands, e.g., fatty acids, warfarin, anesthetics, bilirubin, steroids, lysolecithin, and several dyes. Furthermore, a high binding capacity for Ca^{2+} , Na^+ , K^+ must be mentioned. Serum albumins comprise up to 60% of the dry mass of blood serum, corresponding to a concentration of 42 g L^{-1} , and provide about 80% of the osmotic pressure of blood. The single peptide chain of about 580 aa forms a secondary structure characterized by 67% of α -helix, six turns, and 17 disulfide bridges. The X-ray structure of *human serum albumin* (HSA) shows three domains I, II, and III, which confer to the protein a heart-shaped molecular form. Each domain consists of two subdomains, named IAB, IC, IIAB, IIC, IIIAB, IIIC, respectively. Interestingly, the domains exhibit a certain degree of binding specificity. Domain I, also named the warfarin binding site, binds predominantly indole derivatives, several dyes, long-chain fatty acids, and compounds with alicyclic ring structures, whereas domain II, termed the indole or benzodiazepine binding site, is specific for the binding of short-chain fatty acids, bilirubin, indole derivatives, several dyes, and steroids. Domain III is specific for indole derivatives, long-chain fatty acids, diazepam and other drugs. *Bovine serum albumin* (BSA) shows 76% sequence identity with HSA. BSA contains two tryptophan residues (W^{214} , W^{131}), while HSA has only one (W^{214}). The consequences are different spectroscopic properties of the two proteins. Bovine and human serum

albumin contain 16% nitrogen, and are used as standard proteins for calibration. Further important animal and plant albumins are \rightarrow lactalbumin, \rightarrow ovalbumin and \rightarrow ricin [J. R. Brown, P. Shockley, *Lipid-Protein Interactions*, Vol. 1, Wiley, New York, 1982; D. Carter, J. X. Ho, *Advances in Protein Chemistry*, Vol. 45, Academic Press, New York, 1994, p. 153; E. L. Gelano et al., *Biochim. Biophys. Acta* **2002**, 1594, 84].

Alkanesulfonamide linker, \rightarrow safety-catch linker.

Alkene peptidomimetics, peptides, where an amide bond has been replaced to give E-alkene [M. M. Hahn et al., *J. Chem. Soc. Commun.* **1980**, 234; M. Kranz, H. Kessler, *Tetrahedron Lett.* **1996**, 37, 5359].

2-Alkoxy-5(4H)-oxazolones, azlactones, stereochemically labile intermediates that occur during coupling reactions and can cause \rightarrow racemization at the stereogenic center of an α -amino acid. The propensity toward oxazolone formation strongly correlates with the activation potential of the activating group X in the carboxy component, $R^1\text{-CO-NH-CHR}^2\text{-CO-X}$, and with the electronic properties of the *N*-acyl moiety $R^1\text{-CO-}$ [M. Goodman, L. Levine, *J. Am. Chem. Soc.* **1964**, 86, 2918].



Oxazolone

Alkyl-type protecting groups, protecting groups for the amino function of amino acids during peptide synthesis based on alkyl moieties. The most popular protect-

ing group of the alkyl type is the \rightarrow triphenylmethyl (Trt) group.

All, allyl

Allatostatins (AST), a family of neuropeptides first isolated from the brain of the cockroach *Diploptera punctata*. There are three allatostatin families according to C-terminal sequence homology: (a) the *cockroach type* (>70 peptides, consensus sequence FGLa), comprising e.g. Dippu-AST 1 (LYDFGLa), Dippu-AST 2 (AYSIVSEYKR¹⁰LPVYNFGLa), Dippu-AST 5); (b) the *cricket type* (consensus sequence WX₆Wa), with Grybi-AST 1 (H-Gly-Trp-Gln-Asp-Leu-Asn-Gly-Gly-Trp-NH₂) and Grybi-AST 5 (H-Ala-Trp-Asp-Gln-Leu-Arg-Pro-Gly-Trp-NH₂); and (c) the *Manduca type* (consensus sequence PISCF). Members of the latter family are highly homologous ($<\text{EXRZRQCYFN}^{10}\text{PISCF}$ with X = V, I and Z = F, Y) between the species *Manduca sexta*, *Drosophila melanogaster*, and *Anopheles gambiae*. AST inhibit the synthesis of the juvenile hormone in the *corpora allata*, which regulates insect metamorphosis. However, it has been proposed that this effect appeared secondarily, and that the ancestral function was the modulation of myotropic activity. Further effects of the different AST include endocrine and interneuronal functions, neuromodulatory effects, and direct action on biosynthetic pathways; mostly being species- or order-specific. Picomolar concentrations of the *Drosophila melanogaster* Drome-AST 3 (H-Ser-Arg-Pro-Tyr-Ser-Phe-Gly-Leu-NH₂) from the head of *Drosophila* activate a fruit-fly G protein-coupled receptor that shows striking sequence similarities to mammalian galanin and somatostatin/opioid receptors [A. P. Woodhead et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 5997; W. G. Bendena et al., *Ann. N. Y. Acad. Sci.* **1989**,

897, 311; J. G. Yoon, B. Stay, *J. Comp. Neurol.* **1995**, 363, 475; N. Birgul et al., *EMBO J.* **1999**, 18, 5892].

Alloc (Aloc), → allyloxycarbonyl group.

Allom, Alom, → allyl-type protecting groups.

Allopeptide, a word derived from the noun "peptide" that means in immunology a peptide from different individual (Greek *allos*, other) of the same species [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

Allyl ester, → allyl-type protecting groups.

Allyloxycarbonyl group (Alloc, Aloc), an urethane-type protecting group for the amino function during peptide synthesis. The Alloc group is completely orthogonal to Boc and Fmoc, and is especially suited for the synthesis of labile derivatives. The group can be smoothly removed by treatment with a suitable nucleophile, e.g., amines, amine-borane complexes, organosilanes, in the presence of a palladium catalyst (palladium(0)-catalyzed allyl transfer) [H. Kunz, C. Unverzagt, *Angew. Chem. Int. Ed.* **1984**, 23, 436; A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, 42, 346; F. Guibe, *Tetrahedron* **1998**, 54, 2967].

Allyl-type protecting groups, protecting groups used in peptides synthesis bearing the allyl moiety. This type of protecting group has the advantage of being completely orthogonal to most other protecting groups, and provides an excellent tool for temporary reversible protection in glycopeptide synthesis. Beside the → allyloxy-carbonyl group, *allylester* (OAll) of amino acids are very easy to obtain, are stable under glycosylation conditions, and can be cleaved by Rh^I catalysis. An even milder method for the selective cleavage of allyl esters utilizes palladium(0)-catalyzed allyl transfer to morpholine. Allyl-type linker moieties are also suited for the solid-

phase synthesis of complex glycopeptides. The *allyloxycarbonylaminomethyl* (Allocam) group was described as a thiol-protecting group in 1999, while the *N^T*-allyl moiety was suggested as an imidazole-protecting group by the same authors one year later. Last, but not least, the *N^T*-allyloxymethyl (Allom) group has also been described as an imidazole-protecting group [A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, 42, 346; A. M. Kimbonguila et al., *Tetrahedron* **1997**, 53, 12525; A. M. Kimbonguila et al., *Tetrahedron* **1999**, 55, 6931; S. J. Harding, J. H. Jones, *J. Peptide Sci.* **1999**, 5, 368; H. Herzner et al., *Chem. Rev.* **2000**, 100, 4495].

Alterobactin, a 19-membered macrocyclic → depsipeptide containing two types of unusual building block, two *L*-threo- β -hydroxyaspartic acids and one (3*S*,4*S*)-4,8-diamino-3-hydroxyoctanic acid attached to a catechol carboxylate at the *N^o*-site. It was isolated from a open-ocean bacterium *Alteromonas luteoviolacea* collected off Chub Cay, Bahamas. Alterobactin is a depsipeptide → siderophore exhibiting extraordinary affinity for ferric ion. The total synthesis has been described [R. T. Reid et al., *Nature* **1993**, 366, 455; J. Deng et al., *Synthesis* **1998**, 627].

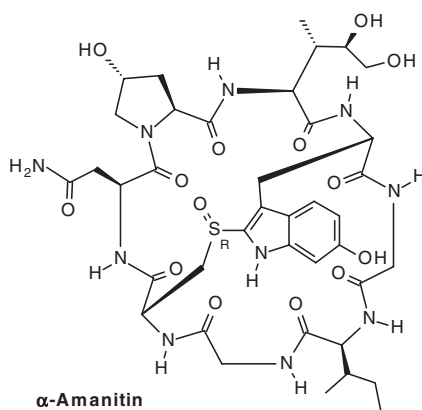
Alytensin, <EGR LGTQWAV¹⁰GHLMa, a 14-peptide amide belonging to the → bombesin family. Alytensin was isolated from the skin of the European amphibian *Alytes obstetricans* in 1971. It is structurally very similar to → bombesin, and displays similar biological activities when applied to mammals [A. Anastasi et al., *Experientia* **1971**, 27, 166; V. Erspamer, P. Melchiorri, *Trends Biochem. Sci.* **1980**, 1, 391].

Alzheimer's disease (AD), the most prominent severe dementia in the elderly population, first described by Alzheimer in 1907. AD is a widespread, neurodegenerative,

dementia-inducing disorder characterized mainly by amyloid deposits surrounding dying neurons (senile plaques), neurofibrillar degeneration with tangles, and cerebrovascular angiopathies. AD is clinically characterized by a progressive loss of cognitive abilities, progressive memory and intellectual deficits. In 1998, it was estimated that 25 million people worldwide suffered from AD. Amyloid- β and tau protein are responsible for the formation of the plaques and tangles of AD. The mechanism of neurodegeneration caused by \rightarrow amyloid- β in AD is controversial. The primary pathogenic event of AD is the progressive cerebral accumulation of amyloid- β ($A\beta$), a proteolytic product of the β -amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments that form a compact filamentous network described as "neurofibrillary tangles." From culture experiments there was derived the existence of a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. The cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3 β are the two main protein kinases involved in the anomalous tau phosphorylations. Inhibitors of both kinases and antisense oligonucleotides exert protection against neuronal death. On the other hand, it has been reported that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells. In brain tissue from AD patients, some major species of soluble $A\beta$ have been identified: the full-length form $A\beta$ (1–42), and at residues Glu³ and Glu¹¹, respectively, truncated $A\beta$ peptides, such as $A\beta$ (3–40/42) and $A\beta$ (11–40/42). The shortened forms bear at the N-terminus a pyroglutamic acid residue which might be result from the corresponding Glu residues

catalyzed by the glutamyl cyclase activity of \rightarrow glutaminyl cyclase. It has been reported that, *in vitro*, these smaller peptides are more neurotoxic and aggregate more rapidly than the full-length isoforms. A rational design of inhibitors against glutaminyl cyclase-associated disorders has been started [R. B. Maccioni et al., *Arch. Med. Res.* **2001**, 35, 367; T. Hashimoto et al., *EMBO J.* **2002**, 21, 1524; C. Morgan et al., *Prog. Neurobiol.* **2004**, 74, 323; S. Schilling et al., *FEBS Lett.* **2004**, 563, 191; K.-F. Huang et al., *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13117; S. Schilling et al., *Biochemistry* **2005**, 44, 13415; M. Goedert, M. G. Spillantini, *Science* **2006**, 314, 777].

Amanitins, a group of toxic components of *Amanita phalloides* (\rightarrow amatoxins).



Amatoxins, heterodetic bicyclic 8-peptides from *Amanita* species, but also detected in *Galerina* and *Lepiota* species, which are responsible for the fatal intoxications by the mentioned toadstools. The toxic peptides are readily absorbed by the intestine, and in humans the lethal dose of amatoxin is ~ 0.1 mg kg⁻¹ body weight, or even lower. The gut cells of humans seem to be the first cells affected, and the intestinal phase begins about 9 h after

administration of the toxins. There is no effective therapy of *amanita* poisoning, as the amatoxins inhibit strongly and specifically the eukaryotic RNA-polymerases II (B) in the nuclei. To date, nine members of the amatoxins have been isolated, among which α -amanitin is the best studied. The individuals are derived from the parent structure, and differ mainly by the number of hydroxyl groups and by an amide versus carboxy function. Amatoxins contain exclusively L-amino acids and glycine, together with uncommon moieties such as the bridging 6'-hydroxytryptathionine-(R)-sulfoxides between residues 4 and 8. The fundamental studies on structure elucidation and biochemical effects were carried out by Theodor Wieland and coworkers [Th. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer Series in Molecular Biology, Springer-Verlag, New York, Berlin, 1986].

American Peptide Society (APS), a non-profit scientific and educational organization founded in 1990, providing a forum for advancing and promoting knowledge of the chemistry and biology of peptides. The near-1000 members of the Society come from North America and from more than 30 other countries worldwide. The establishment of the American Peptide Society was a result of the rapid worldwide growth that has occurred in peptide-related research, and of the increasing interaction of peptide scientists with virtually all fields of science. Members of the APS are involved in research in academia, industry, and government, covering all aspects of peptide chemistry, biology, and pharmaceutical sciences. Research topics include the synthesis of biologically important targets, the isolation and characterization of new products, structure-activity relationship studies, molecular diversity, *de-novo*

design, drug delivery, and the discovery of new pharmaceutical agents. The APS is a member of the Federation of American Societies for Experimental Biology (FASEB). The affiliation with FASEB increases the visibility of APS in the biomedical research community, and allows the participation in any FASEB public affairs initiatives. The APS sponsors *Biopolymers: Peptide Science*, published by Wiley-Interscience, as the official journal of the Society. A full year subscription to this journal is automatically included with membership in the APS. One very important activity of the APS is the organization of a biennial international symposium in North America. The 20th *American Peptide Society Symposium* was held in Montreal, Quebec, Canada, in June 2007. The APS Council administers *The R. Bruce Merrifield Award*, which recognizes the lifetime scientific work of a peptide chemist, *The Vincent du Vigneaud Award* for outstanding achievements in peptide research, which is presented at the Gordon Research Conferences every two years, besides further honors such as the *Makineni Lectureship*, the *Achievement Award for Scientific and Administrative Excellence*, the *Young Investigator's Mini-Symposium*, and the *Young Investigator's Poster Competition*.

Amidation, the formation of amides. Amino acid and peptide amides are synthesized by reaction of the appropriate esters or activated carboxylic acid derivatives with ammonia. Amidation of bioactive peptides is performed using the bifunctional enzyme peptidylglycine α -amidating monooxygenase (PAM) by N-oxidative cleavage of a glycine-extended precursor [S. T. Prigge et al., *Science* **1997**, 278, 1300].

Amide-protecting groups, protecting groups for C-terminal amides of amino

acids and peptides, for backbone amide groups (\rightarrow backbone amide protecting groups), as well as for the side-chain ω -carboxamide groups of Gln and Asn. Although these rather unreactive functionalities usually do not require further protection, side reactions sometimes occur at the side-chain carboxamides of Asn and Gln during peptide synthesis. Under the strongly dehydrating conditions of carbodiimide couplings, unwanted nitrile formation may prevail. Strongly activating reagents (BOP, PyBOP, HBTU) also may favor this dehydration. Asn in the peptide chain has been observed to cyclize, with release of ammonia, to give aspartimides that in turn are hydrolyzed to a mixture of α -aspartyl and β -aspartyl peptides. Most side-chain reactions can be suppressed by reversible blocking of these functionalities with, e.g., substituted *N*-benzyl derivatives, *N*-methoxybenzyl residues, or the *N*-diphenylmethyl moiety, all of which can be cleaved by liquid HF. *N*-Triphenylmethyl (Trt) and *N*-trimethoxybenzyl (Tmb) are very appropriate carboxamide-protecting groups for solid-phase synthesis, in combination with Fmoc as the temporary protecting group. The carbonyl and amino groups of a peptide bond potentially act as hydrogen bond acceptors and donors, favoring aggregation and leading to the formation of secondary structures and aggregation. This may prevent further reactions of the amino terminus and lead to truncated sequences. The phenomenon is sequence-dependent (\rightarrow difficult sequences). In such cases, e.g. \rightarrow backbone amide protecting groups with Hnb or Hmb residues is required [P. Sieber, B. Riniker, *Tetrahedron Lett.* **1991**, 32, 739; B. Riniker et al., *Tetrahedron* **1993**, 49, 9307].

Amine capture strategy, a variant of prior capture-mediated ligation by means of

quinolinium thioester salts. Quinolinium thioester salts has been designed as a so-called new electrophilic platform capable of acting as an amine capture device [S. Leleu et al., *J. Am. Chem. Soc.* **2005**, 127, 15668].

Amino acid analysis, determination of amino acid composition of a peptide by complete hydrolysis followed by the quantitative analysis of the liberated amino acids. For hydrolysis, numerous chemical and enzymatic protocols are known. Based on the pioneering studies of \rightarrow Stein and \rightarrow Moore, amino acid analysis has been automated. Nowadays, instruments are in use for quantitative amino acid analysis which are based on partition chromatography, such as HPLC and gas-liquid chromatography [S. Blackburn, *Amino Acid Determination*, M. Dekker, New York, **1978**; W. S. Hancock, *Handbook of HPLC for the Separation of Amino Acids, Peptides, and Proteins*, CRC Press, Boca Raton, **1984**].

Amino acid anhydrides, \rightarrow anhydrides.

Amino acid chloride, \rightarrow acyl halides.

Amino acids, the monomeric units of peptides and proteins. From analysis of the vast number of proteins, it follows that 20 proteinogenic or "standard amino acids" are the building blocks of all proteins. These amino acids are specified by the genetic code. With \rightarrow selenocysteine and \rightarrow pyrrolysine two additional members have been identified. Besides the imino acid proline, all other building blocks are known as α -amino acids, $\text{H}_2\text{N}-\text{CHR}-\text{COOH}$, but the zwitterion form, $\text{H}_3\text{N}^+-\text{CHR}-\text{COO}^-$, occurs at physiological pH values. The amino acids can therefore act as either acids or bases. Depending on the side-chain residue R, amino acids can be classified into those with: (a) non-polar side chains [Gly/G; Ala/A; Val/V; Leu/L; Ile/I; Met/M; Pro/P; Phe/F; Trp/W];

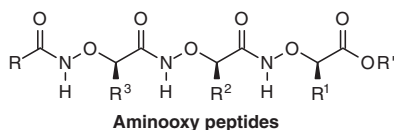
(b) uncharged polar side chains [Ser/S; Thr/T; Asn/N; Gln/Q; Tyr/Y; Cys/C; Sec/U]; and (c) charged polar side chains [Lys/K; Arg/R; His/H; Asp/D; Glu/E; Pyl/O]. In brackets are given the three-letter abbreviations and one-letter symbols of the 22 proteinogenic amino acids. With the exception of glycine, all proteinogenic amino acids are optically active – that is, they have an asymmetric center or chiral center localized at the C_α atom. Threonine and isoleucine each have two asymmetric centers, and therefore four possible stereoisomers (L-, D-, L-*allo*-, and D-*allo*-). The 22 common amino acids are not the only amino acids that occur in biological systems. The number of non-proteinogenic is approaching 300; these occur mostly in plants [H. B. Vickery, *Adv. Protein Chem.* **1972**, 26, 81; L. Fowden et al., *Adv. Enzymol.* **1979**, 50, 117; J. S. Davies (Ed.), *Amino acids and Peptides*, Chapman & Hall, London, **1985**; G. C. Barrat (Ed.), *Chemistry and Biochemistry of Amino Acids*, Chapman & Hall, London, **1985**].

Aminoacyl-tRNA, an amino acid intermediate in ribosomal peptide synthesis. The first step in the aminoacylation process of tRNA is activation of the amino acid, catalyzed by the aminoacyl-tRNA synthetase (aatRS). An amino acid reacts with ATP under the elimination of pyrophosphate to yield a mixed anhydride, the aminoacyl adenylate, which normally remains tightly bound to the aatRS. In the second step, the highly activated aminoacyl moiety is transferred to the appropriate tRNA, thereby forming the aminoacyl-tRNA and liberating ADP.

α -Aminoisobutyric acid (Aib), C^α -dimethylglycine, a strongly helicogenic, non-coded, C^α -tetrasubstituted amino acid. This occurs naturally, and is a building block in \rightarrow alamethicin and other \rightarrow peptaibols. Aib is often incorporated into peptides to in-

vestigate the conformational requirements of receptors. Furthermore, it plays an important role as building block for the stabilization of 3_{10} -helices [I. L. Karle, *Biopolymers* **1996**, 40, 157; F. Formaggio et al., in: *Houben-Weyl: Methods of Organic Synthesis*, M. Goodman et al. (Eds.), Volume E22c, Thieme, Stuttgart, Germany, **2003**, p. 292].

Aminooxy peptides, correlates of β -peptides composed of α -aminooxy acids as analogues of β -amino acids with replacement of C^β by an oxygen atom. The lone pair repulsion of the nitrogen and oxygen atoms renders the backbone of aminooxy peptides more rigid than that of β -peptides [X. Li, *Chem. Commun.* **2006**, 3367].



Amino protection, the reversible blocking of the amino function (\rightarrow temporary protecting groups) during peptide synthesis. The necessity for sequence-specific incorporation of amino acids into a peptide requires protection of the N^α amino function, together with most functional groups present in the side chains. While the latter usually remain attached throughout the synthesis (\rightarrow semipermanent protecting groups), the N^α function requires temporary protection by groups that are cleaved after each coupling step in order to allow for further elongation of the peptide. Temporary and semipermanent protecting groups must be cleaved independently (\rightarrow orthogonal protecting groups) and the nature of the N^α protection determines the tactics of the peptide synthesis and the selection of the side chain-protecting groups. The most widely employed temporary protecting groups are the

→ benzyloxycarbonyl group (Z), → *tert*.-butoxycarbonyl (Boc), and → 9-fluorenylmethoxycarbonyl (Fmoc) groups. Side-chain amino groups (e.g., Lys N^ω) must be protected with semipermanent protecting groups. In the Fmoc approach, Boc protection for Lys N^ω is most appropriate. If completely orthogonal protection of the N^ω -amino group is necessary, the → Tfa, → Dde, → Alloc, or Npys groups are available. Tfa and Npys are well compatible with Boc chemistry, as cleavage occurs in the first case with piperidine and in the latter case with triphenylphosphine. Dde and the related ivDde are orthogonal to Boc and Fmoc, as they are removed with dilute hydrazine solutions.

AMP, acronym for a) → antimicrobial peptides, or b) adenosine monophosphate.

Amphiregulin (AR), a bifunctional cell growth modulator belonging to the → epidermal growth factor (EGF) family. Human amphiregulin contains 84 aa, while a truncated form consists of 78 aa. The amino-terminal region is extremely hydrophilic, and contains a huge number of lysine, arginine, and asparagine, whereas amphiregulin(46-84) exhibits striking sequence homology to the members of the EGF family. AR binds to the EGF receptor, but exhibits a weaker affinity compared to EGF. In murine keratinocyte growth, AR fully supplants the requirement for EGF or transforming growth factor- α . However, in other cell systems it is a much weaker growth stimulator. Recently, it has been reported that T helper 2 cells, but not other T-cell subsets, express AR. EGF receptor ligands induce epithelial cell proliferation, and a lack of AR delayed expulsion of the nematode *Trichuris muris*. The new link between T helper 2 cells and epithelial proliferation provides new aspects for planning therapeutic interventions for helminth in-

fections and other diseases that involve both cell proliferation and allergy, such as asthma [M. Shoyab et al., *Science* **1989**, 243, 1074; D. M. Zaiss et al., *Science* **2006**, 314, 1746].

Amphomycins, a group of lipopeptide antibiotics that are highly active against multi-resistant bacteria. *Amphomycin*, the first member of this group was discovered during the early 1950s. In 1968, there followed the isolation of *tsushimycin*, and later more members of this group of lipopeptides – such as friulimicin B and laspartomycin – are described. Amphomycins are characterized by a peptide framework consisting of a 10-membered cyclopeptide and an exocyclic amino acid acylated at the amino group by a fatty acid residue. Members of this group differ principally in the type of fatty-acid substituent. The lipopeptide antibiotic → daptomycin (Cubicin®), which was approved in the USA for the treatment of skin infections in 2003, may also belong to this group due to the 10-membered cyclopeptide core and the fatty acid constituent. However, the amino acid sequence is markedly different. Amphomycins have been found to be active against Gram-positive bacteria, but the exact mechanism of action remains an ongoing debate. *Tsushimycin* has been crystallized and its X-ray structure determined at 1.0 Å resolution. The backbone of the cyclopeptide core adopts a saddle-like conformation that is stabilized by a Ca^{2+} ion bound within the peptide ring, while an additional Ca^{2+} links the molecule to dimers enclosing an empty space resembling a binding cleft [B. Heinemann et al., *Antibiot. Chemother.* **1953**, 3, 1239; J. Shoji et al., *J. Antibiot.* **1968**, 21, 439; G. Bunkoczi et al., *Acta Crystallogr.* **2005**, D61, 1160].

AM-PS, aminomethyl polystyrene.

Amylin, KCNTATCATQ¹⁰RLANFLVHSS²⁰NNFGAILSST³⁰NVGSNTY^a (human amylin; disulfide bond: C²–C⁷), *islet amyloid polypeptide* (IAPP), *diabetes-associated peptide* (DAP), a 37-peptide amide which belongs to the \rightarrow calcitonin/calcitonin gene-related peptide family. Amylin is generated from a gene located on chromosome 12p12.3 sharing 46% sequence homology with the two \rightarrow calcitonin gene-related peptides and 20% with human \rightarrow calcitonin. Amylin was first isolated from an insulinoma and from pancreatic amyloid deposits of patients with non-insulin-dependent (type II) diabetes mellitus (NIDDM). It may be involved in the pathogenesis of type II diabetes by deposition as amyloid within the pancreas, which leads to β -cell destruction. It shows calcitonin-like activity on bone metabolism and a CGRP-like activity (\rightarrow calcitonin gene-related peptide) action on the vasculature. From studies on knockout mice, it follows that amylin should be important for the regulation of glucose-induced insulin secretion and the rate of blood glucose elimination. Human amylin and other mammalian amylin are synthesized as relatively small precursor proteins. Mature amylin is liberated from the 89-polypeptide precursor by proteolytic processing, in a similar way to that of proinsulin and other islet prohormones. Amylin is co-synthesized with insulin, stored in the β -cell secretory granules (in analogy to insulin), and secreted with insulin from the islet β -cells. Normally, the rate of synthesis is only about 1% of that of insulin, but this can increase after prolonged stimulation *in vivo* with increased concentrations of glucose. This behavior seems to be a link to the contribution of amylin in the pathogenesis of type II diabetes. Amylin has a vasodilatory effect like other members of the calci-

tonin/calcitonin gene-related family. It also acts as an agonist at the calcitonin receptor, but efficient signaling of amylin requires the formation of a receptor complex of the calcitonin receptor with \rightarrow receptor activity-modifying proteins (RAMP). Despite being less potent than insulin, amylin shows growth factor-like effects and inhibits insulin-stimulated incorporation of glucose into muscle glycogen. An action in the brain to reduce body weight has been reported, resulting in a hypothesis that amylin acts as a signal to the brain contributing to the maintenance of long-term energy balance [R. Muffet et al., *Eur. J. Endocrinol.* **1995**, *133*, 17; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, *11*, 167; P.A. Rushing et al., *Endocrinology* **2000**, *141*, 850].

Amyloid- β (A β), β -amyloid, *amyloid- β* peptide, a physiological peptide occurring in the brain, and enzymatically released from the amyloid precursor protein (APP). APP is an ubiquitously expressed membrane-bound protein with elusive function. The accumulation of A β in the brain is a triggering primary event to the pathological cascade for \rightarrow Alzheimer's disease (AD). The accumulation of A β appears to be caused by an increase in the anabolic activity, as demonstrated in familial AD, or by a decrease in catabolic activity. The predominant forms of A β consist of the 40- and 42-peptides, termed A β -(1-42), DAEFRHDSGY¹⁰EVHHQKLVE²⁰AEDVGSNKG³⁰IIGLMVGGVV⁴²IA, and A β -(1-40), respectively. In normal, non-AD, individuals the principal A β forms are A β -(1-40) and A β -(1-42), of which the former constitutes about 90%. The N-terminal partial sequence 1-28 stems from the extracellular domain of APP and is predominantly hydrophilic, whereas the C-terminal part 29-39/43 stems from the

transmembrane domain and is characterized by hydrophobic amino acids. $A\beta$ -(1-42) is thought to have a more critical function than $A\beta$ -(1-40) in amyloid formation and pathogenesis of AD, whereas $A\beta$ -(1-40) is the major component secreted from cultured cells, and occurs in cerebrospinal fluid. Most of the knowledge about APP processing derives from studies with cultured cells. The α -, β - and γ -secretases are involved in APP processing. α -Secretase action provides a large soluble ectodomain, termed sAPP α . The remaining C-terminal part of the protein is subject of γ -secretase cleavage that does not produce full-length $A\beta$ peptides, but leads to a truncated form known as p3 fragment comprising the residues 17- 40/2 of $A\beta$. In an alternative pathway, β -secretase cleaves the bond between 671 and 672 of APP, thereby releasing the soluble ectodomain, sAPP β , whereas the $A\beta$ sequence remains bound to the membrane with the C-terminal domain of the protein. Finally, cleavage by γ -secretase within the membrane-spanning region of APP provides several C-terminal variants of the $A\beta$ peptide bearing 39 to 43 residues. Mutations in APP can cause either increased overall secretion of $A\beta$ or secretion of "long" (42- to 43-residue) forms of $A\beta$ -(1-42) relative to the shorter $A\beta$ -(1-40) form. Despite the increasing production of research data, AD remains an enigma. AD is characterized by a variety of pathological features, such as extracellular senile plaques, synaptic loss, intracellular neurofibrillary, and brain atrophy. The senile plaques are mainly composed of $A\beta$ with 40–43 aa, whereas the neurofibrillary tangles consist of twisted filaments of hyperphosphorylated tau protein. Especially, the heterogeneity of this neuropathology and the lack of screening of AD patients on an early stage and a better delineation of pathological

subtypes of AD inhibit significantly the progress in understanding of AD. In order to develop new methods to prevent and treat AD, it must be possible to diagnose the preclinical stage of AD using biological markers, before the brain damage becomes irreversible. Suitable markers may include high plasma concentrations of $A\beta$ -(1-42) and findings of hippocampal atrophy on magnetic resonance imaging (MRI) of the brain. Solid-state NMR has been developed as a useful probe of amyloid structure. Currently, there are no known cures for AD, although some drugs have been approved for its treatment, such as donepezil (Pfizer), galantamine (Sanochemia), and rivastigmine (Novartis). According to the "amyloid cascade hypothesis," the reduction of $A\beta$ in the brain is discussed as being a therapeutic intervention in AD. Disaggregation of the senile plaques found in the brain is another strategy. For example, the 5-peptide, Leu-Pro-Phe-Phe-Asp, has attracted attention as a β -sheet-breaking peptide. Further future targets may be the inhibition of the activity of β -secretase, besides alternative treatment strategies [J. Kang et al., *Nature* **1987**, 325, 733; J. Wiltfang et al., *Gerontology* **2001**, 47, 65; A. B. Clippingdale et al., *J. Peptide Sci.* **2001**, 7, 227; K. Fassbender et al., *Naturwissenschaften* **2001**, 88, 261; N. Iwata et al., *Pharm. Ther.* **2005**, 108, 129; A. K. Tickler et al., *Prot. Pept. Lett.* **2005**, 12, 513; Y. Sohma, Y. Kiso, *ChemBioChem.* **2006**, 7, 1549; R. Tycko, *Prot. Pept. Lett.* **2006**, 13, 229].

Amyloid-forming proteins, mainly in native state α -helical proteins undergoing α -helix to β -strand conversion before or during fibril formation. Partially unfolded or misfolded β -sheet fragments are discussed as precursors of amyloids. Protein aggregation combined with other events leads to the deposition of insoluble protein

forms, causing an increasing number of neurodegenerative diseases such as \rightarrow Alzheimer's disease, Parkinson's, and Creutzfeld-Jakob disease. The molecular structures of amyloid fibrils are of considerable interest for an understanding of the interactions that drive amyloid formation. The conformational transition shifting the equilibrium from the functional to the pathological protein isoform can occur sporadically. However, the conformational change can also be triggered by mutations as well as by changes of the environmental conditions (oxidative stress, ionic strength, free radicals, pH, metal ions, protein concentration) or physiological or pathological chaperones (\rightarrow molecular chaperones). Furthermore, misfolded protein fragments acting as a structural template can be involved in the initiation of the conformational conversion that causes the disease. Recent investigations with solid-state NMR of fibrils have indicated that the β -sheets in amyloid fibrils have structures that tend to maximize contacts among hydrophobic residues. Amyloid fibrils formed by peptides and proteins lacking hydrophobic segments may be stabilized by different sets of interactions. Protein fragments that are rich in Gln or Asn are of special interest because of their involvement in Huntington's disease, spinocerebellar ataxia, and particularly in amyloid-forming yeast \rightarrow prion proteins [D. J. Selkoe, *Nature* **2003**, 426, 900; C. Soto, *Nat. Rev. Neurosci.* **2003**, 4, 49; R. Tycko, *Prot. Pept. Lett.* **2006**, 13, 229; J. P. Sipe (Ed.), *Amyloid Proteins*, Wiley-VCH, **2005**].

Amythiamicins, naturally occurring \rightarrow thiopeptide antibiotics isolated from a strain of *Amycolatopsis* sp. MI481-42F4. The amythiamicins A–D belong to the very few thiopeptides that do not contain a dehydroalanine moiety. They inhibit both the

growth of Gram-positive bacteria, including the methicillin-resistant *Staphylococcus aureus* (MRSA), and the action of elongation factor Tu (EF-Tu), a GTP-dependent translation factor. Amythiamicin A is the most potent inhibitor (IC_{50} 0.01 μ M) against *Plasmodium falciparum*, the parasite that causes the majority of malarial infections in humans. It has been reported that amythiamicin binds to the EF-Tu of the parasite, thereby blocking protein synthesis. The total synthesis of amythiamicin D was reported in 2005 [K. Shimanaka et al., *Antibiotics* **1994**, 47, 1153; R. A. Hughes et al., *J. Am. Chem. Soc.* **2005**, 127, 15644].

Anabaenopeptins, a main class of cyanobacterial peptides. These cyclic peptides are characterized by a peptide bond between the ϵ -amino group of Lys² with the α -carboxyl function of the amino acid in position 6. An amino acid unit is attached to the ring by an ureido bond formed between the α -amino group of Lys² and the α -amino function of the appropriate building block [K.-I. Harada et al., *Tetrahedron Lett.* **1995**, 36, 1511; M. Welker, H. von Döhren, *FEMS Rev.* **2006**, 30, 530].

Anchoring group, *linker*, a group bound to the polymeric support for the attachment of the first amino acid in polymer-supported peptide synthesis. The chloromethyl group was the first anchoring moiety in the polystyrene/divinylbenzene resin for solid-phase peptide synthesis developed by Bruce Merrifield [R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, 85, 2149].

Ancovenin, a member of the subclass B \rightarrow lantibiotics first isolated from the culture broth of a *Streptomyces* sp. (No. A647P-2) acting as an inhibitor of \rightarrow angiotensin-converting enzyme. In the biosynthesis of ancovenin, the 19-prepeptide (CVQSCS FGPL¹⁰TWSCDGNK) is first modified

and processed by enzyme systems that are involved in the transformation of the acyclic precursors. It contains unusual amino acids such as (2*S*,3*S*,6*R*)-3-methylanthionine, *meso*-lanthionine, and dehydroalanine [T. Wakamiya et al., *Tetrahedron Lett.* **1985**, 26, 665; R. Kellner et al., *Eur. J. Biochem.* **1988**, 177, 53].

Androctonin, RSVCQRQIKIC¹⁰RRRGGCY YKC²⁰TNRPY (disulfide bonds: C⁴–C²⁰/C¹⁰–C¹⁶), a hydrophilic antimicrobial peptide (→ antimicrobial peptides) isolated from the blood of the scorpion *Androctonus australis*. Androctonin inhibits the growth of both Gram-positive and Gram-negative bacteria, and displays a large spectrum of activity against filamentous fungi. In contrast to amphipathic α -helical antimicrobial peptides that bind and permeate negatively charged vesicles, androctonin binds only to negatively charged lipid vesicles; this might explain the selective lytic activity towards bacteria but not to red blood cells [L. Ehret-Sabatier et al., *J. Biol. Chem.* **1996**, 271, 29537; C. Hetru et al., *Biochem. J.* **2000**, 345, 653; L. P. Silva, *Lett. Drug Design Discov.* **2004**, 1, 230].

ANF, atrial natriuretic factor.

Anfinsen, Christian, (1916–1995), American biochemist and winner of the Nobel Prize in Chemistry 1972 (shared with → Moore and → Stein) for his work on ribonuclease (RNase), especially concerning the connection between the amino acid sequence and the biologically active conformation. Anfinsen demonstrated that RNase could be refolded after denaturation without loss of enzymatic activity. In 1943, Anfinsen received his Ph.D from Harvard University, and then held various research and teaching positions. In 1950, he joined the staff of the National Institute of Health (Bethesda, MD), and headed the laboratory

of chemical biology in the National Institute of Arthritis, Metabolism, and Digestive Diseases from 1963 to 1982. Anfinsen was a professor of biology at Johns Hopkins University from 1982 until his death.

Angiotensin-converting enzyme (ACE), *peptidyl dipeptidase A*, a zinc metallopeptidase with great importance in the regulation of blood pressure as well as fluid and salt balance in mammals. ACE is a dipeptidyl-carboxypeptidase that catalyzes the conversion of the inactive 10-peptide angiotensin I into the potent vasoconstrictor, the 8-peptide angiotensin II (→ angiotensins). In addition, ACE inactivates → bradykinin, a vasodilatory peptide; hence, ACE raises blood pressure. The function of ACE in blood pressure control and water and salt metabolism has been elucidated mainly by the use of highly specific → ACE inhibitors. Approaches for regulation of blood pressure based on the ACE homologue → angiotensin-converting enzyme 2 are in progress [N. M. Hooper, *Int. J. Biochem.* **1991**, 23, 641; A. Turner, N. M. Hooper, *Trends Pharmacol. Sci.* **2002**, 23, 177; J. F. Riordan, *Genome Biol.* **2003**, 4, 225; D. Coates, *Int. J. Biochem. Cell Biol.* **2003**, 35, 769; K. M. Esalad et al., *Hypertension* **2005**, 46, 953; L. S. Zisman, *Eur. Heart J.* **2005**, 26, 322].

Angiotensin-converting enzyme 2 (ACE 2), a novel human zinc metalloprotease originally discovered in the testis, heart and kidney, but later found in a wide variety of tissues and seeming to be localized in much the same places as → angiotensin-converting enzyme (ACE). ACE 2 is a glycoprotein of 120 kDa, contains a single HEXXH zinc-binding domain, and shows considerable homology to human ACE (40% identity and 61% similarity). However, it differs greatly in substrate specificity and its activity is not inhibited by classical → ACE inhibitors, but by EDTA. It has

been reported that ACE 2 belongs to several enzymes that catalyze the degradation of angiotensin I (AT I, \rightarrow angiotensins) to angiotensin 1-9 [AT I(1-9)] and angiotensin II to angiotensin 1-7 [AT I(1-7)], respectively. ACE 2 functions as a carboxypeptidase. It has been suggested that ACE 2 and the proteolysis product AT I(1-7) play an important role in the renin-angiotensin system, setting the balance of pressor/depressor tone, and have both cardioprotective and renoprotective potential. ACE 2 functions as a novel target for gene therapy for hypertensive disorders [S. R. Tipnis et al., *J. Biol. Chem.* **2000**, 275, 33238; M. Donoghue et al., *Circ. Res.* **2000**, 87, 1; M. A. Crackower et al., *Nature* **2002**, 417, 822; J. L. Guy et al., *Biochemistry* **2003**, 42, 13185; M. J. Katovich et al., *Exp. Physiol.* **2005**, 90, 299; L. S. Zisman, *Eur. Heart J.* **2005**, 26, 322; C. M. Ferrario, *Hypertension* **2006**, 47, 515; K. M. Elased et al., *Hypertension* **2006**, 47, 1010].

Angiotensinogen, \rightarrow angiotensins.

Angiotensins (AT), *angiotonins*, *hypertensins*, tissue peptide hormones occurring both in the periphery and in the brain, with influence on blood pressure. The source of the AT is *angiotensinogen*, a plasma protein ($M_r \sim 60$ kDa) of the α_2 -globulin fraction which is initially cleaved by the kidney aspartyl protease \rightarrow renin, yielding the inactive 10-peptide *angiotensin I*, AT I, H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu¹⁰-OH. *Angiotensin II*, AT II, H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH, is formed by proteolytic cleavage of AT I catalyzed by \rightarrow angiotensin-converting enzyme (ACE). Angiotensin was initially described as a peripheral hormone that mediates the effects of the classical renin-angiotensin system (RAS). Circulating AT II induces vasoconstriction, aldosterone release, sodium and water retention, increases fluid intake, and plays a key role

in the regulation of blood pressure and fluid homeostasis. Two AT II receptors, AT₁ and AT₂, with similar binding affinity for AT II, are known that belong to the superfamily of seven membrane-spanning G protein-coupled receptors. The AT II effects, including vasoconstriction, increased aldosterone secretion and sympathetic tone and cardiac and vascular hypertrophy, are predominantly mediated via the AT₁ receptor. However, the functions of the AT₂ receptor have not been clearly characterized. AT II is formed in many tissues, including most peripheral organs and the brain. It has been reported that local AT II systems are regulated independently from the classical RAS. The effects of both circulating and locally formed AT II seems to be more complex and widespread than initially envisioned. Although, in the brain all components of RAS (e.g., angiotensinogen, renin, ACE and AT II) are present, it has been suggested that the brain may possess alternative enzymatic mechanisms for the formation of AT II distinct from those occurring in the classical RAS. One-fifth of the adult population suffers from chronic hypertension. The application of AT II inhibition either by \rightarrow ACE inhibitors or by AT₁ receptor blockade with specific non-peptidic antagonists for treatment of hypertension, ischemic heart disease, and heart failure, was started during the early 1970s and remains important to the present day. AT II is inactivated in the blood by angiotensinase. On the basis of structure-activity relationship studies it could be established that, according to modifications of AT II in positions 8 (type I) and 4 (type II), two classes of antagonists can be synthesized. Type I antagonists show protracted effects on smooth muscle tissue, whereas type II antagonists are competitive antagonists at AT II receptors. Furthermore, cyclic analogues of AT II

characterized by their conformational constraint show high activity and selectivity. There are no significant differences in the central effects of AT II and its linear analogues, but cyclic analogues produce sedation or neuroleptic-like activity. *Angiotensin III*, AT III, H-Arg-Val-Tyr-Ile-His-Pro-Phe-OH, is formed by cleavage of the *N*-terminal Asp of AT II under the catalysis of aminopeptidase A. *Angiotensin IV*, AT IV, H-Val-Tyr-Ile-His-Pro-Phe-OH, results from the cleavage of AT III with aminopeptidase N. AT III acts as a central regulator of → vasopressin release and blood pressure. It has been reported that → angiotensin-converting enzyme 2, acting as a carboxypeptidase, catalyzes the formation of both AT I(1-9) and AT II(1-7). The latter is involved in the activation of peripheral vasodilator mechanisms, and shows antitrophic effects mediated by the inhibition of protein synthesis. Furthermore, AT II(1-7) amplifies the vasodilator actions of → bradykinin, and it has been suggested that it reduces the release of norepinephrine acting via a bradykinin/nitric oxide-mediated mechanism [I. H. Page, *Hypertension Mechanisms*, Grune & Stratton, New York, 1987, 1102; K. Sasaki et al., *Nature* 1991, 351, 230; J. M. Saavedra, *Endocr. Rev.* 1992, 13, 329; R. L. Davisson et al., *Circ. Res.* 1998, 83, 1047; Z. Lenkei et al., *Front. Neuroendocrinol.* 1997, 18, 383; A. Reaux et al., *Trends Endocrinol. Metab.* 2001, 12, 157; H. Gavras, H. R. Brunner, *Hypertension* 2001, 37 (part 2), 342; J. M. Saavedra, *Cell. Mol. Neurobiol.* 2005, 25, 485; C. M. Ferrario, *Hypertension* 2006, 47, 515].

Angiotonin, → angiotensins.

Anhydrides, species that readily react with a huge number of nucleophiles. Basic considerations towards the application of anhydrides in peptide synthesis date back

to the early investigations of Theodor → Curtius in 1881. In the course of hippuric acid synthesis from benzoyl chloride and silver glycinate, Curtius had carried out the first peptide bond formation of all. About 70 years later, Theodor Wieland made the → mixed anhydride method available for peptide synthesis. Besides this method, → symmetrical anhydrides and → *N*-carboxy anhydrides are used in peptide coupling.

Anorectin, → somatoliberin.

Anorexigenic peptide, <Glu-His-Gly-OH, a central appetite-inhibiting peptide isolated from the urine of women suffering from anorexia nervosa.

ANP, atrial natriuretic peptide.

Ans, anthracene-9-sulfonyl.

Anserine, β -alanyl-L-1-methylhistidine, a naturally occurring analogue of → carnosine exhibiting numerous biological activities, e.g., pH buffering, complexation of zinc, cobalt and ferrous ions, scavenging of free radical species [E. C. Bate-Smith, *J. Phys.* 1938, 92, 336; E. J. Baran, *Biochemistry (Moscow)* 2000, 65, 789; A. Guiotto et al., *Curr. Medicinal Chem.* 2005, 12, 2293].

Antagonist, an analogue of a biological active peptide that acts as competitive inhibitor. It occupies the appropriate receptor and displaces the → agonist from the receptor, but does not transmit the biological signal.

Antamanide (AA), “*anti-amanita peptide*”, cyclo-(-Val-Pro-Pro-Ala-Phe-Phe-Pro-Phe-Phe¹⁰-), a non-toxic cyclic 10-peptide from *Amanita phalloides*. Antamanide was isolated from the lipophilic part of extracts of *A. phalloides* by chromatographic procedures, structurally characterized, and synthesized by Th. Wieland and co-workers in 1968. Administration at

0.5 mg kg⁻¹ causes full protection of mice from death by phalloidin (→ phallotoxins) after injection about 1 h before or, at the latest, simultaneously with 5 mg kg⁻¹ of the toxin. Antamanide is a competitive inhibitor of the transport system for phallotoxins and amatoxins in the parenchyma cells of the liver [Th. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer Series in Molecular Biology, Springer Verlag, Berlin, New York, 1986; K. Münster et al., *Biochem. Biophys. Acta* 1986, 860, 91].

Antho-Kamide, L-3-phenyllactyl-Phe-Lys-Ala-NH₂, a neuropeptide isolated from the simple sea anemone *Anthopleura elegantissima* [K. Morihara, H. Tsuzuki, *Arch. Biochem. Biophys.* 1971, 146, 291].

Anthopleurin A, GVSLCDSGDG¹⁰PSVR GNTLSG²⁰TLWLPSGCP³⁰SGWHNCKA HG⁴⁰PTIGWCKQ, a 49-peptide containing three disulfide bridges isolated from the sea anemone species *Anthopleura*. Anthopleurin-A causes, in nanomolar concentration, a positive ionotropic effect. This peptide is a member of the → β-defensin-fold family [M. W. Pennington et al., *Int. J. Pept. Protein Res.* 1994, 43, 463; P. K. Pallaghy et al., *Biochemistry* 1995, 34, 3782; A. M. Torres et al., *Toxicon* 2004, 44, 581].

Antho-Rlamide I, L-3-phenyllactyl-Tyr-Arg-Ile-NH₂, a neuropeptide isolated from the sea anemone species *Anthopleura elegantissima* [C. J. P. Grimmelikhuijzen et al., *Proc. Natl. Acad. Sci. USA* 1990, 87, 5410].

Antibodies, proteins (→ immunoglobulins) produced by B lymphocytes or B cells responsible for humoral immunity. An enormously diverse collection of related proteins mediates humoral immunity that is most effective against bacterial infections and the extracellular phases of viral infec-

tions [J. Kuby, *Immunology* 2nd edn., Freeman, 1994].

Antibody-catalyzed synthesis, → abzyme-catalyzed synthesis.

Anticancer peptides, peptides displaying antitumor activity on the basis of different modes of action. They may be derived from sites of protein interaction, phosphorylation, or cleavage and, e.g., interfere with apoptotic pathways. Peptide-based approaches are reported to target, e.g., MDM2, p53, NF-κB, ErbB2, MAPK, Smac/DIABLO, IAP BIR domains, and Bcl-2 interaction domains. Proteasome inhibitors, → integrin binding → RGD peptides (cilengitide), cationic amphipathic peptides, → somatostatin analogues such as octreotide, → gastrin-releasing peptide antagonists, → gonadotropin-releasing hormone agonists, → histone deacetylase (HDAC) inhibitors, → atrial natriuretic peptides, DNA-binding peptides (→ actinomycins), antimetabolic peptides (→ cryptomycins, → dolastatins, phorbolins A), and Ras farnesyl transferase inhibitors form therapeutically important classes. Marine peptides such as → didemns, → kahalalides, → hemiasterlin, → dolastatins, cembranols, and aplidine have also been clinically tested. In addition, peptide conjugates with antimetabolic agents or radioactive isotopes for tumor-selective delivery must be mentioned [Y. L. Janin, *Amino Acids* 2003, 25, 1].

Antifreeze proteins (AFPs), and *antifreeze glycoproteins (AFGPs)*, synthesized from teleost fish that encounter extreme cold seawater conditions for protection against freezing. All fish AFPs lower the solution freezing point through a non-colligative mechanism. Antifreeze proteins bind to particular surfaces of ice crystals, thereby modifying the crystal structure

followed by inhibition of further ice growth. Thermal hysteresis is used as a measure of antifreeze activity. AFPs are divided into four distinct classes: types I to IV. The different classes of AFPs are synthesized by various taxonomic groups. For example, type I AFPs are characterized by a high alanine content (>60 mol.%) and an amphipathic α -helical secondary structure. They occur in sculpins, right-eye flounders, and snailfish. Usually, the type I AFPs are synthesized in the liver for transfer into blood, providing extracellular freeze protection. Furthermore, a novel subclass of type I AFPs, designated skin-type AFPs, have been found in the skin of winter flounder, shorthorn, and longhorn; these AFPs are encoded by a separate subset of genes from liver-expressed proteins [K. V. Ewart et al., *Cell. Mol. Life Sci.* **1999**, 55, 271; G. L. Fletcher et al., *Annu. Rev. Physiol.* **2001**, 63, 359; R. P. Evans, G. L. Fletcher, *J. Mol. Evol.* **2005**, 61, 417].

Antigens, foreign macromolecules, predominantly proteins, carbohydrates and nucleic acids, that trigger the immune response, usually performed by production of defense proteins, known as \rightarrow antibodies [J. Kuby, *Immunology* (2nd edn.), Freeman, 1994].

Antihemophilic factor, Factor VIII, a protein ($M_r \sim 265$ kDa) acting as component of the blood clotting cascade in humans. Activated Factor VIII_a acts as an accessory factor during the activation of Factor X (\rightarrow Stuart factor) by activated Christmas factor IX_a. Factor VIII forms a complex with the Willebrandt factor during circulation in blood [T. Halkier, *Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System*, Cambridge University Press, 1991].

Antimicrobial peptides (AMP), *host defense peptides*, **HDP**, small (<50 aa), cationic (mostly due to the presence of two to nine positively charged Arg and Lys residues), amphiphilic peptides containing up to 50% hydrophobic amino acids with microbicidal activity against both bacteria and fungi. AMP play an important role in protection from invading microorganisms. They have been isolated from all the phyla investigated, such as plants, invertebrates, vertebrates, and humans, including microbes themselves. In amphibians, AMP are usually secreted by the dermal glands located in the outer layer of the skin. In mammals, including humans, AMP are located in the granules of neutrophils and in epithelial cells throughout the body. AMP are an essential part of the innate immunity that has evolved in most living organisms over 2.6 billion years to combat microbial challenge. It has been suggested that AMP are effective adjuvants, synergistic with other immune effectors, polarizing the adaptive response, and support wound healing. The antimicrobial peptides show potent antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi, parasites, and some enveloped viruses. Cationic AMP interact with the negatively charged bacterial phospholipids and permeate the membrane via the formation of transmembrane pores. Furthermore, it has been verified that AMP can also use the passive transport system to enter bacteria, from where they are capable of disrupting multiple cellular processes within the bacteria. However, the vast majority of the cationic peptides appear to act by permeabilization of the bacterial cell membrane. Despite the fact that AMP are considered as endogenous antibiotics, several additional features have recently become clear. Some AMP are chemotactic for leukocytes, or are involved in the

regulation of cell proliferation, angiogenesis, wound healing, epithelialization, or adaptive immunity. AMP are being considered as potential alternatives to current antibacterial agents, especially with the emerging problem of drug-resistant pathogenic bacteria. Therefore, they are promising candidates for drug development. Up until 2006, approximately 900 AMP have been isolated; details may be found in a periodically updated data base on the Internet, for example, at <http://www.bbcm.units.it/~tossi/pag1.htm>. AMP can be divided into classes based on the mechanism of their biosynthesis: non-ribosomally synthesized and ribosomally synthesized peptides. According to their secondary structure, eukaryotic AMP usually can be grouped into four main classes: (i) linear peptides with an α -helix structure, which do not contain Cys residues; the \rightarrow cecropins (insects, pigs), \rightarrow magainins (frogs), LL-37, a human cathelicidin-derived antimicrobial peptide, and CAP18 (rabbits) are members of the first group. (ii) β -Sheets stabilized by disulfide bridges; representatives of the second group are the \rightarrow defensins, divided into α -defensins (humans, rats, guinea pigs, rabbits), β -defensins (humans, cattle, mice), θ -defensins and insect defensins, as well as \rightarrow protegrins (pigs), \rightarrow tachyplesins (crabs), and insect defensins. (iii) Extended structure with a predominance of certain amino acid residues, especially Pro, Arg, Trp; examples of the group are \rightarrow drosocin (insects), \rightarrow bactenecin-5 (cattle, sheep, goats), \rightarrow indolicidin (cattle), and \rightarrow PR-39 (pigs). (iv) Loop structures with an intramolecular disulfide bridge, represented by \rightarrow brevinins (frogs), esculentin (frogs), and \rightarrow bactenecin (cattle). AMP that may belong to either all or none of these four groups include the family of host-defense-related ribonucleases, angiogenin 4, and

the cryptidin-related sequence (CRS) peptides. The \rightarrow cathelicidins, originally identified in myeloid cells, comprise a protein family with members in all of the four groups [T. Ganz, R. Lehrer, *Curr. Opin. Immunol.* **1998**, *10*, 41; H. G. Boman, *Scand. J. Immunol.* **1998**, *48*, 15; A. Tossi et al., *Biopolymers* **2000**, *55*, 4; A.M. Cole, T. Ganz, *BioTechnology* **2000**, *29*, 822; M. Zasloff, *Nature* **2002**, *415*, 389; H. Ulvatne, *Am. J. Dermatol.* **2003**, *4*, 591; R. E. Hancock, D. R. Devine, *Mammalian Host Defence Peptides*, Cambridge University Press, Cambridge, UK, **2004**; C. Beisswenger, R. Bals, *Curr. Prot. Pept. Sci.* **2005**, *6*, 255; J. B. McPhee, R. E. W. Hancock, *J. Peptide Sci.* **2005**, *11*, 677; K. A. Brogden, *Nat. Rev. Microbiol.* **2005**, *3*, 238; K. L. Brown, R. E. W. Hancock, *Curr. Opin. Immunol.* **2006**, *18*, 24].

α_2 -Antiplasmin, $\rightarrow \alpha_2$ -macroglobulin.

Antisense peptide, *complementary peptide*, a peptide sequence hypothetically deduced from the nucleotide sequence that is complementary to the nucleotide sequence coding for a naturally occurring peptide (*sense sequence*). It could be demonstrated that antisense peptide exerts biological responses through the interaction with the receptors for the sense peptides. Potential applications of antisense peptide lie in the area of biomedical research. For example, antisense peptide (or antibodies against it) may promote the purification of both endogenous ligands as well as receptors. Furthermore, the development of highly selective antisense peptides against tumor cell markers may aid in the diagnosis and therapeutic modalities of the appropriate state of the disease. The *in vivo* administration of antisense peptides may help in better modulation of biological responses caused by their endogenous sense counterparts. The concept of antisense peptides was suggested by Mekler in 1969, and three years later

independently proposed and tested by Jones using a synthetic peptide that was antisense to the C-terminal tetrapeptide of gastrin [L. B. Mekler, *Biophys. USSR (Engl. Trans.)* **1969**, 14, 613; D. S. Jones, *J. Chem. Soc. Perkin Trans. I* **1972**, 1407; K. L. Bost, J. E. Blalock, *Methods Enzymol.* **1989**, 168, 16; Y. Shai et al., *Biochemistry* **1989**, 28, 8804; R. S. Root-Bernstein, D. D. Holsworth, *J. Theoret. Biol.* **1998**, 190, 107].

Antistatin (ATS), an anticoagulant protein ($M_r \sim 15$ kDa) isolated from the salivary glands of the Mexican leech *Haementeria officinalis*. ATS has been reported to be a potent inhibitor of Factor X_a (\rightarrow Stuart factor). The C-terminal region ATS-(109-119) has been suggested to be an important determinant of inhibitory potency. Structure-activity relationship studies of fragment analogues have been described [S. S. Mao et al., *Thromb. Haemost.* **1993**, 69, 1046; D. L. Danalev et al., *Bioorg. Med. Chem. Lett.* **2005**, 15, 4217].

Antithrombin III (AT3), a protein (432 aa, $M_r \sim 58$ kDa) acting as inhibitor of thrombin and all active proteases of the blood clotting system (\rightarrow serpins) except Factor VII_a by binding to them in 1:1 complex in similar manner as BPTI binds to trypsin. The presence of heparin enhances the inhibitory activity of antithrombin by several hundredfold. In antithrombin, Arg³⁹³ is the reactive center residue that provides a specific cleavage site for thrombin [T. Halkier, *Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System*, Cambridge University Press, **1991**].

α_1 -Antitrypsin, a glycoprotein (394 aa, $M_r \sim 51$ kDa) acting as an effective inhibitor of \rightarrow trypsin, but its prime physiological function is as an inhibitor of the elastase released by leukocytes. It is the archetype of the serpin family. In α_1 -antitrypsin, Met³⁵⁸

functions as a reactive center residue, providing a cleavage site of choice for leukocyte elastase. Interestingly, in a pathological variant of α_1 -antitrypsin found in a child with a bleeding disorder, Met³⁵⁸ was substituted by an arginine, thus converting this protein from an inhibitor of elastase to a highly effective inhibitor of thrombin [H. Loebermann et al., *J. Mol. Biol.* **1984**, 177, 531; W. Bode et al., *Protein Sci.* **1992**, 1, 426; P. R. Elliott et al., *Nature Struct. Biol.* **1996**, 3, 676].

Anxiety peptide, \rightarrow diazepam-binding inhibitor peptide.

Aoc, 1-azabicyclo[3.3.0]octane-2-carboxylic acid.

AOC, (S)-2-amino-8-oxo-(S)-9,10-epoxidecanoic acid.

AOP, 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

Apa, 6-aminopenicillanic acid.

Apamin, CNCKAPETAL¹⁰CARRCQQHa (disulfide bonds: C¹-C¹¹/C³-C¹⁵), a 18-peptide amide of the bee venom (1-3% of the venom) causing neurotoxic effects. The two arginine residues are of essential importance for the biological activity. Similar to the \rightarrow mast cell-degranulating peptide, apamin blocks selectively Ca²⁺-dependent K⁺ channels in neurons; this results in serious disturbances of CNS function [R. C. Hider, *Endeavour, New Series* **1988**, 12, 60; E. Moczydlowski et al., *J. Membr. Biol.* **1988**, 105].

Apelin, human apelin: LVQPRGSRNG¹⁰PGPWQGGRRK²⁰FRRQRPRLSH³⁰KGPMPF, a 36-peptide acting as the endogenous ligand of the orphan G protein-coupled receptor APJ (putative receptor protein related to the \rightarrow angiotensin II receptor AT₁). APJ consists of 377 aa and

seven transmembrane domains, the gene of which is localized on the long arm of chromosome 11. Angiotensin II does not bind APJ. Apelin and APJ mRNA are widely expressed in several human and rat tissues, and exhibit functional effects in both the CNS and periphery. A 77-aa preproprotein can be cleaved into a 55 aa fragment and then into shorter forms. Apelin-36 is the physiologically active form, although shorter C-terminal sequences also increase extracellular acidification rates and inhibit cAMP production in Chinese hamster ovary cells. Synthetic human [pGlu²⁴]-apelin-(24-36), corresponding to the C-terminal 13 residues with pGlu at the N-terminus, shows a much higher acidification rate than that of parental apelin. The primary structure of apelin was determined by cDNA cloning. The bovine peptide differs in only two residues from the human apelin. Apelin and its receptor have been discovered in heart, large or small conduit vessels, and endothelial cells. Apelin has been reported to be involved in the regulation of cardiovascular functions, fluid homeostasis, vessel formation and cell proliferation. Furthermore, it has been shown that apelin inhibits insulin secretion in mice. Recently, it has been reported that apelin is a newly identified adipokine up-regulated by insulin and obesity. However, despite some very interesting effects, and the demonstration that apelin circulates in plasma, the functions of apelin *in vivo* remains unknown [K. Tatemoto et al., *Biochem. Biophys. Res. Commun.* **1998**, 251, 471; B. Masri et al., *Cell. Signal.* **2005**, 17, 415; M. Sorhede Winzell et al., *Regul. Pept.* **2005**, 131, 12; E. A. Ashley et al., *Cardiovasc. Res.* **2005**, 65, 73].

Apidaecins, proline-rich short peptides from insects. These are highly bactericidal against Gram-negative organisms via

a mechanism that includes stereoselective elements but differs completely from any pore-forming activity. *Apidaecin Ia*, GNNR PVYIPQ¹⁰PRPPHPRIa, has been isolated from honeybee (*Apis mellifera*) [P. Casteels, P. Tempst, *Biochem. Biophys. Res. Commun.* **1994**, 199, 339; M. Castle et al., *J. Biol. Chem.* **1999**, 46, 32555].

Apm, 2-aminopimelinic acid.

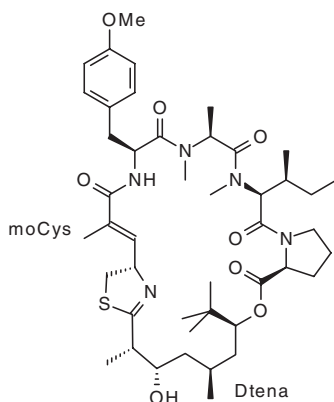
Apolipoprotein, → lipoproteins.

Apopeptide, a word derived from the noun peptide that means the free peptide component of a bioactive peptide missing a cofactor complex, the cofactor having been removed (Greek *apo-*, away from) [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

Apoptotic protease-activating factor 1 (Apaf-1), a protein controlling → caspase activation during apoptosis. Apaf-1 consists of an N-terminal caspase recruitment domain (CARD), a central nucleotide-binding oligomerization domain (NOD), and multiple WD40 repeats at the C-terminal half. The WD40 repeats have been reported to be responsible for cytochrome c binding and fulfill a regulatory role on Apaf-1 function. Apaf-1 occurs in cells in an inactive conformation and requires ATP/dATP for activation. It binds to cytochrome c and, in the presence of ATP/dATP, forms a apoptosome that leads to the recruitment and activation of the initiator caspase, caspase-9. The hydrolysis of ATP/dATP causes conformational changes which are essential for the formation of the apoptosome and the activation of caspase-9. The fine mechanism of Apaf-1 function remains to be investigated. The 2.2 Å crystal structure of ADP-bound, WD40-deleted Apaf-1, were described in 2005 [P. Li et al., *Cell* **1997**, 91, 479; S. J. Riedl, Y. Shi, *Nature Rev. Mol. Cell*

Biol. **2004**, *5*, 897; S. J. Riedl et al., *Nature* **2005**, *434*, 926].

Apratoxin A, a 25-membered cyclodepsipeptide (\rightarrow depsipeptides) isolated from the marine cyanobacterium *Lyngbya majuscula*, and exhibiting potent cytotoxic activity. Apratoxin A consists of a proline, three methylated amino acids (*N*-methylisoleucine, *N*-methylalanine, *O*-methyltyrosine), an α,β -unsaturated modified cysteine residue (moCys) and a dihydroxylated fatty acid moiety, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena) [H. Luesch et al., *J. Am. Chem. Soc.* **2001**, *123*, 5418; H. Luesch et al., *J. Bioorg. Med. Chem.* **2002**, *10*, 1973; J. Chen, C. J. Forsyth, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12067; T. Doi et al., *Org. Lett.* **2006**, *8*, 531; D. Ma et al., *Chem. Eur. J.* **2006**, *12*, 7615].



Apratoxin A

Aprotinin, bovine pancreatic trypsin inhibitor (Kunitz), BPTI, a bovine protein consisting of 58 aa residues and three disulfide bridges ($M_r \sim 6512$ kDa). Aprotinin belongs to the serpins, and acts as inhibitor for serine proteases, but not for \rightarrow thrombin and Factor X_a . In the past, aprotinin was used for the treatment of acute pancreatitis, but today this is no longer valid.

By inhibiting fibrinolysis and preserving platelet function, aprotinin has been shown to reduce blood loss and transfusion requirements in cardiac surgery, lung, and liver transplantations, and surgery for hip replacement. Additional indications are hyperfibrinolytic hemostatic disorders and complications of thrombolytic therapies. In Europe, aprotinin has been in clinical use for about 40 years, but in the United States it has been approved for intravenous applications only since 1993 [M. Kunitz, J. H. Northrop, *J. Gen. Physiol.* **1936**, *19*, 991; H. Fritz, G. Wunderer, *Arzneim. Forsch./Drug Res.* **1983**, *33*, 479; W. Gebhard et al., in: *Proteinase Inhibitors*, A. Barret, G. Salvesen (Eds.), p. 375, Elsevier, Amsterdam, **1986**; W. Beierlein et al., *Ann. Thorac. Surg.* **2005**, *79*, 741].

AQP, aquaporin.

Aquaporins (AQP), members of the major intrinsic protein (MIP) superfamily of integral membrane proteins, which are found throughout Nature. AQP facilitate water transport in various eukaryotes and prokaryotes. The archetypal aquaporin, *AQP1* ($M_r \sim 28$ kDa), also known as CHIP, channel-forming integral membrane protein of 28 kDa, forms a partly glycosylated water-selective channel that is widely expressed in the plasma membranes of various water-permeable epithelial and endothelial cells. The three-dimensional structure (7 Å resolution) of the deglycosylated human erythrocyte *AQP1* shows that the structure has an in-plane, intramolecular 2-fold axis of symmetry located in the hydrophobic core of the bilayer. The monomer is composed of six membrane-spanning, tilted α -helices forming a right-handed bundle surrounding a central density. From these results, a model is suggested that identifies the aqueous pore in the *AQP1* molecule and

indicates the organization of the tetrameric complex in the membrane. Five members of the mammalian aquaporins are described. AQP1 acts as an osmotically driven, water-selective pore, while AQP2 mediates vasopressin-dependent renal collecting duct water permeability. AQP3, located in the basolateral membrane of the collecting duct, forms an exit pathway for reabsorbed water. AQP4 is abundant in brain and seems to participate in the reabsorption of cerebrospinal fluid and osmoregulation, whereas AQP5 mediates fluid secretion in salivary and lacrimal glands [J. S. Jung et al., *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 13052; J. H. Park, M. H. Saier, *J. Membr. Biol.* **1996**, *153*, 171; T. Walz et al., *Nature* **1997**, *38*, 624; A. Cheng et al., *Nature* **1997**, *38*, 627].

Ar, aryl.

Arenastatin A, *cryptophycin-24*, a 16-membered cyclodepsipeptide (\rightarrow depsipeptides) isolated from the Okinawan marine sponge *Dysidea arenaria* with structural similarity to \rightarrow cryptophycins and identical with cryptophycin-24. Arenastatin A inhibits microtubule assembly *in vitro*. It binds to tubulin at the rhizoxin/maytansine binding site. The total synthesis was described in 2000 [M. Kobayashi et al., *Chem. Pharm. Bull.* **1994**, *42*, 2196; M. J. Eggen et al., *Org. Chem.* **2000**, *65*, 7792].

Arene sulfonyl-type protecting groups, Ar-SO₂-NH-R, sulfonamide-based protecting groups used preferentially for reversible blocking of the guanidino side-chain of arginine, and also for the amino function. In the past, mainly the *toluene-4-sulfonyl* (*tosyl*, *Tos*) group has been used, though this suffers from the disadvantage that it is only cleavable with liquid HF or Na/NH₃. *o*- and *p*-nitro substituents in the phenyl moiety led to residues (oNbs,

pNbs, dNbs, Bts) cleavable by treatment with thiophenol or alkanethiols, and hence are orthogonal to *tert*-butyl and 9-fluorenylmethyl-type protecting groups. For the guanidino protection, the arene sulfonyl moiety has been modified with respect to acid lability by the introduction of electron-donating substituents on the aryl residue. 4-Methoxybenzenesulfonyl (Mbs), 2,4,6-trimethylbenzenesulfonyl (Mts), 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) and 2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl (Pbf) have become very popular in SPPS. Acid lability increases in the series Tos < Mbs < Mts < Mtr < Pmc < Pbf, with Pbf displaying the best deprotection kinetics. The 9-anthracenesulfonyl (Ans) is cleavable by mild reducing agents.

Arenesulfonamide linker, \rightarrow safety-catch linker.

Arg, arginine.

Arginine (Arg, R), α -amino- δ -guanidinovaleic acid, C₆H₁₄N₄O₂, M_r 174.2 Da, the most basic of the proteinogenic amino acids.

Argiotoxin-636, a polyamine amide spider toxin. This is a glutamate receptor antagonist with potential as a neuroprotective agent. The toxin paralyzes insects by blocking the neuromuscular transmission mediated via glutamate receptors. The total synthesis by a practical reductive alkylation strategy was described [I. S. Blagbrough, E. Moya, *Tetrahedron Lett.* **1995**, *36*, 9393].

Arrestins, a family of intracellular proteins playing an important role in quenching signal transduction initiated by G protein-coupled receptors (GPCRs). Members of this family are *visual arrestin*, β -*arrestin 1*, and β -*arrestin 2*. All of

these arrestins desensitize GPCRs, while β -arrestin 1 and β -arrestin 2 additionally target desensitized receptors to clathrin-coated pits for endocytosis. Visual arrestin, first named retinal S antigen, is a 48-kDa protein. The 2.8 Å crystal structure shows a bipartite molecule with an unusual polar core. Furthermore, arrestin is described as being a dimer of two asymmetric molecules. In the photoreceptor cell, the activation of rhodopsin by a photon initiates signal transduction and signal termination. Arrestin binds selectively to the light-activated rhodopsin in its phosphorylated form, thereby shutting down the phototransduction cascade by blocking transducing activation [T. Shinohara et al., *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 6975; J. A. Hirsch et al., *Cell* **1999**, *97*, 257; R. H. Oakley et al., *J. Biol. Chem.* **2000**, *275*, 17201; V. V. Gurevich, J. L. Benovic, *Methods Enzymol.* **2000**, *315*, 422; M. Han et al., *Structure* **2001**, *9*, 869].

Aschheim-Zondek reaction, \rightarrow chorionic gonadotropin.

Asn, asparagine.

Asp, aspartic acid.

Asparagine (Asn, N), β -semiamide of aspartic acid, $\text{H}_2\text{N}-\text{CO}-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$, $\text{C}_4\text{H}_8\text{N}_2\text{O}_3$, M_r 132.12, a non-polar proteinogenic amino acid.

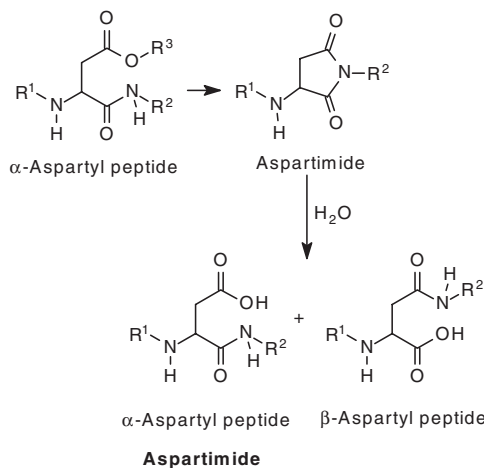
Aspartame (APM), H-Asp-Phe-OMe, a non-nutritive high-intensity sweetener. APM is about 200 times sweeter than sucrose. It was first approved by the FDA in 1981 as a table-top sweetener and an additive, for example, in dry-based beverages, dry cereals, chewing gum, gelatins, puddings, instant coffee, and tea. APM was discovered accidentally during the recrystallization of an intermediate of the synthesis of the C-terminal tetrapeptide of \rightarrow gastrin at Searle & Co. For commercial synthesis, various

methods have been developed including thermolysin-catalyzed synthesis [Y. Isowa et al., *Tetrahedron Lett.* **1979**, *28*, 2611; K. Oyama et al., *J. Org. Chem.* **1981**, *46*, 5242].

Aspartic acid (Asp, D), α -aminosuccinic acid, $\text{HOOC}-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$ $\text{C}_4\text{H}_7\text{NO}_4$, M_r 133.10, an acidic proteinogenic amino acid.

Aspartic peptidases, *aspartic proteases*, *aspartic proteinases*, \rightarrow peptidases catalyzing the hydrolysis of peptide bonds without the use of nucleophilic attack by a functional group of the enzyme. The nucleophile attacking the scissile peptide bond is, in this case, an activated water molecule, and no covalent intermediate will be formed between the enzyme and a fragment of the substrate. The name of this group of peptidases is based on the catalytic apparatus which consists of two aspartic acid side chains (Asp^{32} and Asp^{215} of the porcine pepsin numbering system) activating directly the water molecule. These two side-chain carboxyl groups are close enough to share a hydrogen bond between two of their oxygens, holding the water in place. However, not all members of aspartic peptidases include two Asp residues in the catalytic dyad. An endopeptidase from *nodavirus* has an Asp and an Asn as catalytic residues, whilst in a related *tetravirus* endopeptidase the Asp residue is replaced by Glu. It is interesting to note that all the enzymes so far described are endopeptidases. Members of aspartic peptidases are, for example, pepsin, cathepsin, and \rightarrow renin [V. Kostka (Ed.), *Aspartic Proteinases and their Inhibitors*, de Gruyter, Berlin, **1985**].

Aspartimide, cyclization product of asparagine in a peptide chain involving the β -carboxamide group with release of ammonia. The aspartimide derivative may subsequently undergo hydrolysis to give a mixture of α -aspartyl and β -aspartyl



peptides. The side reaction can be suppressed by reversible blocking of the side-chain carboxamide group. An aspartimide derivative can also be formed from an Asp side-chain ester by nucleophilic attack of the nitrogen atom of the amino acid located C-terminally with respect to the Asp residue in the peptide chain. Aspartimide formation appears to be sequence-dependent, and leads to β -aspartyl moieties and deamidation of L-asparagine. It occurs in peptides and proteins at alkaline, neutral and acidic pH, both *in vitro* and *in vivo* [S. Capasso, P. Di Cerbo, *J. Peptide Res.* **2000**, 56, 382; R. Dölling et al., *J. Chem. Soc. Chem. Commun.* **1994**, 853; P. Stathopoulos et al., *J. Peptide Sci.* **2005**, 11, 658].

β -Aspartylpeptides, aspartic acid-containing peptides in which the β -carboxyl group is a constituent of the peptide bond. The unwanted formation of β -aspartylpeptides occurs by nucleophilic ring opening of \rightarrow aspartimide [M. Bodanszky et al., *Int. J. Pept. Protein Res.* **1978**, 12, 57].

Asperlicin, isolated from *Aspergillus alliaceus* acting as a competitive antagonist

both of CCK-33 (\rightarrow cholecystokinin) in rat pancreatic tissue, and it inhibits CCK-8 induced guinea pig gallbladder contractions [R. S. L. Changet al., *Science* **1985**, 230, 177].

Asu, α -aminosuberic acid.

At, azabenzotriazolyl.

AT, angiotensin.

Ataxin-7, the SCA7 gene product consisting of 897 aa with an expandable polyglutamine tract close to the N-terminus. Spinocerebellar ataxia type 7 (SCA7) is a member of a family of neurodegenerative diseases characterized by a CAG DNA triplet repeat expansion leading to polyglutamine expansion in the gene product. The mutant ataxin-7 protein may contain polyglutamine repeats from 38 to 300 residues in length. Further members of this polyglutamine expansion disease family are, e.g., Huntington's disease and spinobulbar muscle atrophy. Although the precise biological function of ataxin-7 is unknown beside other described actions, it appears to be a transcription factor and a component of the STAGA transcription coactivator complex. Furthermore, ataxin-7 has

the capability to export from the nucleus via a conserved exportin-dependent signal [J. Taylor et al., *J. Biol. Chem.* **2006**, *281*, 2730].

Atosiban, *Tractocile*® (Europe), Mpa-D-Tyr(Et)-Ile-Thr-Asn-Cys-Pro-Orn-Gly-NH₂ (disulfide bond: Mpa¹-Cys⁶), an \rightarrow oxytocin (OT) antagonist that is produced by large-scale, solution-phase synthesis with an future annual production scale in the range of 50–100 kg. It is used to treat preterm labor and delivery. However, the combined \rightarrow vasopressin V_{1a} and OT receptor antagonist atosiban is not an ideal OT antagonist, as it is highly non-selective for OT receptors versus VP V_{1a} receptors. For example, in human receptor binding assays, atosiban exhibits 15-fold greater affinity for the V_{1a} receptor than for the OT uterine receptor [P. Melin et al., *J. Endocrinol.* **1986**, *111*, 125; C. Johansson et al., *Peptides* **1994**, *H. L. S. Maia* (Ed.), Escom, Leiden, **1995**, 34; P. Melin, *Baillieres Clin. Obstet. Gynaecol.* **1993**, *7*, 577; M. Manning et al., *J. Peptide Sci.* **2005**, *11*, 593].

ATP, adenosine triphosphate.

Atrial natriuretic peptide (ANP), *atrial natriuretic factor*, *ANF*, *atriopeptide*, *atriopeptin*, *cardionatrin I*, SLRRSSCFGG¹⁰RMDRIGAQSG²⁰LGCNSFRY (disulfide bridge: C⁷–C²³), a 28-peptide hormone isolated from the atrium of the mammalian heart. It belongs to the family of \rightarrow natriuretic peptides. ANP is a potent hypotensive and natriuretic agent. It is synthesized as prepro-ANP (human: 151 aa), and stored as 126-polypeptide pro-ANP (also termed: atriopeptigen, cardionatrin IV) in specific granules of atrial cardiocytes. The latter is secreted from the atria and then processed proteolytically by corin, a type II transmembrane serine protease, to the hu-

man circulating 28-peptide ANP, and the N-terminal pro-AFP-(1-98). The latter contains three peptide hormones: *long-acting natriuretic peptide*, LANP, AFP-(1-30); *vessel dilator*, AFP-(31-67); and *kaliuretic peptide*, AFP-(79-98). The main known biological properties of these peptide hormones are blood pressure regulation and the maintenance of plasma volume in animals and humans. In the atria, the quantity of ANP is orders of magnitude higher than in extracardiac tissues such as CNS and kidney. Receptors (\rightarrow natriuretic peptides) have been found in blood vessels, kidney, and adrenal cortex. In the adrenal cortex, ANP mediates the decrease of aldosterone release, while in the kidney it increases glomerular filtration rate, renal blood flow, urine volume and sodium excretion [T. G. Flynn et al., *Biochem. Biophys. Res. Commun.* **1983**, *117*, 859; K. Kangawa et al., *Biochem. Biophys. Res. Commun.* **1984**, *118*, 131; K. Kangawa et al., *Nature* **1985**, *313*, 397; A. J. deBold, *Science* **1985**, *230*, 767; G. McDowell et al., *Eur. J. Clin. Invest.* **1995**, *25*, 291; M. Forero McGrath et al., *Trends Endocrinol. Metab.* **2005**, *16*, 469; D. L. Vesely, *Clin. Exp. Pharmacol. Physiol.* **2006**, *33*, 169].

Atriopeptide, \rightarrow atrial natriuretic peptide.

Atriopeptin, \rightarrow atrial natriuretic peptide.

Aurelin, AACSDRAHGH¹⁰ICESFKSFCK²⁰DSGRNGVKLR³⁰ANCKKTCGLC⁴⁰, an antimicrobial 40-peptide (M_r 4297 Da) isolated from the mesoglea of the scyphoid jellyfish *Aurelia aurita*. The six cysteines form three disulfide bonds. Aurelin is synthesized as a 84 aa prepro-aurelin containing a 22 aa signal peptide and a propeptide segment of the same size. Aurelin exhibits activity against Gram-positive and Gram-negative bacteria. It shows structural features of \rightarrow defensins and channel-blocking

toxins [T. V. Ovchinnikova et al., *Biochem. Biophys. Res. Commun.* **2006**, 348, 514].

Aureobasidins, a family of cyclodepsipeptides (\rightarrow depsipeptides) produced by *Aureobasidium pullulans* consisting of more than 20 members. Aureobasidin A, consists of eight lipophilic amino acid residues and one hydroxy acid in its 27-membered macrocycle. Aureobasidins A, B, C, S_{2b}, S₃, and S₄ have been shown to be potent, with MICs of 0.05 to 3.12 $\mu\text{g mL}^{-1}$ for *Candida* species and *C. neoformans* isolates. Aureobasidins are characterized by several desirable properties, including lethality for growing *C. albicans* with a low level of acute toxicity, and improved survival and sterilization of kidneys in a murine model. Aureobasidin A was one of the few peptides that had appreciable oral bioavailability [K. Takesako et al., *J. Antibiot.* **1991**, 44, 919; K. Takesako et al., *J. Antibiot.* **1993**, 46, 1414; T. Kurome et al., *J. Antibiot.* **1998**, 51, 353].

Australian Peptide Association (APA), a non-profit scientific organization founded in 1992 providing a forum for advancing and promoting peptide research throughout Australia by way of support for annual local one-day meetings, as well as a biennial symposium. The first Australian Peptide Symposium was held in 1994, and has been held biennially since then. The 2007 symposium was held jointly with the 2nd Asia-Pacific and 4th International Peptide Symposia. The Association's website is <http://www.peptideoz.org>. Membership of the association is free to any interested people from anywhere in the world, upon registration at this site.

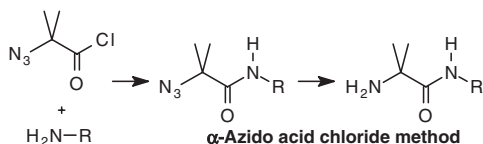
Avidin, a glycoprotein in the egg white of many birds and amphibians. Chicken avidin ($M_r \sim 66$ kDa) consists of four identical subunits (without carbohydrate: $M_r \sim 14$ kDa; 128 aa). Avidin binds four molecules of the vitamin biotin with high affinity (dis-

sociation constant, $K_d \sim 10^{-15}$ M). Each monomer is an eight-stranded antiparallel β -barrel, remarkably similar to that of the genetically distinct bacterial analogue \rightarrow streptavidin. The resulting complex is stable against proteolysis, and prevents its intestinal adsorption. Avidin inhibits the growth of microorganisms in egg whites. Together with biotin, avidin is used for the immobilization of ligands in immunoassays and in affinity chromatography [N. M. Green, *Methods Enzymol.* **1990**, 184, 51; O. Livnah et al., *Proc. Natl. Acad. Sci. USA* **1993**, 90, 5076].

AVP, arginine vasopressin.

Azadepsipeptides, a new class of pseudopeptides. Analogously to \rightarrow azapeptides, the α -carbon atom in \rightarrow depsipeptides is replaced isoelectronically by a trivalent nitrogen. Synthesis and structure evaluation have been demonstrated using a bis-aza analogue of the antiparasitic cyclooctadepsipeptide PF 1022A as a model [H. Dyker et al., *J. Org. Chem.* **2001**, 66, 3760].

Azapeptides, $-\text{NH}-\text{CHR}^1-\text{CO}-\text{NH}-\text{NR}^2-\text{CO}-\text{NH}-\text{CHR}^3-\text{CO}-$, a class of backbone-modified peptides in which the α -CH of one or more amino acid residues in the peptide chain is isoelectronically replaced by a trivalent nitrogen atom. This alteration results in a loss of asymmetry associated with the α -CH, and yields a structure that can be considered intermediate in configuration between D- and L-amino acids. This α -carbon replacement is connected with the capability to provide resistance to enzymatic cleavage, and the capacity to act as selective inhibitor of serine and cysteine proteases [J. Gante, *Synthesis* **1989**, 405; J. Magrath et al., *J. Med. Chem.* **1992**, 35, 4279; R. Xing et al., *J. Med. Chem.* **1998**, 41, 1344; E. Wiczerzak et al., *J. Med. Chem.* **2002**, 45, 4202].



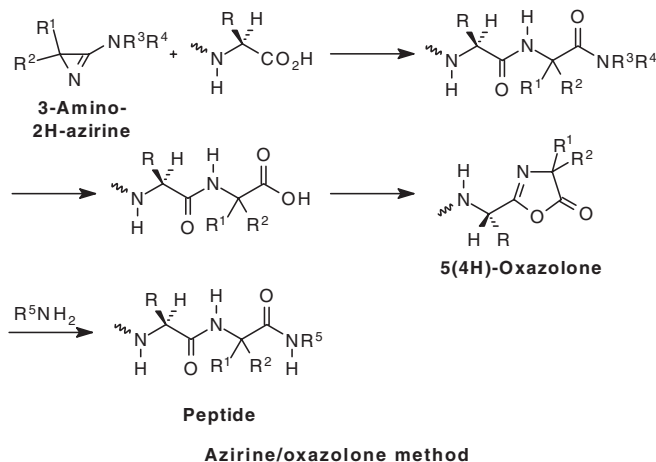
Azatides, $-\text{NH}-\text{NR}^1-\text{CO}-\text{NH}-\text{NR}^2-\text{CO}-\text{NH}-\text{NR}^3\text{CO}-$, biopolymer mimetics consisting of α -aza-amino acids (hydrazine carboxylates). In contrast to an \rightarrow azapeptide, an azatide is a so-called pure azapeptide. The earliest attempts to synthesize pure azatides using hydrazine units was described by Gante and coworkers in 1965, but stepwise chain lengthening of monomeric α -aza-amino acids in a repetitive manner, both as solution and liquid-phase approach, was performed in 1996 [J. Gante, *Chem. Ber.* **1965**, 98, 3340; J. Gante et al., *Proc. 13th American Peptide Symposium* **1994**, 299; H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, 118, 2539].

Aze, azetidine-2-carboxylic acid.

Azide coupling, \rightarrow acyl azide method.

α -Azido acid chloride method, an approach especially useful for the incorporation of α,α -disubstituted amino acids into peptides. It employs α -azido acid chlorides as masked equivalents of activated N^α -protected amino acids; the azido group can easily be reduced to a free amine, even under SPPS conditions [M. Jost et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4267].

Azirine/oxazolone method, a synthetic method for the introduction of sterically highly hindered α,α -disubstituted α -amino acids into peptides. The synthesis of, e.g., Aib-rich peptides requires either highly reactive coupling reagents (e.g., amino acid halides) or special derivatives (such as 3-amino-2H-azirines or α -azido carboxylic acid chlorides). The azirine/oxazolone method utilizes an amino component that



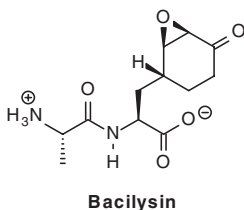
is formally activated by the ring strain. Upon reaction with a carboxy component, dipeptide amides are obtained that undergo acid-catalyzed cyclization with 5(4H)-oxazolone formation, followed by reaction

with, for example, an amino acid ester to give, e.g., tripeptides with α,α -disubstituted amino acids in the middle position [H. Heimgartner, *Angew. Chem. Int. Ed.* **1991**, *30*, 238].

B

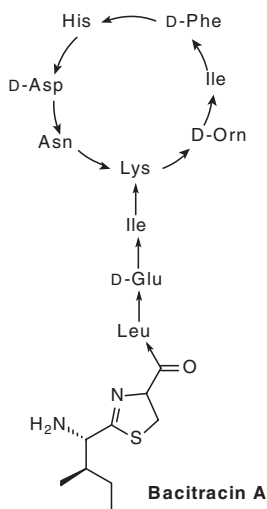
Bac5, batenecin.

Bacilysin, an antibiotic dipeptide produced from the bacterial genus *Bacillus*. In bacilysin, Ala is linked to anticapsin which is derived from prephenate, the aromatic amino acid precursor. Bacilysin inhibits the microbial glucosamine-6-phosphate synthetase [J. E. Walker, E. P. Abraham, *Biochem. J.* **1970**, 118, 563; T. Inaoka et al. *J. Biol. Chem.* **2003**, 278, 2169].



Bacitracins, metallopeptide antibiotics produced by *Bacillus subtilis* and *Bacillus licheniformis*. They show a potent bactericidal activity directed primarily against Gram-positive bacteria, and are useful particularly in ophthalmology. The most well-known member of this group of peptides is *bacitracin A*. The thiazole moiety is formed from the *N*-terminal Ile and the neighboring Cys. Biosynthesis is based on the thiotemplate mechanism, and is catalyzed by bacitracin synthetase. Bacitracin has found considerable medical application, for example, in several antiseptic combinations for the treatment of sore throats and in diagnostic agar formulations to inhibit growth of Gram-positive bacteria. The antibiotic activity of bacitracin A is apparently due to the inhibition of bacterial cell

wall biosynthesis. The bacitracin-sensitive step is dephosphorylation of the lipid carrier intermediate C₅₅-bactoprenyl bisphosphate, which is the membrane-bound car-



rier for the peptidoglycan and teichoic acid subunits, to form bactoprenyl phosphate. It has been reported that bacitracin forms a strong complex with long-chain polyisoprenyl pyrophosphates that requires the presence of a bivalent metal cation such as Zn²⁺ or Ni²⁺. Bacitracin interferes with sterol biosynthesis in mammalian cells by binding to pyrophosphate intermediates, thus accounting for its human toxicity [K. J. Stone, J. L. Strominger, *Proc. Natl. Acad. Sci. USA* **1971**, 68, 3223; D. A. Scogin et al., *Biochemistry* **1980**, 19, 3348; L.-J. Ming, J. D. Epperson, *J. Inorg. Biochem.* **2002**, 91, 46].

Backbone amide linker (BAL), a linker moiety for an approach to solid-phase synthesis of C-terminal-modified and cyclic peptides. The growing peptide is anchored via a backbone nitrogen that allows considerable flexibility in management of the C- and N-termini. The tris(alkoxy)benzylamide-based handle/support has been successfully used as BAL [K. J. Jensen et al., *J. Am. Chem. Soc.* **1998**, 120, 5441].

Backbone amide protecting groups, reversible protecting groups for the backbone nitrogen of a peptide bond to avoid side reactions such as \rightarrow aspartimide formation. Especially, in SPPS backbone protection has been shown to prevent or disrupt unwanted hydrogen-binding networks, both by the removal of the native amide hydrogen and by alteration of the backbone conformation based on the tertiary amide bond that is formed. This strategy leads to enhanced solubility of sparingly soluble peptides, and disfavors the formation of aggregating peptides. For Fmoc chemistry, suitable protecting groups are, for example, the 2-hydroxy-4-methoxybenzyl (Hmb) moiety and similar protecting groups. Alternatively, pseudo-proline dipeptide building blocks have been proposed to disrupt β -sheet formation and improve the quality of the crude synthetic peptide and solubility of the free peptide, provided that the sequence is compatible with the incorporation of the pseudo-proline dipeptide analogues. Unfortunately, these possibilities are not compatible with Boc chemistry-based strategies. *N*-(2-hydroxybenzyl)- and *N*-(2-methoxybenzyl) are suitable under these conditions, but are not stable to treatment with liquid HF. The 2-nitrobenzyl (2-Nbz) group can be cleaved by UV irradiation, and methoxy substituents on the aromatic ring have been reported to increase the kinetics of photocleavage. Recently, it

has been reported that the 4-methoxy-2-nitrobenzyl moiety has potential as a Boc chemistry-compatible fully reversible backbone protecting group that can be split off under optimized photolytic conditions [T. Johnson et al., *J. Chem. Soc. Commun.* **1993**, 369; T. Haack, M. Mutter, *Tetrahedron Lett.* **1992**, 33, 1589; C. P. Holmes, *J. Org. Chem.* **1997**, 62, 2370; E. C. B. Johnson, S. B. H. Kent, *Chem. Commun.* **2006**, 1557].

Backbone cyclization, \rightarrow cyclization reaction.

Backbone modification, alteration of the peptide backbone by exchange of a peptide bond by amide analogues, such as ketomethylene, vinyl, ketodifluoromethylene, amine, cyclopropene, to get modified peptides (\rightarrow peptidomimetics) [A. F. Spatola, in: *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein (Ed.), Marcel Dekker, New York, **1983**, Vol. 7, 267].

Bactenecin 5, (Bac5), RFRPPIRRPP¹⁰ LRP PFYPPFR²⁰ PPIRPPIFPP³⁰ IRPPFRPPLR⁴⁰ FP, a member of the \rightarrow antimicrobial peptides with a high content of Pro and Arg. Bac5 was isolated from ox (*Bos taurus*), and is equally active against Gram-negative and Gram-positive bacteria. Although detailed molecular action is missing, it may interact and disorganize bacterial membranes [D. Hultmark, *Trends Genet.* **1993**, 9, 178].

Bacteriocins, a group of ribosomally synthesized antimicrobial peptides or proteins produced by different bacteria that kill or inhibit the growth of other bacteria. Bacteriocins are characterized by the presence of lanthionine and 3-methylanthionine. Their importance results from the potential application as biopreservatives in food to inhibit the growth of spoilage or pathogenic bacteria. Bacteriocins can be simply

divided into those produced by Gram-positive bacteria and others produced by Gram-negative bacteria. Probably the first bacteriocins were the \rightarrow colicins, produced by various *E. coli* strains, and the prototypes of the first group. In general, these are large, proteinaceous compounds. One domain mediates specific binding to receptor proteins in the outer membrane; another domain mediates translocation through the peptidoglycan layer and the periplasmic space. Furthermore, the toxic activity resides in a third domain. The bacteriocins of Gram-positive bacteria are principally subdivided into five subtypes from which the first subtype are the \rightarrow lantibiotics [J. R. Tagg et al., *Bacteriol. Rev.* **1976**, *40*, 722; R. James, C. Lazdunski, F. Pattus (Eds.), *Bacteriocins, Microcins and Lantibiotics*, Springer, Berlin, **1992**; O. Gillor et al., *Adv. Appl. Microbiol.* **2004**, *54*, 129; Y. Kawai et al., *Curr. Prot. Pept. Sci.* **2004**, *5*, 393; D. Gwiazdowska, K. Trojanowska, *Biotechnologia* **2005**, *1*, 114].

BAL, backbone amide linker.

BAP, the first mammalian BiP-associated protein ($M_r \sim 54$ kDa) acting as a nucleotide exchange factor that regulates the ATPase activity of \rightarrow BiP. BAP consists of an *N*-terminal endoplasmic reticulum (ER) targeting sequence, two sites of *N*-linked glycosylation, and a C-terminal ER retention motif [K. T. Chung et al., *J. Biol. Chem.* **2002**, *277*, 47557].

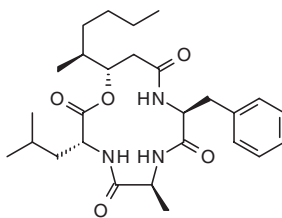
Baratin, H-Asp-Asn-Ser-Gln-Trp-Gly-Gly-Phe-Ala-OH, a 9-peptide from the brain of the cockroach *Leucophaea maderae*. It appears to play a function in modulation of motor patterns in abdominal ganglia [D. R. Nässel et al., *J. Comp. Neurol.* **2000**, *422*, 267].

Barlos resin, an *o*-chlorotriptylchloride resin for SPPS. The steric constraints of the *o*-chlorotriptyl handle impedes diketopiperazine formation on the dipeptide stage. Cleavage occurs upon treatment with 0.5% trifluoroacetic acid (TFA) in dichloromethane [K. Barlos et al., *Int. J. Pept. Protein Res.* **1991**, *37*, 513].

Batchwise solid-phase synthesis, the original procedure of SPPS developed by Merrifield in 1966. Alternatively, SPPS can also be performed in a \rightarrow continuous-flow mode solid-phase peptide synthesis using resin-filled columns.

BBB, blood-brain barrier.

Beauveriolides, cyclodepsipeptides (\rightarrow depsipeptides) isolated from the culture broth of fungal *Beauveria* sp. FO-6979. Beauverolides I and III contain Ala, Phe, D-Leu (or D-allo-Ile), and (3*S*,4*S*)-3-hydroxy-4-methylactanoic acid. They are inhibitors of macrophage foam cell formation, an activity which may prevent the development of atherosclerosis [I. Namatame et al., *J. Antibiot.* **1999**, *52*, 1; K. Nagai et al., *J. Comb. Chem.* **2006**, *8*, 103].



Beauveriolide I

Bence Jones proteins (BJP), members of the \rightarrow paraproteins often found in the blood and urine of patients with multiple myeloma consisting of free light chains of \rightarrow immunoglobulins.

Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, → BOP reagent.

Benzyl ester, a reversible carboxy-protecting group for peptide synthesis cleaved by saponification, HBr/AcOH, HF, and by catalytic hydrogenolysis.

Benzyloxycarbonyl group, Z, (in honor of its inventor Zervas), *carbobenzoxy group*, Cbz or Cbo (elderly abbreviation), Ph-CH₂-O-CO-, the first alkoxy-carbonyl-type amino-protecting group introduced by → Bergmann and → Zervas in 1932. The Z group is normally introduced with the original benzylchlorofomate under Schotten–Baumann conditions. Cleavage of the Z group is achieved by acidolysis using HBr/AcOH or catalytic hydrogenolysis [M. Bergmann, L. Zervas, *Chem. Ber.* **1932**, 65, 1192].

Benzyloxymethyl group (Bom), Ph-CH₂-O-CH₂-, an imidazole protection of histidine groups, often used in combination with N^α-Boc protection. Bom resists TFA, but is easily cleaved by HF or HBr/Ac/OH [T. Brown et al., *J. Chem. Soc., Perkin Trans. I* **1982**, 1553].

Bergmann, Max (1884–1944), a pioneer of peptide and protein research. In 1912, he became research assistant to the renowned Emil → Fischer in Berlin (Germany), and performed outstanding studies on the chemistry of amino acids, depsides, and carbohydrates. Between 1921 and 1934, Bergmann was director of the newly established Kaiser Wilhelm Institute of Leather Research in Dresden, upon which the Max-Planck-Institute is based. In 1932, he discovered together with Leonidas → Zervas the → benzyloxycarbonyl group, the greatest “break-through” in peptide synthesis since the first peptide syntheses pioneered both by Theodor → Curtius in 1881 and

Emil → Fischer in 1901, respectively. On Hitler’s coming to power, Bergmann emigrated to the USA, and was thereafter active at the Rockefeller Institute in New York, investigating the specificity of proteases including basic studies on the reversal of → proteolysis (→ protease-catalyzed peptide synthesis).

Bet, α-betainyl.

Betacellulin (BTC), a member of the → epidermal growth factor family purified from mouse beta tumor cells (betaTC-3). BTC can bind receptor tyrosine kinase, EGF receptor (ErbB1) and ErbB4. Besides other actions, a critical involvement of BTC in vascular remodeling has been reported [J. Miyagawa et al., *Endocr. J.* **1999**, 46, 755; M. Mifune et al., *Am. J. Physiol. Cell Physiol.* **2004**, 287, C807].

BGloc, tetrabenzylglucosyloxycarbonyl.

BGP, bone Gla protein.

BHA, benzhydramine.

Biochemical protein ligation, approaches to protein ligation and protein modification using biochemical tools, complementing existing methods such as → chemical ligation, and → Staudinger ligation. The critical point of an early process rather similar to native chemical ligation is the generation of a recombinant protein α-thioester that is capable of participating in subsequent reactions. *Expressed protein ligation* (EPL) and *intein-mediated protein ligation* (IPL) were the different terms given independently to this approach by two groups in 1998. EPL/IPL uses a genetically engineered intein and a chitin-binding domain (CBD) as fusion partners in order to express a protein or protein segment of interest. CBD allows for the separation of the target protein of interest by binding to a chitin resin. Incubation of the

chitin-bound protein with a suitable thiol reagent results in cleavage between the target protein and the intein, yielding the appropriate α -thioester. The latter can be ligated with the chemically synthesized peptide segments, which also allows unnatural amino acids to be site-specifically introduced into proteins. Interestingly, \rightarrow expressed enzymatic ligation (EEL) combines the latter procedure with the \rightarrow substrate mimetic approach of protease-catalyzed ligation. Recently, \rightarrow protein *trans*-splicing-mediated ligation has been described as an alternative approach with the potential to be generally applicable. \rightarrow Sortase-mediated protein ligation has been described as a new method for peptide and protein engineering. In addition, \rightarrow protease-catalyzed protein modification is a useful technology for irreversible and covalent N- and C-terminal modification of proteins with functional synthetic moieties under native conditions [T. W. Muir et al., *Proc. Natl. Acad. Sci. USA* **1998**, 95, 6705; T. C. Evans, Jr. et al., *Protein Sci.* **1998**, 7, 2256; D. Macmillan, *Angew. Chem. Int. Ed.* **2006**, 45, 7668].

Bioconjugation, an approach to the introduction of non-natural amino acids into proteins for modulating the structures and functions of proteins. This method relies on existing functionalities of native proteins using appropriate chemical reagents suitable for amino acid side-chain modifications. *Cysteine modification* based on the latent nucleophilicity of the thiol side chain group of cysteine offers two important possibilities: alkylation and mixed disulfide formation. Cysteine alkylation using α -halo carbonyl compounds is a widely used method for generating thioether products. Modified enzymes for mechanistic studies can be obtained using this technique. In addition, bioconjugated proteins have also been used to obtain structural

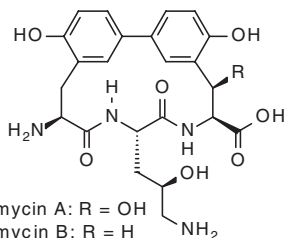
information on the active site(s) of proteins using special thiol-reactive agents, such as fluorophores and structural probes. Mixed disulfide formation offers the advantage of being reversible when using standard reducing agents such as dithiothreitol (DTT) or β -mercaptoethanol. Protein-S-S-labeled bioconjugates can easily be obtained using thiopyridyls and methanethiosulfonates (MTS). The latter can be readily synthesized from organobromide and organoiodide compounds via nucleophilic displacement with sodium methanethiosulfonate. This allows the generation of diverse arrays of MTS reagents. A large number of modified proteins with different structural and functional features can be generated using these reagents. Finally, it must be mentioned that despite the bioconjugation approach being well established, the application of suppressor tRNA techniques offers further new interesting possibilities for the synthesis of proteins containing non-natural amino acid building blocks [G. T. Hermanson, *Bioconjugate Techniques*, Academic Press, San Diego, **1996**; D. F. Qi et al., *Chem. Rev.* **2001**, 101, 3081; B. G. Davis, *Curr. Opin. Biotechnol.* **2003**, 14, 379; D. R. W. Hodgson, J. M. Sanderson, *Chem. Soc. Rev.* **2004**, 33, 422].

BIP, also known as GRP78, a mammalian ER homologue of the Hsp70 family (\rightarrow molecular chaperones). BIP was the first ER chaperone and component of the ER quality control apparatus to be identified. Furthermore, BIP fulfills an essential function, e.g., in maintaining the permeability barrier of the ER translocon during early stages of protein translocation, and targeting misfolded proteins for proteasomal degradation. As with all the Hsp70 family members, BIP binds and hydrolyzes ATP, and its function is regulated by the nucleotide-bound state. The ATPase

activity of BIP is required for most of its functions and, interestingly, the ATPase activity is regulated by the BIP-associated protein \rightarrow BAP [I. G. Haas, M. Wabl, *Nature* **1983**, 306, 387; K. T. Chung et al., *J. Biol. Chem.* **2002**, 277, 47557].

Bip, biphenyl-4-sulfonyl.

Biphenomycins, cyclic peptides containing a biphenyl structure from the culture fluid of *Streptomyces griseorubiginosus* with strong antibiotic activity against Gram-positive, β -lactam-resistant bacteria. *Biphenomycin B* contains (2*S*,4*R*)-hydroxyornithine and (S,S)-diisotyrosine – two non-proteinogenic amino acids –, whereas in *biphenomycin A*, instead of the latter building block, a biphenyl structure consisting of a dimer of (S)-2-hydroxy-phenylalanine and (2*S*,3*R*)-2-hydroxyphenylserine is found [M. Ezaki et al., *J. Antibiot. (Tokyo)* **1985**, 38, 1453; U. Schmidt et al., *J. Chem. Soc., Chem. Commun.* **1992**, 13, 951; F. F. Paintner et al., *Synlett* **2003**, 522].



Biphenomycins

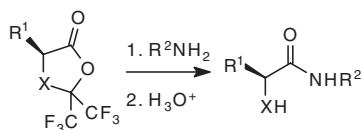
Bistratamides, a family of oxazole- and thiazole-containing macrolactams isolated from *Lissoclinum bistratum* in the southern Philippines. Members of this family show antimicrobial, antitumor, and anti-drug resistance properties. Their interesting biological activity potential has led to the total syntheses of most family members. Bistratamides E–J show moderate cytotoxic activity against a human colon tumor

(HCT-116) cell line [B. Degnan et al., *J. Med. Chem.* **1989**, 32, 1354; E. Aguilar, A. I. Meyers, *Tetrahedron Lett.* **1994**, 35, 2477; S.-Li. You, J. W. Kelly, *Tetrahedron* **2005**, 61, 241].

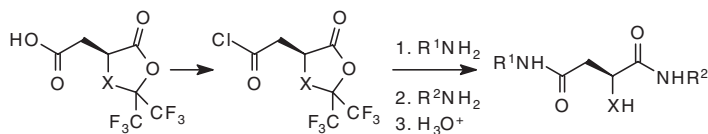
Bis(trifluoromethyl)-1,3-oxazolidin-5-one approach, a procedure developed by Burger et al. for the efficient incorporation of amino acids with additional functional groups in the side chain. Instead of employing additional protection, this approach features a bidentate protecting/activating concept with a minimum number of synthetic steps, because protection of the α -functionality (amino, hydroxyl or mercapto) and activation of the adjacent carboxy group are achieved in one step by using hexafluoroacetone as the protecting reagent. Thus, bis(trifluoromethyl)-1,3-oxazolidin-5-ones (from α -amino acids), bis(trifluoromethyl)-1,3-dioxolan-5-ones (from α -hydroxy acids), and bis(trifluoromethyl)-1,3-thiazolidin-4-ones (from α -mercapto acids), respectively, are obtained. In the presence of an appropriate nucleophile (e.g., amino acid ester), subsequent coupling and deprotection of the α -functionality occur simultaneously. Additionally, derivatives with ω -carboxy group may be further converted via acid chloride formation [J. Spengler et al., *Chem. Rev.* **2006**, 106, 4728].

BK, bradykinin.

Blood-brain barrier (BBB), one barrier separating the central nervous system (CNS) from the periphery, located at the endothelial cells of the brain tissue capillaries besides the blood-cerebrospinal fluid barrier (B-CSF-B) at the choroid plexus and the circumventricular organs. Peptides and protein drugs are generally excluded from transport from blood to brain. However, a chimeric peptide strategy for peptide drug delivery allows the delivery of



X = NH, N-alkyl, O, S



Bis(trifluoromethyl)-1,3-oxazolidin-5-one approach

peptides and proteins through the BBB. Chimeric peptides are formed by coupling of non-transportable peptide drugs with BBB drug transport vectors. The latter are proteins undergoing absorptive-mediated and receptor-mediated transcytosis through the BBB, respectively. Transport vector proteins are, for example, cationized albumin or the OX26 monoclonal antibody to the transferrin receptor. However, small molecules such as glycosylated \rightarrow enkephalins and \rightarrow GLYX-13 are also capable of penetrating the BBB [U. Bickel et al., *Adv. Drug Deliv. Rev.* **2001**, 46, 247].

BLP, bombinin-like peptide.

BLP-1, acronym for \rightarrow bombinin-like peptide 1.

BMP, brain morphogenetic protein.

BNP, brain natriuretic peptide.

Boc, *tert*.-butoxycarbonyl.

Boc/Bzl chemistry, *Merrifield tactics*, a maximum protection scheme for α -amino and side-chain functions used in SPPS. The α -amino function is temporarily protected with the Boc group, while the semiper-

manent protection of the side-chain function is given in brackets: Asp/Glu (OBzl), Arg (Tos/Mts), Lys [Z(2-Cl)], His (Tos/Dnp), Cys [Npys/Fm/Bzl(4-Me)], Ser/Thr (Bzl), Tyr [Z(2-Br)/2,6-Cl₂Bzl], Trp (For), Asn/Gln (Xan). Side-chain deprotection and detachment from the resin are performed in a single step under very strong acidic conditions [HF or trifluoromethane sulfonic acid (TFMSA)].

Boc/Bzl/Pac chemistry, *Sakakibara tactics*, a maximum protection scheme for α -amino, α -carboxy and side-chain functions used in solution segment synthesis of proteins. In this approach, each segment is designed to have a common structure of Boc-peptide-OPac, and all side-chain functions are protected by benzyl-type groups as given in brackets: Asp/Glu (OCy), Arg (Tos), Lys [Z(2-Cl)], His (Bom), Cys (Acm), Ser/Thr (Bzl), Tyr [Z(2-Br)/3-Pn], Trp (For/Hoc), Asn/Gln (Xan). An alternative removal of the Boc or OPac group yields the segments. The OPac group can be removed under mild conditions by reduction with zinc in acetic acid, and is stable to TFA, which is used for the cleavage of the Boc group [S. Sakakibara, *Biopolymers* **1999**, 51, 279].

BOI, 2-[benzotriazol-1-yl]oxy]-1,3-dimethylimidazolidinium hexafluorophosphate.

Bom, benzyloxymethyl.

Bombesin (BN), <EQRLGNQWAV¹⁰GM LMa, a 14-peptide amide belonging to the → bombesin family. BN was isolated from the skin of the European amphibian *Bombina bombina*. When applied to mammals it shows, for example, hypertensive action, potent stimulation on the uterus and digestive tract, stimulation of the gastric secretion, hyperglycemic effect, and increase of insulin levels in blood. BN is used as a diagnostic aid in the gastric stimulation test [A. Anastasi et al., *Experientia* **1971**, 27, 166; V. Erspamer et al., *Trends Biochem. Sci.* **1980**, 1, 391].

Bombesin family, a subfamily of the → bombesin-like family to which belong → bombesin, → alytensin and → gastrin-releasing peptide, a mammalian counterpart for bombesin. The amphibian peptides bombesin and → alytensin are structurally very similar and display biological effects when applied to mammals, such as hypertensive action, stimulation of the uterus and digestive tract, hyperglycemic effect, stimulation on the gastric secretion and increase of insulin levels in peripheral blood.

Bombesin-like family, a peptide family comprising bombesin and bombesin-related peptides which are classified into the three subfamilies → bombesin family, → ranatensin family and → phyllolitorin family.

Bombinakinin M, DLPKINRKGP¹⁰RPP GFSPFR, a bradykinin-related 19-peptide isolated from skin secretions of the frog *Bombina maxima* [R. Lai et al., *Biochem. Biophys. Res. Commun.* **2001**, 286, 259;

W.-H. Lee et al., *Regul. Pept.* **2005**, 127, 207].

Bombinin, GIGALSAKGA¹⁰LKGLAKGLA Q²⁰HFANa, an antimicrobial (→ antimicrobial peptides) and hemolytic 24-peptide amide from the yellow-bellied toad (*Bombina variegata*); parent compound of the → bombinins [A. Csordas, H. Michl, *Monatsh. Chem.* **1970**, 101, 182].

Bombinins, a family of → antimicrobial peptides isolated from skin secretions of frogs of the genus *Bombina*. The bombinin subfamily comprises 27-peptides that display antibiotic activity against Gram-negative and Gram-positive microorganisms and antifungal activity, while the bombinin H subfamily is composed of hemolytic 20-peptide amides (B. H 1-5), some of which contain D-allo-Ile². An enzyme that catalyzes the isomerization of L-Ile² of a model peptide to D-allo-Ile was isolated from skin secretions of *Bombinae*. In addition, this subfamily also comprises the 17-peptide amides B. H6 and B. H7; the latter having a D-Leu residue in position 2. It has been suggested that bombinins H may be potential templates for the development of new drugs acting against *Leishmania*, a worldwide protozoan pathogen [M. L. Mangoni et al., *Peptides* **2000**, 21, 1673; M. L. Mangoni et al., *Biochemistry* **2006**, 45, 4266].

Bombinin-like peptides (BLP), families of antimicrobial peptides related to → bombinins from amphibia (*Bombina variegata* and *Bombina orientalis*). The *B. variegata* bombinin peptides contain 27 residues, bearing a C-terminal amide, differ from each other by only one or a few amino acids, and are characterized by a variable N-terminal sequence and an identical C-terminal region. BLP-1, GIGASIL SAG¹⁰KSALKGLAKG²⁰LAEHFANa, was

isolated from the skin of the Asian toad (*Bombina orientalis*), and shows antibiotic and hemolytic activity. It is more potent in killing bacteria than the \rightarrow magainins. The *B. orientalis* bombinins are 25- and 27-residue peptides, from which the shorter molecules lack the last two C-terminal residues. The precursor contains three peptides, two bombinin-like ones, separated by a 33-mer sequence, followed by a 50-mer spacer region and a C-terminal 17-peptide related to bombinin H. The *maximins*, a series of bombinin H-related peptides, have been isolated from *B. maxima* [B. W. Gibson et al., *J. Biol. Chem.* **1991**, 266, 23103; M. Simmaco et al., *Biopolymers*. **1998**, 47, 435; R. Lai et al., *Peptides* **2002**, 23, 427].

Bombolitin, IKITTMLAKL¹⁰GKVLAHVa, an \rightarrow antimicrobial peptide from bumblebee (*Megabombus pennsylvanicus*).

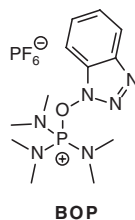
Bombyxin, an insect brain peptide ($M_r \sim 5$ kDa) with structural similarity to \rightarrow insulin. Bombyxin exists in various molecular forms (I–V). The heterodimers of the A and B chains show about 50% and 30% identity to the A and B chains of human insulin. Bombyxin stimulates, together with the prothoracicotropic hormone (PTTH), the synthesis and release of ecdysone. It has been reported that bombyxin is a growth factor for wing imaginal disks in *Lepidoptera* [M. Iwami, *Zool. Sci.* **2000**, 17, 1035; H. F. Nijhout, L. W. Grunert, *Proc. Natl. Acad. Sci. USA* **2002**, 99, 15446].

Bone Gla protein (BGP), \rightarrow osteocalcin, \rightarrow matrix Gla protein.

Bone morphogenetic proteins (BMP), multifunctional growth factors belonging to a rapidly expanding subclass of the transforming growth factor- β superfamily. During the late 1980s these proteins, which are responsible for bone induction, were

first characterized by purification and sequence determination of bovine BMP-3 (osteogenin) and cloning of human BMP-2 and BMP-4. Until now, more than 20 family members have been described. BMPs regulate cartilage and bone differentiation *in vivo*. It could be established that BMPs induce rapid maturation of chondrocytes at the growing stage, transform the cells into rounded cells, and induce a marked accumulation of cartilage matrix. The activities of BMPs are extracellularly regulated by BMP-binding proteins (Noggin and Chordin). BMPs bind to two different types of serine/threonine kinase receptor, type I and type II. In mammals, two BMP type I receptors and a BMP type II receptor have been characterized. The type I BMP receptor substrates include a protein family, the Smad proteins. The latter have a central function in relaying the BMP signal from the receptor to target genes in the nucleus. Human rec-BMP may be used for inducing bone formation in clinical practice [J. M. Wozney et al., *Science* **1988**, 242, 1228; J. M. Wozney, *Mol. Reprod. Dev.* **1992**, 32, 160; H. Nishitoh et al., *J. Biol. Chem.* **1996**, 271, 21345; D. Chen et al., *Growth Factors* **2004**, 22, 233].

BOP reagent, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, a HOBt-derived very efficient \rightarrow phosphonium reagent which has been applied successfully in SPPS. However, the main disadvantage of BOP is the highly toxic and carcinogenic hexamethylphosphoric



triamide (HMPA) that is formed during the course of the reaction [B. Castro et al., *Tetrahedron Lett.* **1975**, 1219].

Bovine dodecapeptide, RLCRIVVIRV¹⁰CR (disulfide bond: C³–C¹¹), an → antimicrobial peptide from ox (*Bos taurus*).

Bpoc, 2-(4-biphenyl)isopropoxyxycarbonyl.

BPTI, basic pancreatic trypsin inhibitor.

Bradykinin (BK), *kinin* 9, H-Arg-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH, a member of the → plasma kinins. Bradykinin is a tissue hormone that is released from the precursor kininogen by → kallikrein. It causes dilation of blood vessels, resulting in a decrease of blood pressure. Bradykinin promotes contraction of the smooth muscles of the bronchia, intestine and uterus. Bradykinin binds to two types of receptor: the poorly expressed but post-injury-inducible B₁-receptor, and the ubiquitous and constitutively expressed B₂-receptor. The B₁ receptor, mainly involved in inflammatory processes, binds more strongly des-Arg⁹-bradykinin than bradykinin, whereas the B₂ receptor shows a greater affinity to the native hormone. The degradation of bradykinin occurs primarily in the lungs by kininase II (identical to ACE), but also by other endopeptidases and exopeptidases. Enzymatic stable agonists for the B₂ receptor are potential therapeutics for infarct treatment, whereas antagonists of bradykinin are potential agents for the treatment of inflammation, pain, pancreatitis, and other inflammatory disorders. Stabilized antagonists have also been developed and tested for the treatment of small cell lung carcinoma and prostate carcinoma. Bradykinin and various analogues such as [Thr⁶]bradykinin and C-terminally shortened or lengthened bradykinins have been isolated from the skin of amphibia

[N.-E. Rhaleb et al., *Br. J. Pharmacol.* **1990**, 99, 445; J. E. Taylor et al., *Drug Dev. Res.* **1989**, 16, 1; J. M. Stewart et al., *Biol. Chem.* **2001**, 382, 37; L. M. F. Leeb-Lundberg et al., *Pharmacol. Rev.* **2005**, 57, 27].

Bradykinin-potentiating peptides (BPP)

peptides of different structure and from different natural sources, which are able to potentiate the bradykinin actions in different systems. Natural sources are venoms (snakes, scorpions, spider), enzymatically fragmented proteins (plasma-, milk-, wheat germ-proteins, hemoglobin) and hormones (insulin, angiotensin fragments, natriuretic peptide precursor). First, the inhibition of → angiotensin-converting enzyme (ACE) was assumed to be the main mechanism of potentiating actions. A large number of analogues of snake venom peptides were synthesized to study structure–activity relationships leading to the first → ACE inhibitors. Distinct differences between potentiation and inhibition of ACE stimulated the intensive search for other mechanisms. Besides ACE inhibition, also inhibition of other bradykinin-degrading enzymes, the influence on the bradykinin receptor, on the signal pathways and crosstalk with pathways of other hormones were observed. Potentiation of bradykinin action is investigated on the contraction of isolated smooth muscle organs, in *in-vivo* models, and on the cellular level by biochemical methods (affinity and density of receptor, intracellular mobilization of Ca²⁺, arachidonic acid, IP₃, NO). Contradictory explanations regarding the mechanism of potentiation result primarily from the use of different factors and tests, and also from the very high complexity of the systems involved [D. W. Cushman et al., *Biochemistry* **1977**, 16, 5484; S. Mueller et al., *Signal Transduction* **2006**, 6, 5 (Review)].

Brain-binding peptide, H-Cys-Leu-Ser-Ser-Arg-Leu-Asp-Ala-Cys-OH (disulfide bond: Cys¹–Cys⁹), a 9-peptide inhibiting the localization of homologous phages into the brain. After coating onto glutaraldehyde-fixed erythrocytes, it causes selective localization of intravenously injected cells into the brain [R. Pasqualini, E. Ruoslahti, *Nature* **1996**, 380, 364].

Brain natriuretic peptide (BNP), also referred to as *B-type natriuretic peptide*, hBNP: SPKMVQSGSGC¹⁰FGRKMDRISS²⁰SSGLGCKVLR³⁰RH (disulfide bond: C¹⁰–C²⁶), a 32-peptide that belongs to the natriuretic peptides. It binds to the particulate guanylate cyclase receptor (→ natriuretic peptides) of vascular smooth muscle and endothelial cells, causing increased concentration of cGMP, which serves as a second messenger to dilate veins and arteries, and causes smooth muscle cell relaxation. The precursors of the BNP of various species have been elucidated through the appropriate cDNAs. The sequence of BNP is located in the C-terminal part of the precursor. Human prepro-BNP (134 aa) is converted proteolytically into pro-BNP (108 aa), and finally processed into the bioactive BNP and the N-terminal part of the pro-hormone pro-BNP-(1-76). Recently, it has been reported that proBNP is an O-linked glycoprotein. BNP is stored together with → atrial natriuretic peptide (ANP) in atrial cardiocytes, especially in storage organelles referred to as specific atrial granules. The natriuretic and hypotensive effects of BNP are quite similar to these of ANP. Furthermore, BNP should be involved in the maintenance of body fluid homeostasis via the regulation of the activity of → vasopressin and the angiotensin II-hypothalamic system. BNP was originally isolated from porcine brain. BNP may be a useful addition for disease monitor-

ing in heart failure patients. The commercially available form of BNP is Nesiritide® [K. Maekawa et al., *Biochem. Biophys. Res. Commun.* **1988**, 157, 410; M. Vanderheyden et al., *Eur. J. Heart Fail.* **2004**, 6, 261; H. M. Azzay et al., *Heart Fail. Rev.* **2003**, 8, 315; A. J. Burger, *Congest. Heart Fail.* **2005**, 11, 30; M. Forero McGrath et al., *Trends Endocrinol. Metab.* **2005**, 16, 469; U. Schellenberger et al., *Arch. Biochem. Biophys.* **2006**, 451, 160].

Branched peptides, assemblies in which amino acid residues with functional side chains that have peptide chain grown not only from the α-functions but also from the side chains [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

Brevenin-1, FLPVLAGIAA¹⁰KVVPALFC KI²⁰TKC, an → antimicrobial peptide from the Japanese frog *Rana brevipedata*.

Brevinin-1, a peptide family of → ranid frog peptides. *Brevinin-1SE*, FLPLVR GAAK¹⁰LIPSVVCAIS²⁰KRC, isolated from *Rana sevosia* skin secretions, exhibits histamine-releasing and antimicrobial activities [C. Graham et al., *Peptides* **2006**, 27, 1313].

Bridged peptides, peptide derivatives in which two parts of a peptide are connected by bonds other than peptide or amide bonds. Peptides with intramolecular connections through peptide or amide bonds are termed → cyclic peptides, cyclization being between α-functions unless otherwise indicated. A disulfide bridge is by far the most familiar type of bridge. Intra- and inter-chain disulfide bridges are widely distributed in peptides and proteins. Synthetically available are carba analogues of disulfide-bridged peptides, in which one

or two sulfur atoms are substituted by CH₂ moieties. Bridges involving peptide backbone nitrogen atoms are special cases, as demonstrated for the → aspartimide residue [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

9-(4-Bromophenyl)-9-fluorenyl group (BrPhF), a novel group for safety-catch amine protection. BrPhF is relatively acid-stable and can be successfully activated by Pd-catalyzed cross-coupling reaction of the aryl bromide with morpholine, followed by cleavage under mild conditions using dichloroacetic acid and triethylsilane [S. Surprenant, W. D. Lubell, *J. Org. Chem.* **2006**, 71, 848].

BroP, bromotri(dimethylamino)phosphonium hexafluorophosphate.

BrPhF, 9-(4-bromophenyl)-9-fluorenyl.

BSA, bovine serum albumin.

Bsmoc, 1,1-dioxobenzo[b]thiophen-2-ylmethoxycarbonyl.

Bspoc, 2-(*tert*-butylsulfonyl)-2-propenyloxy-carbonyl.

Bt, benzotriazolyl.

Btb, 1-*tert*-butoxycarbonyl-2,3,4,5-tetrachlorobenzoyl.

Btm, benzylthiomethyl.

BTU, O-benzotriazolyl-*N,N,N'*-tetramethyluronium hexafluorophosphate.

B-type natriuretic peptide, → brain natriuretic peptide.

Bufokinin, KRPDQFYGL¹⁰Ma, a substance P-related peptide isolated from an extract of the intestine of the toad *Bufo marinus* showing potent spasmogenic actions. This member of the non-mammalian

→ tachykinin family shows high binding affinity, but low selectivity, for mammalian tachykinin receptors. Intravenous bufokinin causes a dose-dependent fall in systemic blood pressure. The vasodepressor activity of bufokinin and the presence of bufokinin-like immunoreactivity in varicose fibers in various vessels suggests a function for bufokinin in hemodynamic regulation and/or sensory nerve function in the toad [J. M. Conlon et al., *J. Peptide Res.* **1998**, 51, 210; L. Liu et al., *Clin. Exp. Pharmacol. Physiol.* **2000**, 27, 911; L. Liu et al., *Biochem. Pharmacol.* **2002**, 63, 217].

Buⁱ, isobutyl.

Bum, *tert*.-butoxymethyl.

α-Bungarotoxin, IVCHTTATIP¹⁰SSAVTCPPGE²⁰NLCYRKMWCN³⁰AFCSRRGKV V⁴⁰ELGCAATCPS⁵⁰KKPYEEVTCC⁶⁰ST NKC�HPPK⁷⁰RQPG (disulfide bonds: C³-C²³/C¹⁶-C⁴⁴/C²⁹-C³³/C⁴⁸-C⁵⁹/C⁶⁰-C⁶⁵), a toxin isolated from the venom of the Chinese krait *Bungarus multicinctus*. α-Bungarotoxin binds strongly to the nicotinic acetylcholine receptor, and has been a useful tool in the characterization of this receptor [D. Mebs et al., *Biochem. Biophys. Res. Commun.* **1971**, 44, 711; J.-P. Changeux et al., *Science* **1984**, 225, 1335].

Buserelin[®], [D-Ser(Buⁱ)⁶]GnRH-(1-9)-nonapeptide-ethylamide, a superagonist of → gonadotropin-releasing hormone. This long-acting synthetic GnRH analogue has found clinical application for disorders such as estrogen-dependent tumors (carcinoma of the prostate and the breast) or endometriosis, and is undergoing evaluation as a contraceptive agent.

Bu^t, *tert*.-butyl.

***tert*.-Butoxycarbonyl group (Boc)**, Me₃O-CO-, like the Z and Fmoc groups, one of the

most important amino-protecting groups of the alkoxy carbonyl (urethane) type. Di-*tert.*-butyldicarbonate, (Boc)₂O, and *tert.*-butoxycarbonyl fluoride are nowadays the preferred standard reagents for introduction of the Boc group. The Boc group is stable to catalytic hydrogenolysis and can be cleaved under mild acidolytic conditions, but it is more labile to acids than the Z group, to which it is for this reason completely orthogonal. Some mild and selective methods for the *N*-Boc deprotection

have been described. Recently, the deprotection of secondary Boc-protected amines with sodium carbonate in refluxing 1,2-dimethoxyethane (DME) has been reported [L. A. Carpino, *J. Am. Chem. Soc.* **1957**, 79, 4427; L. Moroder et al., *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, 357, 1651; S. E. Kazzouli et al., *Tetrahedron Lett.* **2006**, 47, 8575].

Bz, benzoyl.

Bzl, benzyl (Bn in contemporary organic synthesis).

C

C peptide, → insulin.

C105Y peptide, CSIPPEVKFN¹⁰KPFVYLI, a novel synthetic → cell-penetrating peptide based on the amino acid sequence to residues 359–374 of α 1-antitrypsin. C105Y is capable of increasing gene transfer and gene expression both *in vitro* and *in vivo*, when conjugated to polyK–DNA complexes. Generally, it may also serve as a useful carrier for other molecular cargoes [M. Rhee et al., *J. Biol. Chem.* **2006**, 28, 1233].

Cachectin, → tumor necrosis factor- α .

Caerin 1 peptides, a family of antibiotic peptide amides from the skin secretion of the Australian tree frog of the genus *Litoria*. *Caerin 1.1*, for example, has the sequence: GLLSVLGSA¹⁰KHVLPHVVPV²⁰IAEHLA. All members of the family show significant antibiotic activity, especially against Gram-positive microorganisms. Recently, 16 new caerin antibiotic peptides from the skin secretions of the Dainty Green Tree Frog *Litoria gracilentia* have been identified by ion electrospray mass spectrometry. These peptides protect the animal from large and small predators [S. T. Steinborner et al., *J. Peptide Res.* **1998**, 51, 121; M. J. Maclean et al., *Toxicon* **2006**, 47, 664].

Caerulein, → cerulein.

Calcilytics, Ca²⁺ receptor antagonists increasing the secretion of → parathyroid hormone (PTH). The first calcilytic compound was NPS 2143, an orally active compound that elicits 3- to 4-fold increases in circulating levels of PTH. Although this

prototype was not a clinical candidate, it has proven to be a valuable tool to explore more suitable calcilytics [E. F. Nemeth, *J. Mol. Endocrinol.* **2002**, 29, 15].

Calcineurin (Cn), **PP-2B**, a Ca²⁺- and calmodulin (CaM)-dependent phosphatase belonging to the Ser/Thr phosphatase family of enzymes. Cn is a heterodimer consisting of CnA ($M_r \sim 60$ kDa) and CnB ($M_r \sim 19$ kDa) subunits. The CnA subunit is composed of a catalytic domain, a CnB-binding domain, and a C-terminal regulatory region, consisting of a calmodulin-binding and an autoinhibitory domain. The CnB subunit is the Ca²⁺-binding regulatory subunit of the enzyme. The latter is highly conserved and shares structural homology with → calmodulin (CaM). Calcineurin is involved in a number of biological processes, such as T-lymphocyte activation, muscle cell differentiation, apoptosis, learning, and memory. The most studied function of Cn is manifested during an immune challenge. Cn dephosphorylates and promotes the nuclear localization of the NFAT (nuclear factor of activated T cells), a family of transcription factors that increase transcription of T-cell-activation genes. The enzymatic activity of Cn is non-competitively regulated by calcineurin inhibitors, such as the cyclosporin A-cyclophilin A and FK506-FKBP12 complexes, by binding at a site distinct from the active site. Recently, a peptide fragment of Down Syndrome Critical Region 1 (DSCR1) that competitively inhibits Cn activity *in vitro* and *in vivo* has been described [C. B. Klee et al., *Adv. Enzymol. Relat.*

Areas Mol. Biol. **1988**, 61, 149; F. Rusnak, P. Mertz, *Physiol. Rev.* **2000**, 80, 1483; P. G. Hogan et al., *Genes Dev.* **2003**, 17, 2205; B. Chan et al., *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13075].

Calcitonin (CT), human CT: CGNLSTC MLG¹⁰TYTQDFNKFH²⁰TFPQTAIGVG³⁰ APa (disulfide bond: C¹–C⁷), a 32 aa peptide hormone with important functions in calcium homeostasis and bone remodeling. CT belongs to the → calcitonin/calcitonin gene-related family. The sequence and structure of the human hormone was determined in 1968. CT from various species include an N-terminal Cys¹–Cys⁷ disulfide bridge and a C-terminal proline amide. Amino acid residues conserved across species are Cys¹, Leu⁴, Ser⁵, Thr⁶, Cys⁷, Gly²⁸, and, furthermore, both Leu⁹ and Leu¹⁶ are common to 11 of 12 known sequences. Since CT is widely used therapeutically in the treatment of bone disorders, extensive studies on structure–activity relationships have been carried out to understand the structural basis for the activity of this hormone. Interestingly, *elcatonin*, [Asu^{1–7}]eel calcitonin, is an analogue of eel calcitonin in which the disulfide bridge is replaced by an ethylene bridge. It shows full biological activity in comparison to human CT. This analogue and salmon CT are widely used clinically because of their superior potency. In humans, the CT gene is located on chromosome 11p15.1 and is clustered with the genes of → adrenomedullin and → calcitonin gene-related peptide (CGRP). The primary transcript of the CT/ α CGRP gene is spliced almost exclusively to CT mRNA in the thyroid C cells, and to α CGRP mRNA in the central and peripheral nervous systems. CT is synthesized as a larger precursor protein. The leader sequence is proteolytically eliminated during transport

through the ER, providing pro-CT. The latter is then cleaved to yield a 33-peptide bearing a C-terminal glycine which acts as a precursor for the C-terminal amide group of the native CT. CT is primarily secreted by the parafollicular cells (C cells) of the thyroid. These C cells are scattered throughout the thyroid in mammals, but constitute in submammalian species a distinct organ, the ultimobranchial body. CT affects a variety of tissues and organs including bone, intestine kidney, breast, and the hypothalamopituitary axis. The physiological function of CT is to maintain skeletal mass during periods of calcium stress, such as during growth, pregnancy, and lactation. Furthermore, it plays a central role in controlling calcium homeostasis and maintaining serum calcium without significant fluctuations. The calcitonin receptor (CTR) belongs to the type II G protein-coupled receptors, and is widely distributed. Multiple receptor isoforms arising from alternative splicing of the primary mRNA transcript have been described. The most common human isoforms are termed CTRa and CTRb. The main receptor variants represents the type present on osteoclast cells, but other receptor isoforms were found, for instance, in certain brain regions, testes, skeletal muscle, lymphocytes, placenta, and in the renal cortex. The CTR can couple in a cell-specific manner to multiple members of the GTP-regulated G protein family. In clinical use, CT and special analogues have been found safe for the treatment of a number of bone disorders, such as Paget's disease, Sudeck's atrophy, high-turnover osteoporosis, and hypercalcemia caused by malignancy. Salmon calcitonin (sCT) is a well-tolerated peptide drug with a wide therapeutic importance. Beside its administration parenterally for long-term treatments, suitable oral formulation should

facilitate the application of sCT in the treatment of osteoporosis and other bone diseases. Studies along this line are in progress. Especially, second-generation analogues of CT with reduced side effects and new dosage forms (nasal and, potentially, oral) will enhance the usefulness of calcitonin therapy [R. Neher et al., *Nature* **1968**, 220, 984; D. N. Copp, *Clin. Invest. Med.* **1994**, 17, 268; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, 11, 167; R. Muff et al., *Eur. J. Endocrinol.* **1995**, 133, 17; P. M. Sexton et al., *Curr. Med. Chem.* **1999**, 6, 1067; T. J. Martin, *Bone* **1999**, 24, 63; D. M. Findlay, P. M. Sexton, *Growth Factors* **2004**, 22, 217; C. L. Chang et al., *Peptides* **2004**, 25, 1633].

Calcitonin family, → calcitonin/calcitonin gene-related peptide family.

Calcitonin gene-related peptide (CGRP), ACDTATCVTH¹⁰RLAGLLSRSG²⁰GVVKNNFVPT³⁰NVGSKAFa (*h-α-CGRP* or *hCGRP1*: disulfide bond: C²–C⁷), a 37-peptide belonging to the → calcitonin/calcitonin gene-related family. The *h-β-CGRP* or *hCGRP2* differs from the homologous peptide *h-α-CGRP* by three residues (Asn³/Met²²/Ser²⁵). CGRP was discovered by alternative RNA processing of the → calcitonin (CT) gene in 1982. It is a product from alternative splicing of the primary RNA transcript of the CT/CGRP gene encoded on chromosome 11p15.1. In the CNS, splicing of the CT/α-CGRP gene produces α-CGRP, whereas in the C cells of the thyroid gland CT is formed. The *h-β-CGRP* gene, also located on chromosome 11p15.1, was predicted from cDNA analysis in humans and a number of vertebrates, and encodes only β-CGRP. In contrast to *h-β-CGRP*, *r-α-CGRP* differs only in one amino acid from *r-β-CGRP*. CGRP is widely distributed in the nervous system and in the cardiovascular system. Besides these

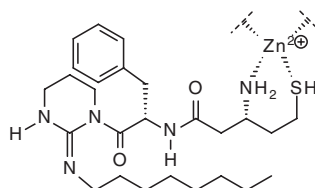
areas, the CGRP receptor are also present in the adrenal and pituitary glands, kidney, bone, and exocrine pancreas. CGRP shows 19% sequence homology to salmon → calcitonin, and 46% to → amylin. CGRP signals mainly through the type II G protein-coupled calcitonin receptor-like receptor (CRLR) together with → receptor activity-modifying proteins (RAMPs), especially through the CRLR/RAMP1 receptor (→ calcitonin/calcitonin gene-related peptide family). CGRPs have been reported are involved in the regulation of responses to sensory stimuli and to play a role in the regulation of the dilation of blood vessels and heart contractility. CGRP is expressed in the trigeminovascular system, and is released into the cranial circulation in various headaches. The blockade of its release offers a realistic possibility for a successful treatment of acute migraine and cluster headache. Recently, it has been reported that antagonists of CGRP should provide a real opportunity for the treatment of such diseases [S. G. Amara et al., *Nature* **1982**, 298, 240; H. R. Morris et al., *Nature* **1983**, 304, 129; R. Muff et al., *Eur. J. Endocrinol.* **1995**, 133, 17; S. J. Wimalawansa, *Endocr. Rev.* **1996**, 17, 533; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, 11, 167; D. R. Poyner et al., *Pharmacol. Rev.* **2002**, 54, 233; C. L. Chang et al., *Peptides* **2004**, 25, 1633; P. J. Goadsby, *Drugs* **2006**, 65, 1].

Calcitonin/calcitonin gene-related peptide family, a group of structurally related peptide hormones important for homeostasis maintenance. The members of this family contain an N-terminal intramolecular disulfide-bridged ring with six to seven amino acid residues connected to an amphipathic α-helix followed by an unstructured region and bearing an amidated C-terminus. The calcitonin/calcitonin gene-related peptide family consists of →

calcitonin (CT) → amylin, → adrenomedullin (ADM), → calcitonin gene-related peptides (CGRP1 and 2), and → intermedin/adrenomedullin-2 (IMD). Calcitonin and CGRP are encoded by the CT/CGRP gene, which is located on chromosome 11p15.1, whereas amylin is generated from a gene encoded on chromosome 12p12.3. The latter is thought to be an evolutionary duplication of chromosome 11. Adrenomedullin shares 24% homology with CGRP. A portion of the B-chain of → insulin is strongly homologous to these four members of this family. IMD, the latest member of this family, has <20% sequence identity with known family members, and exists both in teleosts and in mammals. The peptides of the calcitonin/calcitonin gene-related family show overlapping biological effects owing to their structure and cross-reactivity between receptors. Amylin and calcitonin are essential for optimal glucose metabolism and calcium homeostasis, whereas ADM and the CGRPs function as important endocrine and neurocrine regulators in the vascular and respiratory systems. IMD is expressed primarily in the pituitary and gastrointestinal tract, suggesting that it could function as a paracrine factor in the regulation of anterior pituitary hormone secretion. The biological actions of the members of this peptide family are mediated through binding to the two closely related type II G protein-coupled receptors (GPCRs), the calcitonin receptor, and the calcitonin receptor-like receptor (CRLR). IMD acts via the calcitonin receptor-like receptor/receptor activity-modifying protein receptor complex. Based on sequence data and functional characterization, it has been indicated that ADM, CGRPs and IMD comprise a sub-branch of the family, whereas calcitonin and amylin form a separate evolutionary branch [S. J.

Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, *11*, 167; D. R. Poyner et al., *Pharmacol. Rev.* **2002**, *54*, 233; C. L. Chang et al., *Peptides* **2004**, *25*, 1633; C. L. Chang et al., *Mol. Endocrinol.* **2005**, *19*, 2824].

Caledonin, a modified peptide isolated from the marine tunicate *Didemnum rodriguessi*. The amino group of the central Phe residue is linked with (S)-3-amino-5-mercaptopentanoic acid, whereas the carboxy function is connected with a six-membered cycloguanidine ring system bearing a *n*-octyl side chain. Caledonin is a natural peptide bolaphile capable of complexing Zn^{2+} and Cu^{+} ions, and may also be involved in ion transport through membranes [M. J. Vazquez et al., *Tetrahedron Lett.* **1995**, *36*, 8853].



Caledonin

Calexcitin, a neuronal protein ($M_r \sim 20$ kDa) originally identified in the photoreceptor neurons of the marine snail *Hermisenda crassicornis*. It has been reported that calexcitin regulates both voltage-dependent and calcium-dependent potassium channels. Furthermore, it was able to reproduce the electrophysiological effects of learning when injected into *Hermisenda* neurons. Calexcitin has also been isolated from the optic lobe of the long-finned squid *Loligo pealei*. This protein consists of 191 aa ($M_r \sim 22$ kDa), and shows sequence similarities with several sarcoplasmic calcium-binding proteins. Crystallization and preliminary X-ray diffraction analysis

has been described [T. J. Nelson et al., *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 13808; G. D. E. Beaven et al., *Acta Crystallogr.* **2005**, *F61*, 879].

Callipeltins, cyclodepsipeptides (\rightarrow depsipeptides) isolated from the marine sponges *Callipelta* sp. and *Latrunculia* sp. *Callipeltin A*, the first member of this group, is composed of a 22-membered macrocycle bearing a side chain, and contains some unusual structural features, for example the presence of numerous non-ribosomal amino acids and a unique *N*-terminal aliphatic hydroxy acid moiety. It shows structural similarities to \rightarrow papuamides. *Callipeltin A* exhibits antifungal and anti-HIV activities, as well as cytotoxicity against several human carcinoma cell lines. Furthermore, *callipeltin A* acts as a powerful inhibitor of the $\text{Na}^+/\text{Ca}^{2+}$ cardiac exchanger and as a positive inotropic agent in guinea pig atria. *Callipeltin B* is characterized by a different side-chain moiety. *Callipeltin C* is the acyclic derivative of *callipeltin A*, which shows antifungal activity against *Candida albicans*, *Phytophthora hevea*, *Helminthosporium sativum*, and *Fusarium oxysporum*. Later, *Callipeltin D*, a truncated open-chain derivative of *callipeltin A*, was isolated from *Latrunculia* sp. From the same marine sponge, but collected off Vanuatu islands, the *callipeltins F–I* were isolated which are minor *callipeltin*-related open-chain derivatives exhibiting anti-*Candida* activity in the 10^{-4} M range [A. Zampella et al., *Tetrahedron Lett.* **2002**, *43*, 6163; V. Sepe et al., *Tetrahedron* **2006**, *62*, 833].

Calmodulin, *calcium-dependent regulator, CDR, calcium modulator, CaM*, a Ca^{2+} -binding protein (148 aa; $M_r \sim 17$ kDa) that mediates various functions in eukaryotes. It contains two similar globular domains separated by a seven-turn α -helix, and two

high-affinity Ca^{2+} binding sites on each of its globular domains. The binding sites are formed by helix-loop-helix motifs named EF hands. Binding of Ca^{2+} causes calmodulin to change conformation, exposing a hydrophobic site that interacts with the protein to be regulated. Calmodulin belongs to the so-called Ca^{2+} sensors that undergo conformational changes on Ca^{2+} binding, enabling them to bind to and to activate target proteins to translate changes in intracellular $[\text{Ca}^{2+}]$ into signaling cascades [W. Y. Cheung, *Science* **1980**, *207*, 19; Y. S. Babu et al., *Nature* **1985**, *315*, 37; S. W. Vetter, E. Leclerc, *Eur. J. Biochem.* **2003**, *270*, 404].

Calprismin, a novel member of molluscan shell proteins. Calprismin is a glycosylated protein ($M_r \sim 38$ kDa) isolated from the shell calcitic prisms of the Mediterranean fan mussel *Pinna nobilis*. It is soluble in acetic acid, and is acidic due to its high Asp content. It has been assumed that calprismin may act as calcite crystal-binding rather than a Ca^{2+} -binding protein [F. Marin et al., *J. Biol. Chem.* **2005**, *280*, 33895].

Calsensin, an invertebrate neuronal Ca^{2+} -binding protein ($M_r \sim 9$ kDa) with two EF-hand Ca^{2+} -binding motifs. It is expressed by a subset of peripheral sensory neurons that fasciculate into a single tract in the leech CNS. Calsensin consists of four helices forming a unicornate-type, four-helix bundle. Solution structure and backbone dynamics were described in 2005 [K. K. Briggs et al., *J. Cell Biol.* **1995**, *129*, 1355; D. V. Venkitaramani et al., *Protein Sci.* **2005**, *14*, 1894].

Calycins, a protein superfamily comprising the fatty acid binding proteins (FABPs), \rightarrow streptavidin, a group of metalloproteinase inhibitors, \rightarrow lipocalin family, and triabin.

The calycons are characterized by a similar structure (a repeated +1 topology β -barrel) and by the conservation of a remarkable structural signature [D. R. Flower, *FEBS Lett.* **1993**, 333, 99].

CaM, calmodulin.

Cam, carboxamidomethyl.

CAMD, computer-aided molecular design.

CAMM, computer-assisted molecular modeling.

Campath[®], *alemtuzumab*, a humanized monoclonal antibody used in the treatment of B-cell chronic lymphocytic leukemia. The campath-1H family of antibodies recognize an abundant glycoprotein on virtually all human lymphocytes. Campath[®] (Millenium Pharm. Inc. and ILEX Oncology Inc.) was registered in the USA in 2001 [M. A. van Dijk, J. G. J. van den Winkel, *Curr. Opin. Chem. Biol.* **2001**, 5, 368].

Cap E, a 47-peptide encoded by *cap E* and localized in the membrane of *Bacillus anthracis*. Cap E is required for *B. anthracis* polyglutamate capsule synthesis. The capsule is composed of poly- γ -D-glutamate and is covalently bound to the peptidoglycan [T. Candela et al., *J. Bacteriol.* **2005**, 187, 7765].

Capping, acylation of the unreacted amino groups in SPPS using acetic anhydride, *N*-acetyl imidazole, or other acylating agents in order to avoid further chain elongation of the mismatch sequence at a later stage. These capped core sequences can usually easily be separated from the desired final peptide.

Capreomycin, an antitubercular antibiotic isolated from *Streptomyces capreolus* A250 in 1960. The cyclopeptide is strongly basic. Four components, designated capreomycin IA (1), IB (2), IIA (3), and IIB (4), have been described as being produced

by *S. capreolus*. Primarily, capreomycins 1 and 2 are components in the clinical agent. Generally, capreomycin is a second-line therapeutic agent employed in combination with other antitubercular drugs [E. B. Herr Jr. et al., *Proc. Indiana Acad. Sci.* **1960**, 69, 134; T. Wakamiya et al., *Tetrahedron Lett.* **1970**, 3497; M. Wang, S. J. Gould, *J. Org. Chem.* **1993**, 58, 5176].

Captopril, 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline, the first orally active inhibitor of the \rightarrow angiotensin-converting enzyme (ACE) on the market. The positive effects of captopril and other \rightarrow ACE inhibitors like \rightarrow enalapril in hypertension and heart failure result primarily from suppression of the renin-angiotensin-aldosterone system. Captopril causes a fall in blood pressure in hypertensive patients [M. A. Ondetti et al., *Science* **1977**, 196, 441; D. W. Cushman et al., *Biochemistry* **1977**, 16, 5484].

Carbodiimide/additive method, \rightarrow carbodiimide method.

Carbodiimide method, a procedure for peptide bond formation using carbodiimides, $R-N=C=N-R$, such as dicyclohexyl carbodiimide (DCC), diisopropyl carbodiimide (DIC) and \rightarrow water-soluble carbodiimides. The carbodiimide reacts in a one-pot procedure with the carboxylate anion of the carboxy component to form a highly reactive *O*-acylisourea intermediate. The former reacts immediately with the amino function of the amino component to yield the desired peptide derivative and the urea byproduct. Indeed, a more complex mechanism must be taken into consideration. Unwanted side reactions are racemization via the oxazolone mechanism and formation of the unreactive *N*-acylurea by base-catalyzed acyl migration from the isourea oxygen to nitrogen. The side reactions can be diminished by preparing the *O*-acylisourea at 0 °C

before adding the amino component, and by application of the *carbodiimide/additive method* first introduced by Wünsch and Weygand. Suitable nucleophilic additives intercept the highly reactive *O*-acylisourea, thereby forming an \rightarrow active ester which has lower reactivity but is still sufficiently potent to allow for rapid amide bond formation. The König–Geiger protocol using 1-hydroxybenzotriazole (HOBt) as additive belongs to the DCC-based coupling methods that have found widespread application. However, the most efficient additive is currently the 7-aza analogue of HOBt, commonly referred to a 1-hydroxy-7-azabenzotriazole [J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, 77, 1067; D. H. Rich, J. Singh in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York, **1979**, 241; J. Izdebski, D. Kunce, *J. Peptide Sci.* **1997**, 3, 141; W. König, R. Geiger, *Chem. Ber.* **1970**, 103, 788; L. A. Carpino, A. El-Faham, *Tetrahedron* **1999**, 55, 6813; S. Nozaki, *J. Peptide Sci.* **2006**, 12, 147].

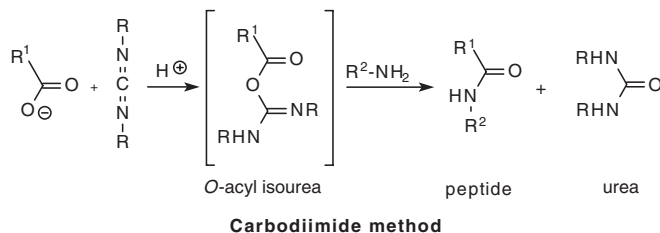
Carbohydrate-mimetic peptides, peptides capable of acting as molecular mimetics of carbohydrates. The first carbohydrate-mimetic peptides that bound to the lectin concanavalin A acting as mimics of mannose-containing oligosaccharides were identified in 1992. One year later, the first peptide to mimic a carbohydrate

in binding to an antibody was identified. The 8-peptide H-Ala-Pro-Trp-Leu-Tyr-Gly-Pro-Ala-OH has been identified as a molecular mimic of the Lewis Y (Le^Y) tumor antigen, with potential importance in the development of cancer vaccines. Since the use of carbohydrates as drugs and vaccines has several limitations, the molecular mimicry of carbohydrates by peptides provides an alternative source of drug and vaccine design [K. R. Oldenburg et al., *Proc. Natl. Acad. Sci. USA* **1992**, 89, 5393; R. Hoess et al., *Gene* **1993**, 128, 43; M. A. Johnson, B. M. Pinto, *Aust. J. Chem.* **2002**, 55, 13 (Review)].

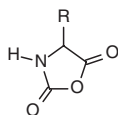
Carbopeptides, oligomers of carbohydrate-derived amino acids belonging to the \rightarrow pseudobiopolymers [M. D. Smith et al., *J. Chem. Soc. Chem. Commun.* **1998**, 2041; E. Locardi et al., *J. Am. Chem. Soc.* **2001**, 123, 8189].

Carbopeptoid, a word derived from the noun peptide that means an oligomer in which carbohydrate units are linked through amide bonds [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

N-Carboxy anhydrides (NCA), Leuchs's *anhydrides*, 1,3-oxazolidine-2,5-diones, cyclic compounds containing an activated carboxy group and an acyl-protected amino function, first discovered by Hermann \rightarrow Leuchs in 1906. Under carefully controlled conditions, NCAs can be mono-coupled to the nitrogen of an unprotected amino



acid, with high optical purity. Amino acids and peptides are rapidly acylated by NCA at low temperature and at pH 10.2. The intermediate peptide carbamates are decarboxylated by a decrease of the pH to values between 3 and 5. The sulfur analogues of the NCAs, *N*-thiocarboxy anhydrides (NTA), can be favorably applied in peptide synthesis, because of the higher stability of the thiocarbamate salts. The NCA methodology has again attracted significant interest as \rightarrow urethane-type protected amino acid *N*-carboxy anhydrides (UNCA) have been synthesized and applied to peptide synthesis. NCA can be acylated with suitable reagents for the introduction of a Boc, Z, or Fmoc group to give the corresponding UNCA. A comprehensive review on *N*-carboxy anhydrides including historical aspects, the literature after 1985, and new aspects of the polymerization processes, the synthesis of cyclic peptides and the role of polypeptides as drugs or drug carriers was published in 2006 [H. Leuchs, *Chem. Ber.* **1906**, 39, 857; R. Hirschmann, R. G. Denkwalter, *Naturwissenschaften* **1970**, 57, 145; W. D. Fuller et al., *J. Am. Chem. Soc.* **1990**, 112, 7414; H. R. Kricheldorf, *Angew. Chem. Int. Ed.* **2006**, 45, 5752].



N-Carboxy anhydrides

Carboxypeptidases (CP), single-chain exopeptidases that remove successive amino acids from the C-terminal end of peptides and proteins. CPs are highly specific for the side-chain moieties of the amino acids to be cleaved, and are classified into various groups and families. The CP approach is used for the end group analysis in primary structure determination. Normally,

CPs are highly stereospecific for C-terminal L-amino acids, but LD-carboxypeptidases have been named for their unusual capability to cleave amide bonds between L- and D-amino acids [H. J. Korza, M. Bochtler, *J. Biol. Chem.* **2005**, 280, 40802].

ω -Carboxy protection, the protection of side-chain carboxylic groups. The amino dicarboxylic acids Asp and Glu require orthogonal protection. This is for instance achieved in Fmoc chemistry by using ω -tert.-butyl esters. In Boc chemistry, the ω -cyclohexyl ester is mostly favored over the benzyl ester for protection of the Asp or Glu side-chain carboxylic acid. The formation of isoaspartyl peptides via the corresponding succinimide derivatives represents a severe detrimental side reaction, especially for ester derivatives of Asp. \rightarrow Aspartimide formation is sequence-dependent and can be suppressed to a large extent upon the application of tert.-butyl esters. It is especially prominent when sequences containing -Asp(OtBu)-Gly-, -Asp(OtBu)-Thr(OtBu)-, -Asp(OtBu)-Cys(Acm)-, -Asp(OtBu)-Asn(Trt)-, or -Asp(OtBu)-Asp(OtBu)- are to be synthesized. If full orthogonal protection (\rightarrow orthogonal protecting groups) of the side chains of Asp and Glu is required, the base-labile 9-fluorenyl methyl ester (OFm), the allyl ester (OAll) and the hydrazine-labile Dmab can be used, depending on the temporary N^α -protecting group (\rightarrow amino protection) [P. Kocienski, *Protecting groups*, Georg Thieme Verlag, Stuttgart, **2003**].

Cardiac natriuretic peptides, \rightarrow atrial natriuretic peptides.

Cardionatrin I, \rightarrow atrial natriuretic peptides.

Cardiotrophin-1 (CT-1), a 21.5 kDa-protein secreted from the heart and involved in

hypertrophic and protective actions on cardiocytes. In the heart it is primarily expressed in myocardial cells. Furthermore, CT-1 expression is also found in other tissues, including skeletal muscle, liver, and dorsal root ganglia. CT-1 plasma levels correlate with systolic blood pressure and also with left ventricular hypertrophy in hypertensive patients. It has been demonstrated that CT-1 plasma levels are also increased in heart-failure patients and following acute myocardial infarction. CT-1 is a member of the interleukin 6 (IL-6) leukemia inhibitory factor (LIF) \rightarrow cytokines [D. Pennica et al., *Proc. Natl. Acad. Sci. USA* **1995**, 92, 1142; S. Asai et al., *Biochem. Biophys. Res. Commun.* **2000**, 279, 320; S. Talwar et al., *Clin. Sci.(Lond.)* **2002**, 99, 83; B. Lopez et al., *Hypertension* **2005**, 23, 625].

Carnosine, H- β -Ala-His-OH, a naturally occurring dipeptide found in mammalian tissue, notably in skeletal muscle cells, in as high as 20 mM concentrations. Carnosine is involved in a variety of activities related to detoxification of the body from free radical species and the byproducts of membrane lipid peroxidations. Recently, it has been shown that carnosine also exhibits membrane-protecting activity, an ability to form complexes with transition metals, proton-buffering capacity, and regulation of macrophage function. Carnosine has also been shown to act as a potent and selective scavenger of α,β -unsaturated aldehydes, and to inhibit aldehyde-induced protein-protein and DNA-protein crosslinking in neurodegenerative disorders such as \rightarrow Alzheimer's disease, in inflammatory diseases, and in cardiovascular ischemic damage. Possible anti-aging actions have been described, and appropriate preparations have been sold as dietary or anti-aging

cosmetic products – the so-called “elixir of youth”, “miraculous anti-aging supplement”, and “anti-aging amino acid supplement”. *N* $^{\alpha}$ -acetylcarnosine (NAC) is known as the “best-selling” derivative of carnosine. It is stable against the human serum carnosinase which cleaves carnosine into its constituents of β -alanine and histidine. NAC has been developed for ophthalmic application as lubricating eye drops. Carnosine was first isolated and characterized by Gulewitsch in 1900 [A. R. Hipkiss, C. Brownson, *Cell. Mol. Life Sci.* **2000**, 57, 747; V. P. Skulachev, *Biochemistry (Moscow)* **2000**, 65, 749; A. Guiotto et al., *Curr. Medicinal Chem.* **2005**, 12, 2293].

CART peptides, neuropeptides acting as putative neurotransmitters/co-transmitters involved in feeding and body weight, stress, drug abuse, sensory processing, and neuroendocrine regulation. The name CART is an acronym for cocaine-amphetamine-regulated transcript, and refers to the mRNA discovered by Douglass et al. in 1995. CART peptides are highly expressed in the brain, and exhibit anorexigenic properties. Furthermore, they are also expressed in the peripheral nervous system, including primary sensory, sympathetic preganglionic, and enteric neurons, and in endocrine cells, e.g., pituitary endocrine cells, adrenomedullary cells, islet somatostatin cells, and antral gastrin cells. Human CART (hCART) are thought to have neurotrophic properties, as they promote neuronal development and survival in culture. Furthermore, CART peptides inhibit feeding behavior and show psychostimulant-like effects on locomotor behavior. Data demonstrating specific receptor binding for CART peptides were first published in 2005, but recently CART peptides have emerged as

important islet regulators, where they may play a role in normal islet function and in the pathophysiology of type 2 diabetes [J. Douglass et al., *J. Neurosci.* **1995**, *15*, 2471; M. J. Kuhar et al., *Trends Neurosci.* **1999**, *22*, 316; L. D. Adams et al., *Brain Res.* **1999**, 848, 137; M. J. Kuhar et al., *Regul. Pept.* **2000**, 89, 1; M. J. Kuhar et al., *Aaps J.* **2005**, 7, E259; K. G. Murphy, *Brief. Funct. Genomics Proteomics* **2005**, 4, 95; N. Wierup, F. Sundler, *Peptides* **2006**, 27, 2031].

α -Casein exorphin, \rightarrow milk protein-derived opioid peptides.

β -Casomorphins (β -CM), β -casorphins, β -casein-derived opioid peptide receptor ligands which belong to the \rightarrow exorphins. They are the first \rightarrow milk protein-derived opioid peptides acting as receptor ligands. β -CM with opioid activity have been found in human, bovine, ovine, and water buffalo β -casein. They can be released from β -casein both in the adult and neonate organism, where they might exert opioid activities. β -casomorphin-7 (β -CM-7), H-Tyr-Pro-Phe-Pro-Gly-Pro-Ile, the first example of a peptide with morphine-like activity, was isolated from commercial casein peptone in 1979. This sequence corresponds to bovine β -casein-(60–66). Contrary to moderate potencies and receptor selectivities of the natural β -CMs, some of the synthetic analogues display high agonist potencies and remarkable μ -receptor selectivities. *Morphiceptin*, H-Tyr-Pro-Phe-Pro-NH₂, the N-terminal tetrapeptide amide of β -CM-7, had been synthesized prior to isolation. It is regarded as a standard μ -selective opioid receptor ligand [V. Brantl et al., *Hoppe-Seyler's Z. Physiol. Chem.* **1979**, 360, 1211; V. Brantl et al., *Peptides* **1982**, 3, 793; K. Neubert et al., in: *β -Casomorphins and Related*

Peptides, F. Nyberg, V. Brantl (Eds.), p. 15, Fyris-Tryk, Uppsala, **1990**].

Casoxins, \rightarrow milk protein-derived opioid peptides.

Caspartin, a novel member of the shell calcitic prisms of the Mediterranean fan mussel *Pinna nobilis*. Caspartin ($M_r \sim 17$ kDa) is acidic due to the high Asp content, and soluble in acetic acid. It self-aggregates spontaneously into multimers. It has been suggested that caspartin may play a central role in calcite prism formation [F. Matin et al., *J. Biol. Chem.* **2005**, 280, 33895].

Caspases, a number of cytosolic endopeptidases having strict specificity for hydrolysis of aspartyl bonds. They are essential enzymes in programmed cell death (apoptosis) and inflammation. Up until 2005, 15 mammalian members of this family had been characterized. The best known member of this clan are caspase-1 (EC 3.4.22.36) and caspase-3, having a catalytic dyad in the order His, Cys in the sequence. Three-dimensional structures are known for both members, and show an α/β protein fold. Caspase-1, formerly known as interleukin 1 β -converting enzyme (ICE), is a heterodimer consisting of a heavy chain ($M_r \sim 22$ kDa) and a light chain ($M_r \sim 10$ kDa). It mediates the processing of interleukin 1 β at aspartyl bonds. Caspase-3 was identified as protein homologous to caspase-1 and is also a heterodimer. Caspase-15 is expressed in various mammalian species, including dog, pig, and cattle. In the name caspase, the “c” reflects a cysteine peptidase mechanism, while “aspase” relates to ability to cleave after Asp [N. A. Thornberry, S. M. Molineaux, *Protein Sci.* **1995**, 4, 3; W. Earnshaw et al., *Annu. Rev. Biochem.* **1999**, 68, 283; J. Rotonda

et al., *Nature Struct. Biol.* **1996**, 3, 619; L. Eckhart et al., *J. Biol. Chem.* **2005**, 280, 35077].

Catalytic antibody, → abzyme.

Cathelicidins, a family of → antimicrobial peptides or host defense peptides (HDPs) including a group of cationic and usually amphipathic peptides. They show a variety of activities to host defense functions, among which the most acknowledged is a direct antimicrobial activity against various microbial pathogens. The members of this family are considerably diverse in length, sequence and structure, variously adopting α -helical, elongated, or β -hairpin conformations. The cathelicidins are widely distributed, which suggests that they may play a highly relevant role in protecting the host from microbial infection [L. Tomasinsig, M. Zanetti, *Curr. Prot. Pept. Sci.* **2005**, 6, 23].

Caveolin (Cav), structural protein necessary and sufficient for the formation of caveolae. Cav-1 and Cav-3 are co-expressed in most cell types, including endothelial cells, epithelial cells, and fibroblasts, whereas Cav-3 are expressed by cardiomyocytes. However, smooth muscle cells express all three caveolins. It has been reported that administration of a cell-permeable Cav-1 prevents the development of monocrotaline-induced pulmonary hypertension and right ventricular hypertrophy [T. Okamoto et al., *J. Biol. Chem.* **1998**, 273, 5419; J.-F. Jasmin et al., *Circulation* **2006**, 114, 912].

CBD, chitin-binding domain.

CCAP, crustacean cardioactive peptide.

CCK, cholecystokinin.

CD, circular dichroism.

CDI, carbonyldiimidazole.

cDNA, complementary DNA.

CE, capillary electrophoresis.

Cecropins, a group of insect-derived antimicrobial peptides first isolated from *Drosophila* and from the pupae of the giant silk moth *Hyalophora cecropia*, from which the name is derived. *Cecropin A*, KWKLFKKIEK¹⁰VGQNIRDGII²⁰KAGPAVAVVG³⁰QATQIAKa, and *cecropin B* with 35 aa, are positively charged linear peptides from *H. cecropia*, forming time-variant and voltage-dependent ion channels in planar lipid membranes. The linear peptides form α -helices in solution. Furthermore, homologous peptides were found in several other insect species. It was surprising that a porcine cecropin was discovered in the upper intestinal tract, cecropin P 1, SWLSKTAKKL¹⁰ENSAKKRISE²⁰GIAIAIQGGP³⁰Ra. Later, the discovery of this peptide was rescinded when it was confirmed that the cecropin P1 had originated in fact from the pig intestinal parasitic nematode, *Ascaris suum*. In 2005, further studies led to the discovery of a bacteria-inducible antimicrobial peptide family in the nematode, *Ascaris suum*, designated cecropins P2, P3, and P4. Cecropins are not lethal for mammalian cells at microbiocidal levels, and have been administered safely to animals. A direct correlation between cationic character and activity has been established for the cecropins, where the less-cationic members also show lower activity [H. G. Boman, D. Hultmark, *Annu. Rev. Microbiol.* **1987**, 41, 103; H. G. Boman et al., *FEBS Lett.* **1989**, 259, 103; W. F. Broekaert et al., *Crit. Rev. Plant Sci.* **1997**, 16, 297; A. Pillai et al., *Biochem. J.* **2005**, 390, 207].

Cell-penetrating peptides (CPPs), *Trojan horse peptides*, *protein transduction domains*, peptides of different structural classes that are capable to cross the plasma membranes of mammalian cells in an

apparently energy- and receptor-independent fashion. CPP translocate rapidly into cells and act as peptidic delivery factors. They have found application for the intracellular delivery of macromolecules with molecular weights several times greater than their own. In order to differentiate from larger proteins that have been shown to function as transporters across biological membranes, CPP on average contain no more than 30 aa residues. According to an actually proposed classification, CPPs are arranged into three classes: (i) protein-derived CPPs; (ii) model peptides; and (iii) designed CPPs. *Protein-derived CPPs*, also designated as *protein transduction domains* or *membrane translocation sequences*, usually consist of the minimal effective partial sequence of the parent translocation protein. To the first group belong *penetratin*, RQIKIWQNR¹⁰RMKWKK, corresponding to *Drosophila* Antennapedia homeodomain-(43–58), *tat fragment*(48–60), GRKKRRQRRR¹⁰PPQ, derived from human immunodeficiency virus 1 protein TAT (86 aa), and *pVEC*, LLILRRRIR¹⁰KQAHASKa, derived from murine vascular endothelial cadherin. *Model CPPs* consist of sequences that have been designed with the aim of obtaining well-defined amphipathic α -helical structures, or to mimic the structures of known CPPs. Members of this group are (Arg)₇, RRRRRRR, and MAP, KLALKLALKA¹⁰LKAALKLAa. *Designed CPPs* are usually chimeric peptides comprising hydrophilic and hydrophobic domains of different origin. MPG, GALFLGFLGA¹⁰AGSTMGAWSP²⁰KSKLRKV, derived from the fusion sequence of HIV-1 gp41 protein coupled to a peptide derived from the nuclear localization sequence of SV40 T-antigen, and *transportan*, GWTLNSAGYL¹⁰LGKINL

KALA²⁰ALAKISILa, derived from the minimally active part of \rightarrow galanin-(1–12) coupled to mastoparan via Lys¹³, are members of this class. The penetration is to some degree an energy-independent mechanism of peptide translocation across the cell membrane. The sequence of CPP allows the addressing of cargoes into the cytoplasm and/or the nucleus. However, the mechanism of cellular translocation by CPPs is still not fully understood, although macropinocytosis seems to be the commonly assumed route. It seems likely that CPPs from the different groups act by distinct transport mechanisms. For many CPPs, the cargoes must be covalently conjugated, but in some cases (MPG) a mixture is sufficient. Independent of the binding of the cargo, an excess of CPP is necessary. Examples of cargoes internalized by CPPs include the transport of a fibroblast growth factor (FGF) receptor phosphopeptide by penetratin to inhibit FGF receptor signaling in living neurons, and internalization of the 21-mer galanin receptor antisense by penetratin or transportan in order to regulate galanin receptor levels and modify pain transmission *in vivo*. A broad range of therapeutics such as proteins, DNA, antibodies, oligonucleotides, PNAs and imaging agents are translocated by CPPs into target cells. Until now, CPP-based technologies have served as useful tools in biomedical research, especially due to their non-invasive and efficient delivery of bioactive molecules into cells, both *in vitro* and *in vivo*. Of special importance are those CPPs with an affinity towards actively proliferating cells, as they open new vistas in cancer and developmental biology research [M. Lindgren et al., *Trends Pharmacol. Sci.* **2000**, *21*, 99; U. Langel (Ed.), *Handbook of Cell-Penetrating Peptides*, CRC Press, Boca Raton, USA, **2007**; M. Zorko, U. Langel, *Adv. Drug Deliv. Rev.*

2005, 57, 529 (Review); K. M. Wagstaff, D. A. Jans, *Curr. Med. Chem.* **2006**, 13, 1371; A. Kerkis et al., *IUB MB Life* **2006**, 58, 7].

Cepacidines, glycopeptides produced by *Burkholderia cepacia*. Cepacidines A₁ and A₂ belong to the class of antifungal peptides derived from bacteria and fungi. Both peptides display potent antifungal activity for *Candida* and other species [C. H. Lee et al., *J. Antibiot.* **1994**, 47, 1402].

Cereulide, a cyclodepsipeptide (→ depsipeptides) isolated from the marine bacterium *Bacillus cereus*. Cereulide and *homocereulide* are 36-membered macrocycles which differ only in one methyl group. They are characterized by a trimeric sequence of alternating amino acids and hydroxy acids reminiscent of → valinomycin. The structure of cereulide was confirmed by total synthesis. Cereulide forms 1:1 complexes with alkali metals with preference in binding of K⁺ and Rb⁺. In addition to their action as emetic food poisons, cereulide and homocereulide show potent cytotoxicity against P388 murine leukemia and Colon 26 cell lines [S. Suwan et al., *J. Chem. Soc., Perkin Trans. I* **1995**, 765; G.-Y. Wang et al., *Chem. Lett.* **1995**, 791; M. Isobe et al., *Bioorg. Med. Chem. Lett.* **1995**, 5, 2855; K. Kawamura-Sato et al., *Microbiol. Immunol.* **2005**, 49, 25].

Cerulein, *caerulein*, **CRL**, pGlu-Gln-Asp-Tyr(SO₃⁻)-Thr-Gly-Trp-Met-Asp-Phe¹⁰-NH₂, a peptide amide firstly isolated from the skin of the Australian frog *Litoria caerulea* and from the skin of other amphibians. Cerulein belongs as a member of non-mammalian origin to the → gastrin family. Synthetic CRL, named *ceruletide*, was predominantly used for studies of the activity spectrum, and is applied in X-ray diagnostics and in the diagnosis of pan-

creatic function. Activation of the receptor causes, for example, breakdown of phosphoinositides, and mobilization of cellular calcium. In general, it acts in a similar manner as → cholecystokinin. Due to the stimulating effect of the small intestine, ceruletide is used therapeutically in post-operative intestinal atonia and paralytic ileus, and can also be employed for the expulsion of gallstones and in biliary colic.

Ceruletide, → cerulein.

CF₃-BOP, 6-(trifluoromethyl)benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

CF₃-HBTU, 2-[6-trifluoromethylbenzotriazol-1-yl]1,1,3,3-tetramethyluronium hexafluorophosphate.

CF₃-PyBOP, 6-(trifluoromethyl)benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate.

CG, chorionic gonadotropin.

Cg, chromogranin.

cGMP, cyclic guanosine monophosphate.

CGRP, calcitonin gene-related peptide.

Cha, β-cyclohexylalanine or cyclohexylammonium salt.

Chaperonins, a family of the → molecular chaperones.

Chemerin, also named *tazarotene-induced gene-2 (TIG2)-encoded peptide*, a natural ligand of the G protein-coupled receptor termed ChemR23. Chemerin is biosynthesized as a 163-aa prepro-protein, consisting of a hydrophobic 20-aa N-terminal sequence, an intervening 137-aa cystatin-fold containing domain, and a 6-aa C-terminal sequence region. The cystatin-fold contains three intrachain disulfide bonds, three potential sites for phosphorylation,

and one site for myristoylation. In human, processing yields a 16 kDa heparin-binding bioactive 137-aa chemerin comprising the prepro-sequence-(21–157). The active site seems to be concentrated in the prepro-sequence-(149–157). The corresponding nonapeptide *chemerin-9*, H-Tyr-Phe-Pro-Gly-Gln-Phe-Ala-Phe-Ser-OH, retained most of the full-size chemerin receptor-activating potential. It has been reported that the structural organization of chemerin is reminiscent of that of chemokins. Although the understanding of biological function seems still to be in its infancy, a physiological function can be expected in inflammation, skin physiology, bone metabolism, and immune response [W. Meder et al., *FEBS Lett.* **2003**, 555, 495; V. Wittamer et al., *J. Biol. Chem.* **2004**, 279, 9956; C. Kutzleb et al., *Curr. Prot. Pept. Sci.* **2005**, 6, 265].

Chemical ligation, native chemical ligation, NCL, an approach to the synthesis of large polypeptides and small proteins by the chemoselective reaction of unprotected peptide segments in aqueous solution at neutral pH, thereby preventing their secondary or tertiary structure. Native peptide bond formation at the site of ligation results from a spontaneous rearrangement of a thiol exchange product. The thioester-linked intermediate is formed chemoselectively between ligated peptides during a reaction of a \rightarrow C-terminal α -thioester with the thiol group of an N-terminal cysteine residue. This capture reaction brings the reactive sites of the two segments into close proximity, and the thioester-linked intermediate undergoes an irreversible intramolecular rearrangement to give a near-quantitative yield of a single product linked by a native peptide bond at the ligation site. The resulting ligation

product can be purified by reverse-phase HPLC and characterized by electrospray MS. In the *extended native chemical ligation (ENCL) approach* the N-terminal cysteine is replaced by a thiol-containing auxiliary that can be conveniently cleaved after the reaction. Until now, chemical ligation has been focused on peptides and proteins in the size range of 50 to \sim 150 aa, which can be constructed from two or three peptide segments. However, chemical synthesis of proteins with a typical size of \sim 300 aa would require approximately six synthetic segments. In practice, the requirement for purification and characterization would be enormous. In attempts to overcome such problems, various methods to facilitate the handling of the intermediate products formed within the course of chemical protein synthesis have been introduced, such as solid-phase chemical ligation and “one-pot” *synthesis approaches*. In the *solid-phase approach*, unprotected building blocks are consecutively ligated onto a water-compatible polymeric support. Similar to usual SPPS technique after each ligation step, any excess of soluble reactants and co-products is removed by filtration and washing. However, additional chemistry is required for the synthesis of suitably cleavable peptide-polymer linkers for every new target protein. The *one-pot approach* allows, for example, a three-segment ligation synthesis in one pot without purification of the intermediates, though a near-quantitative yield for each ligation step is necessary. Last, but not least, a His₆ tag-assisted procedure has been developed. A \rightarrow His₆ tag at the C-terminus of the target polypeptide chain enables the isolation of peptide and protein intermediates by Ni-NTA affinity column purification, reduces handling losses, and provides for rapid chemical protein synthesis. Recent advances in convergent methodology have

led to a more efficient synthetic strategy for the total chemical synthesis of proteins. In *kinetically controlled ligation* (KCL), one peptide with a C-terminal arylthioester reacts selectively with a second peptide having an N-terminal Cys and a C-terminal alkylthioester to form the ligated peptide with a C-terminal alkylthioester in high yield, because of the higher intrinsic reactivity of the arylthioester. This strategy enables the synthesis of a protein in a fully convergent fashion, as has been demonstrated in the convergent chemical synthesis both of human lysozyme (133 aa) and a 203-aa "covalent dimer" HIV-1 protease enzyme molecule by Kent and coworkers in 2007. An interesting variant in chemical ligation chemistry is the \rightarrow Staudinger ligation. The ability to efficiently assemble proteins from four synthetic peptide segments, combined with the increased flexibility in the design of a synthetic route, will promote the progress of chemical protein synthesis [M. Schnolzer, S. B. Kent, *Science* **1992**, 256, 221; P. E. Dawson, S. B. Kent, *Annu. Rev. Biochem.* **2000**, 69, 923; B. L. Nilson et al., *Annu. Rev. Biophys. Biomol. Struct.* **2005**, 34, 91; D. Bang, S. B. Kent, *Proc. Natl. Acad. Sci. USA* **2005**, 102, 5014; D. Bang et al., *Angew. Chem. Int. Ed.* **2006**, 45, 3985; D. Bang et al., *Angew. Chem. Int. Ed.* **2006**, 45, 3985; D. Macmillan, *Angew. Chem. Int. Ed.* **2006**, 45, 7668; V. Y. Torbeev, S. B. H. Kent, *Angew. Chem. Int. Ed.* **2007**, 46, 1667; T. Durek et al., *Proc. Natl. Acad. Sci. USA* **2007**, 104, 4846].

Chemical protein synthesis, access to protein molecules using chemical procedures. Over the past decade the applicability of chemical protein synthesis has been greatly expanded, as this approach has emerged as a powerful technique for the investigation of structure–function relationships in pro-

teins. Chemical protein synthesis allows the facile site-specific introduction of unnatural moieties (e.g., fluorescent labels) into the protein, a procedure not possible by recombinant DNA-based methods that are subject to the limitations of ribosomal protein synthesis. The convergent chemical synthesis in solution of maximally protected segments has already been used for the synthesis of the 124-aa enzyme ribonuclease A by Yajima, in 1981. However, the procedure was problematic because, during the segment elongation process of 30 coupling steps, a large excess (between 3- and 30-fold) of each carboxy segment was required, and serious problems of insolubility of the intermediates were reported. A general procedure for the solution synthesis of peptides containing more than 100 aa has been developed by Sakakibara's group at the Peptide Institute in Osaka. Synthesis of the green fluorescent protein (GFP) precursor molecule with 238 aa was a masterly performance of a highly sophisticated synthesis technique which, belongs to the state-of-the-art protein synthesis by the classical solution strategy. The need for custom-designed and labeled proteins as drug discovery tools has required new innovative methods to broaden the applicability of chemical protein synthesis. Since the mid-1990s, chemical synthesis has emerged as a powerful new approach based on the development of \rightarrow chemical ligation. Subsequently, a variety of ligation chemistries has been developed, and this has significantly broadened the general potential for chemical protein synthesis, including techniques of \rightarrow biochemical protein ligation [N. Fujii, H. Yajima, *J. Chem. Soc., Perkin Trans. I* **1981**, 831; S. Sakakibara, *Biopolymers* **1999**, 51, 279; G. G. Kochendoerffer, *Curr. Opin. Drug Discov. Dev.* **2001**, 4, 205; N. Budisa, *ChemBioChem* **2004**, 5, 1176].

Chemogenomics, a term coined comprising the discovery and description of all possible drugs to all possible targets. It is based on integrated → high throughput technology and computational data management, and is expected to bring about fundamental changes in the pharmaceutical drug discovery process. In contrast to chemical genetics approaches, where defined chemical probes are used to address and validate biological targets and pathways with respect to therapeutic relevancy, it is the goal of chemogenomics approaches to overcome the focusing of one target at a time while addressing multiple related targets simultaneously, in a highly parallel approach. This is combined with information available on the human genome sequence [P. R. Caron et al., *Curr. Opin. Chem. Biol.* **2001**, 5, 464].

Chemokines, a sub-family of the → cytokines. They are composed of a core domain containing two or three disulfide bonds in a flexible *N*-terminal domain whose truncation affects the potency of receptor activation. The chemokines are homologous 8- to 10-kDa proteins with 20 to 70% sequence homology. They are subdivided into at least four families based on the relative position of the Cys residues in the mature protein, although only the α - and β -chemokines (both of which contain four Cys residues) have been well characterized. In the α -chemokines (CXC chemokines), the first two Cys residues are separated by a single amino acid residue (Cys-Xaa-Cys), whereas in the β -chemokines (CC chemokines) the first two Cys residues are adjacent to each other (Cys-Cys). α -Chemokines are roughly 70 to 130 aa in size and are secreted with leader sequences of ~ 20–25 aa which are cleaved before release. Besides the conserved Cys-Xaa-Cys motif near the *N*-terminus of the protein,

there are two additionally conserved cysteine residues. A three-dimensional folding stabilized by the disulfide bonds is a characteristic feature of these peptides. Until now, six α -chemokine receptors (CXCRs) have been identified which are members of the superfamily of serpentine proteins that signal through heterotrimeric G proteins. α -Chemokines which contain the sequence Glu-Leu-Arg preceding the Cys-Xaa-Cys sequence, are chemotactic for neutrophils, while those lacking this sequence act on lymphocytes. Lymphotactin and fractalkine represent two additional families that do not fit into the classification. *Lymphotactin* contains only two Cys residues in the mature protein, while *fractalkine* is a membrane-bound glycoprotein in which the first two Cys residues are separated by three amino acids (Cys-Xaa-Xaa-Xaa-Cys). Chemokines mediate cell migration and activation by binding to specific G protein-coupled receptors on the surface of the target cells. The functions of chemokines in the pathophysiology of disease are still being defined, but based on studies in animals it can be concluded that the neutralization of chemokine activity may have therapeutic value. Chemokine-receptor antagonists may inhibit allergic, autoimmune, and septic processes. Chemokines may also improve the host response to infection, vaccines, and tumors. Although chemokines were originally defined as soluble factors able to control the migration of leukocytes, they are now known to play an important role in a variety of cell types, including tumor cells. For example, a novel chemokine, named VCC-1, which promotes tumor growth has recently been described [A. D. Luster, *N. Engl. J. Med.* **1998**, 338, 436; J. A. Belperio et al., *J. Leukoc. Biol.* **2000**, 68, 1; M. Baggiolini, *J. Int. Med.* **2001**, 250, 91; R. Horuk, *Cytokine Growth Factor Rev.* **2001**, 12, 313; E. J. Weinstein et al.,

Biochem. Biophys. Res. Commun. **2006**, *350*, 74].

Chemotactic peptides, a class of chemoattractant peptides of bacterial or mitochondrial origin with For-Met-Leu-Phe-OH (fMLF) being the prototype. Chemotactic peptides bind, e.g., to the human formyl-peptide receptor (FPR) and its variant FPRL1 (FPR-like 1). They belong to the family of G_i protein-coupled receptors (GPCR), and are expressed at high levels on neutrophils and monocytes. Activation of FPR by peptide agonists promotes cell chemotaxis, phagocytosis, and the release of pro-inflammatory agents. The interaction of FPR and FPRL1 with diverse pro- and anti-inflammatory ligands is associated with amyloidosis, → Alzheimer's disease, prion disease (→ prions) and → HIV. Non-formylated peptide ligands for FPR have also been identified. The synthetic peptide → T20 (DP178) derived from HIV gp41, which has potent anti-HIV-1 activity, also activates FPR. *N*-ureido-substituted small peptides are also ligands for FPR. The agonist or antagonist behavior can be achieved depending on the nature of the substituent R of the urea. Benzylureido-Met-Leu-Phe-OH is an antagonist, while 4-methoxyphenylureido-Met-Leu-Phe-OH displays agonist activity [E. Schiffmann et al., *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 1059; J. D. Higgins et al., *J. Med. Chem.* **1996**, *39*, 1013; Y. Le et al., *Trends Immunol.* **2002**, *23*, 541].

Cherimolacyclopeptides, cyclic peptides isolated from the methanol extract of the seeds of *Annona cherimola*. The cherimolacyclopeptides A, B, C, D, E, and F have been isolated and structurally elucidated. In addition, *glauca* **cyclopeptides** A and B have been discovered in the seeds of *Annona glauca*. The cyclopeptides were described as having cytotoxic activity *in*

vitro against cell cultures, such as human nasopharyngeal carcinoma cell lines. The sources of the cyclopeptides are small trees which grow in America, Africa and Asia and are now cultivated for their edible fruits in Europe [F.-R. Chang et al., *Phytochemistry* **1998**, *47*, 1057; A. Wele et al., *Chem. Pharm. Bull.* **2006**, *54*, 690].

Chinese Peptide Society (CPS), a scientific and educational organization of Chinese scientists with the primary role of fostering the advancement of peptide research throughout China. It is a fundamental aim of the CPS to continue the notable Chinese achievements in peptide and protein research, such as the first ever chemical synthesis of crystalline insulin during the early 1960s. Although a period of austerity followed the Cultural Revolution, in recent years peptide research has been reinvigorated, including the establishment of the Chinese Peptide Society as a branch of the Chinese Society of Biochemistry and Molecular Biology. Membership is restricted to Chinese scientists, but the CPS hosts a biennial conference

Chlamydocine, a cyclotetrapeptide belonging beside WF3161 to the most potent cancerostatics *in vitro*. By using the Boc/OPfp protocol, both 4-peptides can be synthesized in high yields. The non-natural amino acid (S)-2-amino-8-oxo-(S)-9,10-epoxidecanoic acid (AOE) present as a building block in both cyclopeptides was assembled stereoselectively in a seven-step synthesis [U. Schmidt et al., *Tetrahedron Lett.* **1988**, *29*, 3057].

Chloromethyl resin, *Merrifield resin*, a polystyrene/divinylbenzene resin functionalized with the chloromethyl group introduced by Friedel-Crafts-type chloromethylation with the alkoxy-substituted chloromethane in the presence of tin(IV)

chloride. The original resin was used by Merrifield during the development of SPPS [R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149].

2-Chlorotriylchloride resin, → Barlos resin.

Cholecystokinin (CCK), a family of peptides involved in the control of multiple functions, both in the gastrointestinal tract regulating digestive functions, and in the CNS acting as neurotransmitters. CCK was formerly named *cholecystokinin/pancreozymin*, **CCK-PZ**, and is one of the first gastrointestinal hormones discovered and structurally elucidated, in 1968. CCK was originally isolated from the porcine duodenum as a 33-peptide (CCK-33) with sequence similarities to → gastrin, another gut hormone characterized some years earlier. CCK-8, H-Asp-Tyr(SO₃⁻)-Met-Gly-Trp-Met-Asp-Phe-NH₂, was found later in the rat brain. Since that time, large amounts of CCK have been identified in various areas of the CNS and in peripheral nerve endings. In humans, CCK and gastrin are encoded by two distinct genes located on chromosomes 3p22-p21.3 and 17q21, respectively. CCK displays major tissue and species-specific differences in post-translational processing. The major difference is between the brain and the intestine. The CCK gene which is expressed in gastrointestinal tissues encodes preprocholecystokinin, which by differentiated endoproteolytic cleavages is processed to six CCK peptides varying in length from 58 to 5 amino acids: CCK-5, CCK-8, CCK-22, CCK-33, CCK-39, and CCK-58. CCK-33 and CCK-39 are the most abundant CCK peptides and have a pivotal function in regulating the exocrine pancreas. The six CCK peptides have the same C-terminal octapeptide sequence as shown for CCK-8, in which the tyrosine residue is *O*-sulfated.

Biologically active CCKs also exist in non-sulfated forms. CCK-8 has the full activity spectrum of the longer CCK peptides. The CCK gene is also expressed in neural tissue, yielding mainly the sulfated form of CCK-8 and acting as neurotransmitter or neuromodulator, both in the central and peripheral nervous systems. In addition, smaller fragments such as CCK-5 and CCK-4, as well as larger forms (CCK-58 and CCK-33), have also been found in brain extracts. CCK-8 is one of the most abundant neuropeptides in mammalian brain, being found in the cerebral cortex, thalamus, hippocampus and caudate-putamen. It acts as an excitatory neurotransmitter, and is an important component in the neurochemical balance of the brain. CCK appears to function in anxiety, satiety, analgesia, opiate tolerance, learning and memory, psychostimulant-induced locomotion and sensitization, and neuroprotection. A huge number of publications has emerged describing the distribution of CCK neurons, their projections, and the two CCK receptor subtypes A ("alimentary") and B ("brain"). Nowadays, the CCK-A receptor has been renamed CCK1 receptor (CCK1R), and the CCK-B receptor is now termed CCK2 receptor (CCK2R). CCK1R binds to sulfated CCK with 500- to 1000-fold higher affinity than sulfated gastrin or non-sulfated CCK. The CCK2R binds to gastrin or CCK with almost the same affinity, and discriminates poorly between sulfated and non-sulfated hormones. Recently, it was reported that CCK peptides may also induce neurogenic vasodilation both in cerebral and mesenteric vessels. CCK is a member of the → gastrin family. In 1928, CCK was discovered in small intestine extracts as a gallbladder-emptying hormone, whilst during the 1940s a stimulator of pancreatic enzyme secretion, named pancreozymin, was identified. However, some 20 years

passed before Jorpes and Mutt showed that CCK and pancreaticoymymin were identical. Today, only the acronym CCK is used [V. Mutt, J. E. Jorpes, *Eur. J. Biochem.* **1968**, 6, 156; R. J. L. Deschenes et al., *Proc. Natl. Acad. Sci. USA* **1984**, 81, 726; G. P. Smith, J. Gibbs, *Ann. N. Y. Acad. Sci.* **1985**, 448, 417; J. F. Rehfeld, *Physiol. Rev.* **1998**, 78, 1087; M. C. Beinfeld, *Life Sci.* **2003**, 72, 747; M. Dufresne et al., *Physiol. Rev.* **2006**, 86, 805; M. Ruiz-Gayo et al., *Regul. Pept.* **2006**, 137, 179].

Chorionic gonadotropin (CG), *human chorionic gonadotropin*, **hCG**, a placental proteohormone stimulating secretion of the pregnancy-sustaining steroid progesterone. CG is a member of a family of glycoprotein hormones (\rightarrow gonadotropins) characterized by a disulfide-rich heterodimeric structure consisting of a common α -chain and distinctive β -chain. It is synthesized in the syncytiotrophoblasts of the placenta. CG is secreted in the first weeks of pregnancy, and stimulates the corpus luteum via the G protein-coupled hCG receptor in order to continue the secretion of progesterone rather than regressing, and this prevents menstruation. Immunoassay pregnancy tests are based on the detection of CG in blood or urine within a few days after embryo implantation. The α -chain (96 aa) is identical with that of \rightarrow lutropin (LH), \rightarrow thyrotropin (TSH) and \rightarrow follitropin (FSH), whereas the β -chain (145 aa) shows a high degree of sequence identity to those of LH (85%), FSH (45%), and TSH (36%). The three-dimensional structure of hCG indicates that each of the two different subunits has a similar topology characterized by three disulfide bonds forming a cystine knot. The heterodimer is stabilized by a segment of the β -subunit which wraps around the α -subunit and is covalently linked, like a seat belt, by

the disulfide bond Cys²⁶–Cys¹¹⁰. Human CG (Predalon, Prednesin, Choragon, Primogonyl) is used in the treatment of disturbances of gonadal functions [L. Liu et al., *Endocrinology* **1989**, 124, 175; A. J. Laphorn et al., *Nature* **1994**, 369, 455].

Chorionic mammatropin (CM), *human chorionic somatomammatropin*, **hCS**, *placenta lactogen*, **PL**, a single-chain proteohormone formed in the placenta during the first trimester of pregnancy. It shows more structural similarities to \rightarrow growth hormone than to \rightarrow prolactin (PRL), but it combines the function of both hormones. CM initially stimulates the development of the breast, without influence on milk secretion. With decreasing levels of CM after birth, PRL stimulates milk secretion. The growth-stimulating effect of CM is weaker than that of human STH, but CM might play a more important function in the development of the fetus. CM promotes the release of progesterone and estrogen from the corpus luteum, but this effect is additionally potentiated by \rightarrow chorionic gonadotropin [S. Aloj, H. Edelhoch, *J. Biol. Chem.* **1971**, 246, 5047; P. A. Kelly et al., *Endocrinology* **1975**, 96, 1187].

cHp, cycloheptyl.

Chromogranins (Cg), *secretogranins*, a family of water-soluble acidic glycoproteins. The Cg consist of four distinct members: CgA, CgB (secretogranin I), CgC (secretogranin II), and the neuroendocrine secretory protein 55 (NESP 55). The three Cg are rich in Glu, have calcium-binding capacity, and the capability to be glycosylated, phosphorylated and sulfated. Human CgA is a single-chain glycoprotein (439 aa; $M_r \sim 50$ kDa) located predominantly in the dense core of granula storing peptide hormones and catecholamine-containing vesicles. Due to the high sensitivity and

specificity of CgA, it can be successfully used as a circulating marker in diagnosis, prognosis and follow-up of neuroendocrine tumors. The Cg are precursors of various peptides showing biological activities. CgA is a precursor of \rightarrow pancreastatin, \rightarrow peptide WE-14, chromostatin (involved in human pancreatic insulin β -cell function), vasostatin (inhibits vasoconstriction), and parastatin (inhibits PTH secretion), while CgB is cleaved proteolytically to give secretolytin. Similarly, \rightarrow secretoneurin is a derivative of CgC and NESP 55 produces a tetrapeptide named LSAL which is an endogenous antagonist of the serotonergic 5-HT1B receptor subtype [L. Taupenot et al., *N. Engl. J. Med.* **2003**, 348, 1134].

Chrysosporide, cyclo-(-Val-D-Ala-Leu-Leu-D-Leu-), a cyclic 5-peptide isolated from a New Zealand sample of the mycoparasitic fungus *Sepedonium chrysospermum* by bioactivity-guided fractionation [M. I. Mitova et al., *J. Nat. Prod.* **2006**, 69, 1481].

Chymotrypsin, EC 3.4.21.1, a digest enzyme synthesized by the pancreatic acinar cells. Chymotrypsin is a member of the \rightarrow serine proteases and catalyzes the hydrolysis of peptide bonds with high specificity for a bulky hydrophobic residue preceding the scissile peptide bond, such as Tyr, Phe, Trp [Y. Okamoto, T. Sekine, *J. Biochem.* **1985**, 98, 1143; V. Schellenberger et al., *Eur. J. Biochem.* **1991**, 199, 623].

Cicadapeptins, a family of non-ribosomal peptides isolated from the fermentation extracts of *Cordyceps heteropoda*, an entomopathogenic fungus from an Australian cicada. The structures of the two major components, cicadapeptin I and II, have been elucidated. Both peptides are acylated at the N-terminus by *n*-decanoic acid and amidated at the C-terminus by 1,2-diamino-4-methylpentane. The sequence

between the two blocked termini of the peptide chain is the following for cicadapeptin I: -Hyp-Hyp-Val-Aib-Gln-Aib-Leu-, while in cicadapeptin II Ile substitutes for Leu. Both peptides show antibacterial activity and limited antifungal activity [S. B. Krasnoff et al., *J. Nat. Prod.* **2005**, 68, 50].

Cinnamycin, a peptide antibiotic (M_r 2042 Da) produced by several *Streptomyces* strains including *Streptomyces cinnamoneus cinnamoneus* DSM 40005. Cinnamycin is a member of the Type B \rightarrow lantibiotics. It is characterized by a threefold thioether-based bridging pattern containing an additional lysinoalanine bridge connecting the C-terminus with 2,3-didehydroalanine (Dha) in position 6. Cinnamycin shares considerable sequence similarities with *ancovenin* (M_r 1959 Da), *duramycin* (M_r 2014 Da), *duramycin B* (M_r 1951 Da) and *duramycin C* (M_r 2008 Da). These peptides are all derived from 19 aa propeptides, having lanthionine moieties in similar positions, and form a group of analogues of the prototype C. In general, only seven amino acids vary, and the substitutions are mainly conservative. Besides their general antimicrobial activity, the members of this group have attracted special interest because of their activity directed towards specific enzyme functions, e.g., phospholipase A_2 and \rightarrow angiotensin-converting enzyme. Furthermore, members of this group of type-B lantibiotics show some antiviral activities, for example against *herpes simplex* type II and other related retroviruses. Cloning and sequence analysis of the complete cinnamycin biosynthetic gene cluster from *S. cinnamoneus cinnamoneus* DSM 40005 was described in 2003 [R. W. Jack, G. Bierbaum, H.-G. Sahl, *Lantibiotics and Related Peptides*, Springer, Berlin,

Heidelberg, New York, **1998**; D. A. Widdick et al., *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4316].

Cionin, H-Asn-Tyr(SO₃⁻)-Tyr(SO₃⁻)-Gly-Trp-Met-Asp-Phe-NH₂, a disulfotyrosyl hybrid of → cholecystokinin and → gastrin from the neural ganglion of the protochordate *Ciona intestinalis*. It was concluded that the structure of cionin meets that of a common ancestor for cholecystokinin and gastrin [A. H. Johnsen, F. R. Rehfeld, *J. Biol. Chem.* **1990**, *265*, 3054].

cis Peptide bond, a rotamer of the → peptide bond with the torsions angle $\omega \approx 0$. The *cis*-type arrangement of the peptide bond occurs mainly in -Xaa-Pro-sequences. In native proteins, the percentage of *cis*-configured Xaa-Pro bonds (6.5%) is approximately two orders of magnitude higher compared to non-proline *cis* peptide bonds (>0.03%), usually involved in β -turns. In aqueous solution, proline-containing linear oligopeptides as well as unfolded proteins equilibrate relatively slowly to a mixture of *cis/trans* isomers (→ peptidyl prolyl *cis/trans* isomerases), the ratio of which mainly depends on the nature of the amino acid preceding the proline residue. A comprehensive database of non-proline *cis* peptide bonds in proteins is available at: http://www.imb-jena.de/ImgLibDoc/cispep/non_proline/IMAGE_CISPEP2.html.

Cit, citrulline (2-amino-5-ureidovaleric acid).

CJD, Creutzfeldt-Jakob disease.

Clavanins, α -helical → antimicrobial peptides isolated from a mixed tunicate population of *Styela clava* hemocytes. Clavanin A, VFQFLGKIIH¹⁰HVGNFVHGFS²⁰HVF_a, and the clavanins B–E are 23-peptide antibiotics containing 18 identical residues

bearing a C-terminally amidated amino acid moiety [I. H. Lee et al., *FEBS Lett.* **1997**, *400*, 158; R. T. Lehrer et al., *Integr. Comp. Biol.* **2003**, *43*, 313].

Click peptides, peptides that are obtained in a quick and irreversible reaction. The name “click” chemistry was coined originally by Sharpless to characterize a set of powerful, reliable, and selective reactions, for the rapid synthesis of interesting new compounds through heteroatom linkers. The Cu^I-catalyzed 1,3-dipolar cycloaddition between azides and terminal alkynes providing 1,2,3-triazoles, is probably the most frequently used click reaction, employable under a broad range of conditions and, hence, is applicable to biopolymer conjugation. According to Kiso and coworkers, “click peptides” are the products obtained in the frame of the → O-acyl isopeptide method [Y. Sohma, *ChemBioChem* **2006**, *7*, 1549; H. C. Kolb et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 2004].

CLIP, corticotropin-like intermediate lobe peptide.

Clostripain, EC 3.4.22.8, a member of the → cysteine peptidases, isolated from the anaerobic bacterium *Clostridium histolyticum*. It is a heterodimeric protein of 526 amino acid residues. The heavy chain (M_r ~ 43 kDa) and the light chain (M_r ~ 1.5 kDa) are held together by strong non-covalent forces rather than by disulfide bridges. Cys⁴¹ of the heavy chain was identified as the catalytic residue of the active site. This peptidase is well known for the selective cleavage of arginyl bonds, whereas lysyl bonds are hydrolyzed at a lower rate [W. M. Mitchell, W. F. Harrington, *Methods Enzymol.* **1970**, *19*, 635; D. Ullmann, H.-D. Jakubke, *Eur. J. Biochem.* **1994**, *223*, 865].

Clt, 2-chlorotriptyl.

Cm, carboxymethyl.

CM, casomorphin or chorionic mam-motropin.

CN, calcineurin.

CNBr, cyanogen bromide.

Cne, 2-cyanoethyl.

CNP, C-type natriuretic peptide.

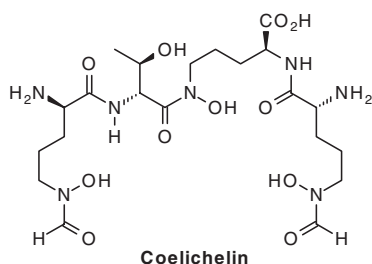
CNS, central nervous system.

Cnu, a novel *oriC*-binding 71-peptide ($M_r \sim 8.4$ kDa) of *Escherichia coli*. The name is derived from *oriC*-binding nucleoid-associated. It binds to a specific 26-base-pair sequence (named *cnb*) in the origin of replication of *Escherichia coli*, *oriC*. Cnu was found using a genetic strategy that employs transcriptional repression that is caused by DNA binding of a protein to an operator. Independently, it was detected as a protein that could complex with H-NS, a non-specific nucleoid-associated DNA-binding protein. It was shown that *oriC* binding of Cnu depends on this complexation [M. S. Kim et al., *J. Bacteriol.* **2005**, 187, 6998; S. Paytubi et al., *Mol. Microbiol.* **2004**, 54, 251].

Cobratoxins, polypeptides from the venoms of cobras or poisonous vipers (*Elapidae*) consisting of 60 to 62 aa and 4 to 5 disulfide bonds. α -Cobratoxin is a 62-peptide containing four disulfide bridges ($C^3-C^{24} / C^{17}-C^{41} / C^{43}-C^{54} / C^{55}-C^{60}$). It is a potent, postsynaptic neurotoxin, and the major toxic component of the venom of the Thai cobra, *Naja kaouthia*, the monocellate cobra. Cobratoxins show neurotoxic actions; the toxins of Asian cobras are additionally cardiotoxic. It has been reported that venomous snakebites result in almost 125.000 death per year, worldwide.

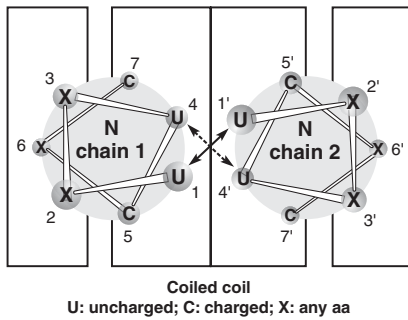
cOc, cyclooctyl.

Coelichelin, D-hfOrn-D-*allo*-Thr-L-hOrn-D-hfOrn, a tris-hydroxamate 4-peptide discovered by *Streptomyces coelicolor* genome mining. The ferric-iron-chelating peptide coelichelin contains, beside D-*allo*-threonine, two unusual amino acid residues: D- δ -N-formyl- δ -N-hydroxyornithine (D-hfOrn) and L- δ -N-hydroxyornithine (L-hOrn) [S. Lautru et al., *Nature Chem. Biol.* **2005**, 1, 265].



Coiled coil, motifs of super-secondary structure found in proteins. Approximately 2–3% of all proteins form coiled coils, where two to seven amphipathic α -helices are wrapped around each other, like the strands of a rope. The interaction surface of these amphipathic helices is of hydrophobic nature, and leucine is often found in the position of the hydrophobic amino acids (leucine zipper). This hydrophobic interaction provides, in an aqueous environment, the driving force for the di- or oligomerization. Coiled coils of two or three helical domains are the most commonly found types. In the former case, the two helices are wound up against each other in a left-handed twist with a seven-residue periodicity. Packing of unpolar side chains (u) into a hydrophobic core mainly contributes to the stability of this super-secondary fold. The dimeric coiled coil is, for example, responsible for DNA recognition by some transcription factors.

Colicins, plasmid-encoded \rightarrow bacteriocins produced by *E. coli*, cytotoxic towards



related bacteria. Colicins parasitize outer membrane receptors, the physiological purpose of which is the transport of metabolites, metals, vitamins, and sugars for entry into susceptible cells; the lethal effects are either pore formation or intracellular nuclease activity. The colicins sequences comprise an N-terminal T domain responsible for translocation, a central R domain, which mediates outer membrane receptor binding, and a C-terminal C domain which exerts the cytotoxic effects. The colicin-producing strain is protected by a ~ 10 kDa protein [O. Gillor et al., *Adv. Appl. Microbiol.* **2004**, 54, 129; S. D. Zakharov et al., *Front. Biosci.* **2004**, 9, 1311].

Collagen, the major component of the natural extracellular matrix, playing a central role in its organization and mechanical properties. Collagen is the main protein of connective tissue in animals and the most abundant proteins in mammals, comprising about 25% of the total protein content. Collagen occurs as the important stress-bearing component of connective tissues such as bone, cartilage, teeth, ligament, tendon, and the fibrous matrices of skin and blood vessels. Collagen is composed of three polypeptide chains. At least 30 genetically distinct polypeptide chains comprising 16 collagen variants

have been found in mammals. Within the types of collagen, the most abundant is *type I collagen* ($M_r \sim 285$ kDa; width: ~ 14 Å; length: ~ 3000 Å) characterized by the chain composition $[\alpha 1(I)]_2\alpha 2(I)$, and mainly occurring in bone, tendon, skin, blood, cornea, and blood vessels. Further important members are *type II collagen* $[\alpha 1(II)]_3$, which is found in cartilage and intervertebral disk, and *type III collagen* $[\alpha 1(III)]_3$, which occurs in blood vessels and fetal skin. The amino acid sequence of collagen $\alpha 1(I)$ contains repeating-Gly-Xaa-Yaa-sequence triplets (Xaa often Pro and Yaa often Hyp) over a continuous 1011-residue stretch of its 1042-residue polypeptide chain. In the triple helix of collagen, the left-handed peptide helices are twisted together to form a right-handed superhelical structure. The triple helix has 10 Gly-Xaa-Yaa units per turn, and a pitch of 86.1 Å. Collagen is organized into fibrils showing a periodicity of 680 Å and a diameter of 100 to 2000 Å, depending on the type of collagen. The molecule contains covalently linked carbohydrates ranging from ~ 0.4 to 12% by weight and consisting mainly of glucose, galactose, and their disaccharides. Collagen fibrils are covalently crosslinked. Specific lysyl and hydroxylysyl residues are oxidized by lysyl oxidase, resulting in the formation of an aldehyde from the side-chain amino group. The resulting aldehydes undergo Schiff's base formation and aldol condensations with neighboring side chains, forming a variety of crosslinks that contribute to the strength of collagen. A variety of hereditary and environmentally caused disorders result from the impairment of collagen synthesis. Mutations of type I collagen usually result in *osteogenesis imperfecta* (brittle bone disease) [M. E. Nimni (Ed.), *Collagen*, Volume I, CRC Press, Boca Raton, FL, **1988**; E. Y. Jones, A. Miller, *J. Mol. Biol.* **1991**, 218,

209; M. van der Rest, P. Bruckner, *Curr. Opin. Struct. Biol.* **1993**, 3, 430].

Collectins, a family of mammalian plasma and cell-surface proteins containing collagenous regions and lectin regions. They are soluble pattern-recognition receptors (PRRs), and belong to the superfamily of collagen-containing C-type lectins. The collectins comprise serum mannan binding protein (MBP), also termed mannan-binding lectin (MBL), conglutinin, the lung surfactant proteins SP-A and SP-D, collectin liver 1 (CL-L1), collectin placenta 1 (CL-P1), and the collectins of 43 kDa (CL-43) and of 46 kDa (CL-46), respectively. The MBL is secreted into the blood by the liver, whereas the SP-A and SP-D are secreted into the pulmonary alveolar and airways lining fluid. The collectins share a very similar modular domain composition and overall three-dimensional structure. The overall domain organization is characterized by four distinct regions: a cysteine-rich domain at the *N*-terminal end, a collagen domain located directly *N*-terminal to an α -helical bundle, a coiled-coil neck domain, and a C-type lectin domain (carbohydrate recognition domain, CRDs) which is located at the *C*-terminal end. The peptide chains form trimers which may assemble into larger oligomers. The biological roles of collectins seem to be the preimmune defense against microorganisms both in serum and lung surfactant. The C-type lectin domains bind to carbohydrate ligands on the cell surface of pathogens and fulfills a recognition function that can elicit effector functions via the collagen-like region, such as complement activation in the case of serum mannan binding protein, or binding to cell-surface receptors to trigger phagocytosis or oxidative killing [H.-J. Hoppe, K. B. M. Reid, *Protein Sci.*

1994, 3, 1143; J. K. van de Wetering et al., *Eur. J. Biochem.* **2004**, 271, 1229].

Colony-stimulating factors (CSF), *hematopoietic growth factors*, glycoprotein growth factors involved in proliferation, differentiation and survival of hematopoietic progenitor cells. Human CSFs are: *granulocyte/macrophage CSF* (GM-CSF), produced by T lymphocytes, endothelial cells and fibroblasts ($M_r \sim 18\text{--}20$ kDa; monomer, hGM-CSF: 127 aa), *granulocyte CSF* (G-CSF), produced by macrophages and fibroblasts ($M_r \sim 20$ kDa; monomer, hG-CSF: 174 aa), *macrophage CSF* (M-CSF), produced by fibroblasts, macrophages and endothelial cells ($M_r \sim 70$ kDa; dimer), and *multi-CSF* [also called *interleukin-3* (IL-3), \rightarrow interleukins], produced by T lymphocytes and epidermal cells ($M_r \sim 25$ kDa, mouse IL-3: 139 aa). The action of the CSFs is completed by the hormone-type CSF \rightarrow erythropoietin. Some human CSFs are now produced in larger quantities as recombinant proteins, and used clinically to counteract leukocyte death during chemotherapy and to facilitate bone marrow transplantation. Specific receptors for each CSF are coexpressed on granulocytes and monocytes [S. C. Clark, R. Kamen, *Science* **1987**, 236, 1229; D. Metcalf, N. A. Nicola, *The Hemopoietic Colony-Stimulating Factors: From Biology to Clinical Applications*, Cambridge University Press, New York, **1995**; A. Chakraborty et al., *Am. J. Physiol. Cell Physiol.* **2003**, 284, C103].

Combinatorial library, a collection of chemically and structurally diverse compounds, e.g., peptides, derived from \rightarrow combinatorial peptide synthesis.

Combinatorial peptide synthesis, an approach for the simultaneous synthesis of a large number of different peptides. The requirement for large numbers of

compounds to be tested in the pharmaceutical drug development and optimization process prompted the development of combinatorial synthesis and combinatorial organic synthesis. Both of these aim towards generating high synthetic and structural diversity. As many different compounds as possible must be synthesized and tested in biological assays in order to identify a pharmacological lead compound in a \rightarrow high-throughput screening approach which enables the testing of thousands of compounds per day in sophisticated test systems. Combinatorial synthesis of peptides can be approached in two different ways: either a large number of peptides are synthesized by \rightarrow multiple peptide synthesis. Single compounds are then isolated in this approach and can be tested separately with a vast potential for automation. Parallel synthesis also includes the spatially resolved synthesis of immobilized peptides. On the other hand, complex mixtures of compounds (libraries) may be obtained in a combinatorial manner. Parallel synthesis can be achieved either by the so-called \rightarrow teabag method, \rightarrow multipin synthesis, \rightarrow spot synthesis or by \rightarrow light-directed spatially addressable parallel synthesis. The teabag method makes use of combining resin material that is supposed to provide the same sequence in a solvent-permeable containment. The washing steps are performed for all teabags together. For peptide couplings, teabags that require coupling of the same amino acid derivative are combined accordingly. The \rightarrow multipin synthesis provides peptides in much smaller amounts than the teabag synthesis, as the resin material used for immobilization of the peptide is mounted on a pinnacle on a solid support. Usually, one polyethylene pin provides 10 to 50 nmol of covalently bound compound peptide. In spot synthesis, the target com-

pounds are obtained in immobilized form on cellulose sheets or other polymeric support materials in rather small amounts. The light-directed spatially addressable parallel synthesis utilizes photolithographic masks to obtain libraries of pure compounds in a spatially resolved manner. On the other hand, the synthesis of mixtures suffers, in principle, from the fact that not all activated amino acid derivatives display the same reaction rate when acylating a resin-bound amino group. To overcome this problem, so-called isokinetic mixtures may be employed. Alternatively, the \rightarrow split and combine method developed by Furka provides single compounds on every bead (one bead – one compound). After the synthesis, the beads displaying biological activity can be separated physically and the peptide sequence determined by microsequencing or mass spectrometry. Alternatively, low molecular-weight organic tags may be used to encode the information on the peptide sequence present on a single bead. A highly sophisticated method uses resin beads with a core containing a radiofrequency transponder that can be used to electronically store the sequence present on a single bead [G. Jung (Ed.), *Combinatorial Chemistry: Synthesis, Analysis, Screening*, Wiley-VCH, 1999; M. C. Pirrung, *Molecular Diversity and Combinatorial Chemistry*, Elsevier, 2004; S. Miertus, G. Fassina (Eds.), *Combinatorial Chemistry and Technologies*, CRC Press, Boca Raton, 2005].

Complement system, an essential biological defensive system consisting of a complex series of ~ 20 interacting plasma proteins. It is directed against foreign invaders by eliminating foreign cells via complement fixation; this means killing foreign cells by binding and lysing their cell membranes, by inducing phagocytosis of

foreign particles (opsonization), and triggering local acute inflammatory processes that wall off the area and attract phagocytotic cells. The complement system is characterized by two related activation pathways: the antibody-dependent classical pathway, and the antibody-independent alternative pathway [K. B. M. Reid, *Essays Biochem.* **1986**, 22, 27; G. D. Ross (Ed.), *Immunobiology of the Complement System*, Academic Press, **1986**; H. J. Müller-Eberhard, *Annu. Rev. Biochem.* **1988**, 57, 321].

Complementary peptide, → antisense peptide.

Complestatins, rigid bicyclic hexapeptides inhibiting HIV replication by disruption of gp120 binding to the CD4 receptor of T lymphocytes. To this group of HIV-1 integrase inhibitors belong *complestatin*, first isolated from the mycelium of *Streptomyces lavendulae* SANK 60477, *isocomplestatin*, an axial-chiral isomer of complestatin, *chloropeptin I*, obtained by HCl-catalyzed rearrangement of complestatin, and both *complestatin A* and *complestatin B* possessing oxidized tryptophan instead of tryptophan. The latter two congeners of isocomplestatin have been discovered from cultured broth of *Streptomyces* sp. [I. Kaneko et al., *J. Antibiot.* **1989**, 42, 236; H. Tanaka et al., *J. Antibiot.* **1997**, 50, 58; S. B. Singh et al., *J.*

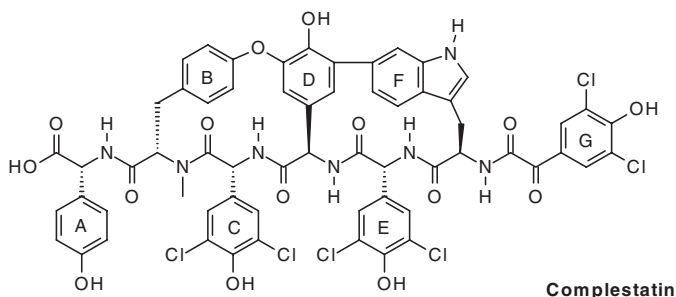
Nat. Prod. **2001**, 64, 874; T. Shinohara et al., *J. Am. Chem. Soc.* **2005**, 127, 7334].

Conantokins, → conotoxins.

Conopeptide, a word derived from the noun peptide that means a peptide from the marine snail genus *Conus* (→ conotoxins) [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

Conopressins, → conotoxins.

Conotoxins, toxic peptides from the venom of marine snails (genus *Conus*) comprising on average 8 to 30 aa residues and a content of Cys between 22 and 50%. The genus *Conus* contains approximately 500 different species of predatory cone snails, each containing its own distinctive, complex and peptide-rich venom. Although small in size, the conotoxins contain many of the structural elements found in larger proteins, including α -helices, β -sheets and β -turns, hence they are often referred to as mini-proteins. Some post-translational modifications have been found in conotoxins, including amidation of the C-terminus, epimerization to a D-amino acid, O-glycosylation of serine and threonine, disulfide formation, γ -carboxylation of glutamic acid, cyclization of glutamine, bromination of tryptophan, sulfatation of tyrosine, and hydroxylation of proline. The different species of sea snails



live on worms, mollusks, and fish. The fish-hunting sea snails bite the fish, and the simultaneously injected toxin quickly paralyzes the prey. It is assumed that there are potentially 50 000 different conotoxins present in the venoms of living species in the genus *Conus*. Conotoxins have been divided into superfamilies (A, T, O, M, P, I, and S), determined by their disulfide bond framework, and further subdivided into classes according to their mode of action. Selected classes of conotoxins are, for example, α -, μ -, χ -, ρ -, δ -, μ O-, κ -, κ M-, γ -, δ -, ψ - and ω -conotoxins, conotoxin K, sleeper-conotoxin, convulsant-conotoxin, and conopressins. α -Conotoxins consisting of 13–20 aa are a class of Cys-enriched peptides occurring in several marine snails from the genus *Conus*. These peptides behave pharmacologically as competitive antagonists of the nicotinic acetylcholine receptor. α -Conotoxins are perhaps the most widespread members of this peptide group so far discovered, and the venom of most *Conus* species is likely to contain several of these. α -Conotoxins (GIA), EC-CNPACGRH¹⁰YSCGKa (disulfide bonds: C²–C⁷/C³–C¹³), and shortened, slightly sequence-altered forms (GI, GII and MI) block postsynaptic cholinergic receptors in neuromuscular connections. μ -Conotoxins belonging to the M-superfamily are Cys-rich 23-peptide amides (GVIIIA, GVIIIB, GVIIIC), and were the first known peptide inhibitors that block muscular Na⁺ channels, causing paralysis and death. ω -Conotoxins belong to the O-superfamily. After injection into mice, they cause shaking and are therefore named also *shaker-peptides*. They block voltage-sensitive Ca²⁺ channels at cholinergic nerve terminals, thus inhibiting the release of acetylcholine. The first δ -conotoxin to be characterized, TxVIA (originally termed “King Kong Peptide”), was isolated

from the venom of the molluscivorous *Conus textile*. The κ -conotoxin class belongs to the O-superfamily. The members of this class contain three disulfide bonds, and were the first conotoxins known to block voltage-gated potassium channels. The μ O-conotoxins belong to the same superfamily and are unusually hydrophobic peptides. χ -Conotoxins are reversible, non-competitive inhibitors of the neuronal noradrenaline transporter, whereas ρ -conotoxins are selective, non-competitive inhibitors of α_1 -adrenoreceptors. All mentioned conotoxins paralyze and kill fish after injection. These peptides have also been used as model systems in neuroscience research. The convulsant-conotoxins containing about 100 residues ($M_r \sim 13$ kDa), and conotoxin K from *Conus magus* (25 aa; three disulfide bridges) are significantly longer, but the CNS effects have not yet been well elucidated. Conopressins are basic 9-peptide amides with structural similarities to \rightarrow vasopressin. Smooth muscle effects result after injection into mice; therefore, they may be involved in the distribution of paralyzing toxins in the guest organism. [Lys⁸]conopressin-G, H-Cys-Phe-Ile-Arg-Asn-Cys-Pro-Lys-Gly-NH₂ (disulfide bond: Cys¹–Cys⁶), and [Arg⁸]conopressin-S, H-Cys-Ile-Ile-Arg-Asn-Cys-Pro-Arg-Gly-NH₂ (disulfide bond: Cys¹–Cys⁶) are typical members of this family. The conantokins (also named “sleeper peptides”) are further peptides with neurotoxic effects from sea snails. The name is derived from the Philippine “antokin”, which means “sleepily”. Conantokin-G (conantokin-GV), H-Gly-Glu-Gla-Gla-Leu-Gln-Gla-Asn-Gln-Gla¹⁰-Leu-Ile-Arg-Gla-Lys-Ser-Asn-NH₂, and the conantokins-T and -GS have been identified. It is assumed that the Gla residues in conantokin-G promote the binding of the receptor on cell membranes. The conantokins-G and -T are antagonists

of the NMDA receptor, which is a subtype of the glutamate receptor. In 2001, Olivera and Cruz reported on the conotoxin story in retrospect. Five years later, an excellent review was published by Armishaw and Alewood [W. R. Gray, B. M. Olivera, *Annu. Rev. Biochem.* **1988**, 57, 665; B. M. Olivera, *J. Comp. Physiol. A* **1999**, 185, 353; H. R. Arias, M. P. Blanton, *Int. J. Biochem. Cell. Biol.* **2000**, 32, 1017; J. L. Dutton, D. J. Craik, *Curr. Med. Chem.* **2001**, 8, 327; B. M. Olivera, L. J. Cruz, *Toxicon* **2001**, 39, 7; C. J. Armishaw, P. F. Alewood, *Curr. Prot. Pept. Sci.* **2005**, 6, 221; R. S. Norton, B. M. Olivera, *Toxicon* **2006**, 48, 780].

Continuous epitope, a peptide sequence used in peptide epitope mapping where the amino acids involved occur consecutively in the sequence.

Continuous-flow mode solid-phase peptide synthesis, a procedure of SPPS using resin-filled columns contrary to the \rightarrow batchwise solid-phase peptide synthesis originally developed by Merrifield. The major advantages lie in the reduced reagent and solvent consumption, and in the very short coupling cycles (for example 1–2 min for TentaGel polymers of size 8 μ m). The reaction progress may be monitored on a real-time basis by recording the conductivity of the solution. Special types of polymeric support with sufficient pressure stability and homogeneous swelling behavior are required [A. Dryland, R. C. Shepard, *J. Chem. Soc., Chem. Commun.* **1986**, 125; R. Frank, H. Gausepohl, in: *Modern Methods in Protein Chemistry*, Volume 3, H. Tschesche (Ed.), de Gruyter, Berlin, **1988**].

Contryphan, H-Gly-Cys-Hyp-D-Trp-Xaa-Trp-Cys-NH₂, unusual peptides containing a distinctive post-translational modification in form of D-Trp or D-Leu isolated from venoms of fish-hunting cone snails.

In the known mature peptides, seven of eight amino acids are conserved. *Contryphan-R* (Xaa = Glu) from the venom of *Conus radiatus*, [*desGly1*]contryphan-R and [6-bromo-Trp]contryphan-R were the first members to be discovered. With *contryphan-Sm* (Xaa = Gln) from *C. stercusmuscarum* and *contryphan-P* (Xaa = Asp) from *C. purpurascens*, two further members from other *Conus* venoms have been characterized. cDNA clones encoding new members from the mollusk-hunting cone snail *Conus textile* were identified and the peptides synthesized: *contryphan-Tx*, H-Gly-Cys-Hyp-D-Trp-Gln-Pro-Tyr-Cys-NH₂, *Leu-contryphan-Tx*, H-Cys-Val-D-Leu-Tyr-Pro-Trp-Cys-NH₂, and *contryphan R/Tx*, which is identical to contryphan-R. The contryphanes show a remarkable sequence conservation, in contrast to the multiply disulfide-bonded \rightarrow conotoxins [R. Jacobsen et al., *J. Peptide Res.* **1998**, 51, 173; E. C. Jimenez et al., *Toxicon* **2001**, 39, 803].

Convergent solid-phase peptide synthesis (CSPPS), the \rightarrow convergent synthesis on polymeric support. This strategy requires some modification of the chemistry, since linear SPPS usually provides the free peptide. Hence, the first stage of CSPPS is the linear SPPS of the various protected peptide segments corresponding to the sequence of the target molecule, but procedures are required for detachment of the protected segment from the polymeric support. A high degree of compatibility between the protecting groups of the segment and the peptide resin anchorage is of particular interest in this respect. The assembly of segments to produce the target molecule can be performed both in the C \rightarrow N and N \rightarrow C directions, or it may start in a middle region and proceed in both directions. However, until now

the C→N strategy has been the preferred method [P. Athanassopoulos et al., in: *Solid Phase Synthesis and Combinatorial Libraries*, R. Epton (Ed.), Mayflower Scientific, Birmingham, 1996, 243].

Convergent synthesis, *segment condensation*, *fragment condensation*, defined as the construction of the target structure by final assembly of separately synthesized intermediate segments.

Copeptin, 39-glycopeptide, the C-terminal part of provasopressin (→ vasopressin). Although the function of copeptin is unknown, it may be involved in the intracellular processing of the propeptide by stabilizing the correct conformation during proteolytic maturation. A new assay for quantifying AVP release based on measurement of copeptin has been developed [C. Barat et al., *Biochemistry* 2004, 43, 8191; J. Struck et al., *Peptides* 2005, 26, 2500; N. G. Morgenthaler et al., *Clin. Chem.* 2006, 52, 112].

Corazonin, <ETFQYSRGWT¹⁰Na, a cardioexcitatory 11-peptide amide from the *corpora cardiaca* (CC) of the American cockroach, *Periplaneta americana*. CC store and release neurohormones that are produced in neurosecretory cells of the CNS. Corazonin plays a role in molting, ecdysis, and adult development, and is implicated in circadian rhythm and diapause of insects. [His⁷]corazonin is capable of inducing dark pigmentation in an albino locust strain, while [Thr⁴,His⁷]corazonin has been isolated from the honey bee *Apis mellifera*. Recent comprehensive peptide screening by mass spectrometry provides a general idea of the occurrence of corazonin forms in insects [R. Predel, *Peptides* 2007, 28, 3].

Core sequences, → truncated sequences of a target peptide on the polymeric support caused by incomplete conversion in SPPS.

Corin, a type II transmembrane serine protease linked to the processing of proANP (→ atrial natriuretic peptide) and proBNP [W. Yan et al., *Proc. Natl. Acad. Sci. USA* 2000, 97, 8525].

Corticoliberin, *corticotropin-releasing hormone*, **CRH**, *corticotropin-releasing factor*, **CRF**, SEEPPI¹⁰SLDL¹⁰TFHLLREVLE²⁰MARAEQLAQ³⁰AHSNRKLMEI⁴⁰Ia (human, rat CRH), a 41-peptide amide expressed throughout the CNS and in peripheral tissues playing diverse roles in physiology, behavior, and development. CRH is the central trigger of the hypothalamic-pituitary-adrenal axis and, together with the related peptides urocortin 1, 2, and 3 (→ urocortins, Ucn), it is involved in the regulation of behavioral, endocrine, autonomic, cardiovascular, reproductive, metabolic, gastrointestinal and immune systemic activities. CRH and the urocortins comprise the CRH family. CRH stimulates the synthesis and release of → proopiomelanocortin and its processing to adrenocorticotropin (ACTH), and also functions as thyrotropin-releasing factor in non-mammalian species. In vertebrates exist four paralogous genes that encode CRH, urocortin/urotensin 1, urocortin 2, or urocortin 3, comprising the CRH family. CRH is formed in the neurons of the hypothalamus, and delivered to the adenohypophysis via a direct circulatory connection. Besides nerve fibers, corticoliberin has also been found, for example, in the pancreas, adrenal medulla, placenta, stomach, testes and in the tissues of ACTH-producing tumors. CRH is also produced in skin depending on species and anatomical location. This local production is regulated by ultraviolet radiation, glucocorticoids and phase of the hair cycle. Generally, the actions of CRH and

related peptides are mediated through the seven-transmembrane domain, G protein-coupled CRH receptor subtypes 1 and 2 (CRF₁ and CRF₂). It has been followed from *in vitro*-binding studies that r/hCRH and oCRH both exhibit preferential affinity to CRF₁, whereas Ucn 1 displays equally high affinity for both receptor subtypes. Human/mouse Ucn 2 shows a binding affinity equal to Ucn 1 at the CRF₂ but very low affinity at CRF₁. Ucn 3 shows the highest degree of potency in binding to CRF₂, but is less potent than mUcn 2 in activating adenylate cyclase in cells expressing endogenous CRF_{2(b)} receptors. Selective CRH agonists and antagonists are powerful tools for studying the CRH receptor subtype mediating the physiological responses to exogenous and endogenous CRH and CRH-related peptides. CRH can be used as a diagnostic aid for hypophyseal function. Furthermore, CRH has been implicated in the onset of pregnancy, the "fight or flight" response, and also many physiological disorders. Even though the earliest actions of these peptides may have been connected with osmoregulation and diuresis, physiological effects associated with stress and anxiety, thermoregulation, vasoregulation, growth and metabolism, metamorphosis and reproduction have been established in various vertebrate species [W. Vale et al., *Science* **1981**, 213, 1394; A. J. Dunn, C. W. Berridge, *Brain Res. Rev.* **1990**, 15, 71; J. Gulyas et al., *Proc. Natl. Acad. Sci. USA* **1995**, 92, 10575; K. D. Dieterich et al., *Clin. Endocrinol. Diabetes* **1997**, 105, 65; K. Eckart et al., *Curr. Med. Chem.* **1999**, 6, 1035; D. A. Lovejoy, R. J. Balment, *Gen. Comp. Endocrinol.* **1999**, 115, 1; M. H. Perrin, W. Vale, *Ann. N. Y. Acad. Sci.* **1999**, 885, 312; P. A. Keller et al., *Bioorg. Med. Chem.* **2000**, 8, 1213; F. M. Dautzenberg, R. L. Hauger, *Trends Pharmacol. Sci.* **2002**, 23, 71; A. Slominski et al., *Front. Biosci.* **2006**,

11, 2230; G. C. Boorse, R. J. Denver, *Gen. Comp. Endocrinol.* **2006**, 146, 9].

Corticostatins, *corticostatin I*, CSI, GI CACRRRFC¹⁰PNSERFSGYC²⁰AVNGARY VRC³⁰CSRR (disulfide bonds: C⁵–C²⁰/C¹⁰–C³⁰/C³–C³¹), a 34-peptide with a high content of Arg and Cys first isolated from rabbit fetal and adult lung. It inhibits the → corticotropin-stimulated formation of corticosterone by rat adrenal cells *in vitro*. Later, seven cationic peptides of 29 to 32 aa (R-1, R-1a, R-1b, R-2, R-3, R-4, and R-5) that belong to the corticostatin/defensin family of leukocyte-derived peptides were isolated from extracts of rat bone marrow. These participate in oxygen-independent killing of phagocytosed bacteria. A corticostatin/defensin-like peptide (RK-1, 32 aa) has been also isolated from the kidney [Q. Zhu et al., *Proc. Natl. Acad. Sci. USA* **1988**, 85, 592; D. Belcourt et al., *Regul. Pept.* **1992**, 40, 87; A. Bateman et al., *J. Biol. Chem.* **1996**, 271, 10654].

Corticotropin, *adrenocorticotropin*, *adrenocorticotrophic hormone*, **ACTH**, SYSME HFRWG¹⁰KPVGKKRRPV²⁰KVYPNGAE DE³⁰SAEAFPLEF, a 39-peptide hormone formed as a proteolytic cleavage product of proopiomelanocortin (POMC) in the adenohipophysis. The N-terminal sequence 1–13 is identical to that of α-MSH (→ melanotropin). Corticotropin is the key mediator of pituitary-dependent regulation of adrenal steroidogenesis. ACTH is synthesized in response to stimulation by → corticoliberin, and stress. An opposite action in the sense of a corticostatin is exerted by the → corticotropin release-inhibiting factor. In the adrenal cortex, ACTH stimulates a Ca²⁺-dependent process of the synthesis of glucocorticoids and mineralocorticoids. According to a proposal of Schwyzer, the partial sequence 11–18 is the receptor binding region, while

termed as “address” sequence 5–10 is the active site (“message”), the N-terminal tripeptide is the “amplifier”, and the C-terminal fragment 25–39 (“envelope”) is responsible for the antigenicity and transport. The species specificity is mainly located in the sequence 31–33. In porcine ACTH, Ser³¹ is substituted by Leu, whereas bovine and ovine ACTH is characterized by Gln³³ instead of Glu. With regard to *in-vitro* corticosteroid-releasing activity, ACTH-(1–24) shows higher activity than native ACTH. ACTH binds to its cognate receptor, the melanocortin 2 receptor (MC2-R), that activates several pathways, including protein kinase A, protein kinase C, MAP kinases and phospholipase C, as well as calcium channels. The MC2-R-dependent pathways have been implicated in the regulation not only of steroidogenesis but also of adrenocortical growth, differentiation, and tumorigenesis. Native ACTH and active analogues are used as a diagnostic aid for adrenal cortex function, and also as therapeutic agents in the treatment of several disorders, such as insufficient function of the adrenal cortex, multiple sclerosis, collagen diseases, inflammatory rheumatic diseases, radicular pain syndrome, etc. Recently, it has been reported that ACTH-(1–24) inhibits the proliferation of adrenocortical tumors *in vivo* [L. Proulx et al., *J. Endocrinol. Invest.* **1984**, 7, 257; K. J. Mountjoy et al., *Science* **1992**, 257, 1248; N. Gallo-Payet, M. D. Payet, *Microsc. Res. Tech.* **2003**, 61, 275; O. Zwermann et al., *Eur. J. Endocrinol.* **2005**, 153, 435].

Corticotropin release-inhibiting factor (CRIF), FIDPELQRSW¹⁰EEKEGEGVLM²⁰ PE, a 22-peptide from the cryptic region of the prepro-thyrotropin releasing hormone (→ thyroliberin) assumed to fulfill the criterion of the endogenous CRIF. It corresponds to the partial sequence

prepro-TRH-(178–199). CRIF inhibits basal and corticoliberin-stimulated corticotropin synthesis and secretion in cultured primary anterior pituitary cells [E. Redei et al., *Ann. N. Y. Acad. Sci.* **1998**, 840, 456; D. Engler et al., *Endocr. Rev.* **1999**, 20, 460].

Corticotropin-releasing hormone, → corticoliberin.

Corticotropin-releasing hormone (CRH) family, a family of related peptides comprising → corticoliberin and the → urocortins.

Cortistatin (CST), a cyclic neuropeptide related to → somatostatin released from prepro-cortistatin. It is named after its predominantly cortical expression and ability to depress cortical activity. The rat precursor protein is predicted to have 112 residues with a striking sequence homology to somatostatin at its distal C-terminal end. After removal of the 27 aa signal sequence, procortistatin could be further cleaved to rCST-29, rCST-14, PCKNFFWKTF¹⁰SSCK (disulfide bond: C²–C¹³) and additional products by further cleavage. CST-29 and CST-14 show close similarities to the analogous → somatostatin (SST) peptides, such as SST-28 and SST-14. CST-14 shares 11 of the 14 residues of SST-14, despite being the products of separate genes. Furthermore, CST has also been cloned from humans, and mouse sources. CST is capable of binding to all five cloned somatostatin receptors, and shares many pharmacological and functional effects with SST, including the depression of neuronal activity and inhibition of cell proliferation. In addition, it shows many effects distinct from SST, such as the induction of slow-wave sleep, reduction of locomotor activity, and activation of cation-selective currents. Recently, it has been reported that CST acts as an

anti-inflammatory peptide with therapeutic action on both lethal endotoxemia and inflammatory bowel disease (IBD) [L. de Lecea et al., *Nature* **1996**, 381, 242; A. D. Spier, L. de Lecea, *Brain Res. Rev.* **2000**, 33, 228; E. Gonzalez-Rey et al., *J. Exp. Med.* **2006**, 203, 563].

COSY, correlated spectroscopy.

Coupling reaction, \rightarrow peptide bond formation.

Coupling reagents, *peptide coupling reagents*, reagents suitable for \rightarrow peptide bond formation. In 1903, Emil \rightarrow Fischer started peptide bond formation with the introduction of the acid chloride method. Since that time a plethora of methods have been developed because an ideal, universally applicable coupling reagent for chemical formation of the peptide bond has still not been found. Activation of the carboxy component is achieved by the introduction of electron-accepting moieties, such as groups which exert either an inductive (-I) effect or mesomeric (-M) effect (or both), decreasing the electron density at the C=O group and thereby favoring the nucleophilic attack of the amino component. For the coupling of a reactive carboxy component with an amino component to produce a peptide, different methods are available. An acylating agent can be generated *in situ* from the carboxy component in the presence of the amino component by the addition of an activating or coupling agent. Alternatively, a reactive acylating agent is formed from the carboxy component in a separate step, followed by intermediate treatment with the amino component, or an intermediate acylating agent is formed, isolated and then subjected to aminolysis. During peptide bond formation, difficulties such as low yields, racemization, difficult purification,

and degradation are very often observed. To overcome these problems, numerous mild coupling reagents and procedures have been developed that not only are high-yielding but also potentially help to prevent \rightarrow racemization, including racemization suppressants. Classical methods involving \rightarrow acyl halides, \rightarrow anhydrides, \rightarrow acyl azide method, \rightarrow carbodiimide/additive method, etc. are still largely used, whereas the predominance of \rightarrow active ester, the classical \rightarrow carbodiimide method has been gradually replaced with the so-called onium salts. HOBt- and HOAt-based \rightarrow uronium, \rightarrow phosphonium and \rightarrow immonium reagents should be mentioned in this respect. At present, peptides are routinely synthesized on solid supports using automated systems. Especially, in multiple parallel synthesizers, the requirements for coupling reagents differ from those normally used in SPPS. Surprisingly, it was not uronium and phosphonium salt-based reagents but rather diisopropylcarbodiimide that was found to be the optimal reagent, based on the purity of the product, stability of the reagent, and convenience of handling on the plate-based, multiple parallel centrifugation synthesizer [S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, 60, 2447; C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, 61, 10827; J. Hachmann, M. Lebl, *Biopolymers (Pept. Sci.)* **2006**, 84, 340].

Cpa, 4-chlorophenylalanine.

CPD, carboxypeptidase.

cPe, cyclopentyl.

CPP, cell-penetrating peptides.

CPS, convergent peptide synthesis.

Crabolin, FLPLILRKIV¹⁰TALA, a 13-peptide amide from the venom of European hornet. It lacks any lytic activity against cells

and shows only minor mammalian toxicity [A. Argiolas, J. J. Pisano, *J. Biol. Chem.* **1984**, 259, 10106; R. C. Hider et al., *Endeavour, New Series* **1988**, 12, 60].

Crambin, a 46-peptide isolated from *Crambe abyssinica* (Abyssinian cabbage) belonging to a large family of \rightarrow thionins expressed differentially in different tissues of this organism. Crambin is non-toxic because it lacks crucial amino acid residues that were suggested to be necessary for membrane activity. Crambin has an $\alpha + \beta$ architecture consisting of a short β -sheet and two α -helices [F. Ponz et al., *Eur. J. Biochem.* **1986**, 156, 131; G. Schrader-Fisher, K. Apel, *Mol. Gen. Genet.* **1994**, 245, 380].

CREC family, a group of multiple EF-hand, low-affinity Ca^{2+} -binding proteins involved in the secretory pathway of mammalian cells. Until now, this family is known to comprise reticulocalbin, ERC-55/TCBP-49/E6BP, Cab45, calumenin, and crocalbin/CBP-50. In addition, similar proteins are found in quite diverse invertebrate organisms, e.g., DCB-45, and SCF in *Drosophila melanogaster*, SCF in *Bombyx mori*, CCB-39 in *Caenorhabditis elegans*, and Pfs40/PfERC in *Plasmodium falciparum*. The proteins of this family show rather low Ca^{2+} affinity, with K_d around 10^{-4} – 10^{-3} M, and may participate in Ca^{2+} -regulated activities. There is evidence that some family members are involved in pathological activities, for example, in malignant cell transformation, putative participation in amyloid formation, and in mediation of the toxic effects of snake venom toxins [B. Honore, H. Vorum, *FEBS Lett.* **2000**, 466, 11].

CRF, corticotropin-releasing factor.

CRIF, corticotropin release-inhibiting factor.

Cripto, teratocarcinoma-derived growth factor, **TDGF**, a epidermal growth factor (EGF)-related peptide involved in mammary gland development and neoplasia. **CR-1** (**TDGF-1**) was isolated and sequenced from a human NTERA2/D1 embryonal carcinoma cDNA expression library, whereas the mouse homologue, *Cr-1* (*tdgf-1*) was isolated from a F-9 mouse embryonal carcinoma cDNA expression library. Cripto induces branching morphogenesis in mammary epithelial cells both *in vitro* and *in vivo*, and inhibits the expression of various milk proteins [L. Panico et al., *Int. J. Cancer* **1996**, 65, 51; D. S. Salomon et al., *BioEssays* **1999**, 21, 61].

CRL, cerulein.

Cropeptide, *cropeptide W*, a word derived from the noun peptide that means in cosmetic and toiletry formulations a hydrolysis product of wheat which is used in lotions, shampoos, etc., and which is said to have moisturizing properties [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

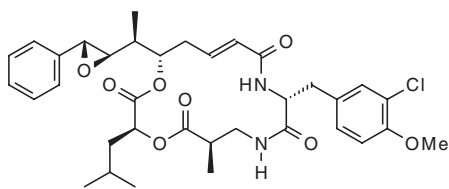
Crotamine (Crt), YKQCHKKGGH¹⁰CFPKEKICLP²⁰PSSDFGKMDC³⁰RWRWKCCKKK⁴⁰GS, a myotoxic 42-peptide from the South American rattlesnake *Crotalus durissus terificus*. Crt belongs to the \rightarrow β -defensin-fold family. It has been reported that Crt can rapidly penetrate into different cell types and mouse blastocysts *in vitro* acting as a novel \rightarrow cell-penetrating peptide [C. J. Laure et al., *Hoppe-Seyler's Z. Physiol. Chem.* **1975**, 356, 213; A. M. Torres et al., *Toxicon* **2004**, 44, 581; A. Kerkis et al., *FASEB J.* **2004**, 18, 1407].

Crowfoot-Hodgkin, Dorothy, (1910–1994), English chemist and winner of the Nobel Prize in Chemistry 1964 for her determinations of the structures of important biochemical compounds by X-ray crystallography. She read Chemistry at Sommerville College, Oxford, where she began research in X-ray crystallography, but later transferred to Cambridge to work with J. D. Bernal, and received her Ph.D. After her return to Oxford, where she was to remain throughout her career, she determined the crystal structure of penicillin in 1945, followed by vitamin B₁₂ in 1954, and \rightarrow insulin in 1969. For her achievements, she was awarded the Order of Merit in 1965, a Fellow of the Royal Society, and Chancellor of Bristol University from 1970 to 1988 [G. Ferry, *Dorothy Hodgkin: A Life*, Granta Books, London, 1998].

Crustacean cardioactive peptide (CCAP), H-Pro-Phe-Cys-Asn-Ala-Phe-Thr-Gly-Cys-NH₂, a 9-peptide amide first identified in the shore crab, *Carcinus maenas*. In the meantime, CCAP has been identified in many insect species. It stimulates the release of \rightarrow adipokinetic hormone from the *corpus cardiacum* of locusts *in vitro*. Furthermore, it is thought to be a mediator in the neuronal pathway leading to the ecdysis behavior [J. Stangier et al., *Peptides* **1988**, 9, 795; D. Veelaert et al., *Endocrinology* **1997**, 138, 138].

c-RW, cyclo-(-Arg-Arg-Trp-Trp-Arg-Phe-), an antimicrobial, cationic cyclopeptide. Based on NMR studies, c-RW has a rather flexible but ordered structure in water, and a distinct structure is formed when c-RW is bound to a detergent micelle [C. Appelt et al., *ChemBioChem* **2005**, 6, 1654].

Cryptophycins (Crp), a family of cyclodepsipeptides (\rightarrow depsipeptides) isolated from the blue-green algae (cyanobacterium) *Nostoc* sp. They are comprised of a 16-membered macrocycle including tyrosine, leucine, and polypropionate units. The side chains of the cyclodepsipeptides contain either an epoxide or an olefin. Cryptophycin-1 exhibited extremely potent activity against filamentous fungi of the genus *Cryptococcus*, leading to the name of this family. Cryptophycin-1 shows significant tumor-selective cytotoxicity. Treatment of tumor cells with cryptophycin 1 in picomolar concentrations quickly leads to morphological changes of the cells, and to apoptosis. The cysteine protease caspase 3, an apoptosis effector, is being activated. Mitotic arrest is observed in the presence of low concentrations of cryptophycin 1 and abnormal mitotic spindles are formed. Cryptophycin 1 binds to tubulin and not only inhibits irreversibly tubulin polymerization, but also depolymerizes microtubuli *in vitro*. The binding site overlaps somewhat with the binding site of the vinca alkaloids, but differs from that of colchicine. Mainly, cryptophycin 1 is therapeutically active against a series of multidrug-resistant tumors. The activities of cryptophycin 1 and taxol are comparable. More than 25 compounds of the cryptophycin family have been reported by isolation. It was shown that cryptophycin-24 is identical with \rightarrow arenastatin [R. E. Moore et al., *Curr. Pharm. Design* **1996**, 2, 317; K. Morita et al., *Biol. Pharm. Bull.* **1997**, 20, 171; M. J. Eggen,



Cryptophycin-1

G. I. Georg, *Medicinal Res. Rev.* **2002**, *22*, 85; Z. Q. Beck et al., *Biochemistry* **2005**, *44*, 13457; S. Eißler et al., *Synthesis* **2006**, 3747].

CsA, cyclosporin A.

CSF, colony-stimulating factor.

CSPPS, convergent solid-phase peptide synthesis.

CST, cortistatin.

CT, calcitonin.

C-terminal end group analysis, determination of the C-terminal amino acid residue of a peptide or protein. The analysis can be performed chemically by the → Aka-abori method, or enzymatically by the carboxypeptidase (CP) approach. CP with different specificities are capable of liberating C-terminal amino acids.

C-terminal peptide α -thioester, mildly activated peptide ester acting as a valuable key intermediate for the synthesis/semi-synthesis of polypeptides and proteins by both → chemical ligation and the → Aimoto thioester approach. The synthesis of the peptide α -thioester (→ thioester) can be performed by standard SPPS using Boc- or Fmoc-based chemistry or, for larger target polypeptides, by application of intein-based bacterial expression systems. Peptide α -thioester synthesis can also be carried out based on an N-S acyl shift reaction mediated by a thiol ligation auxiliary [F. B. Perler, E. Adams, *Curr. Opin. Biotechnol.* **2000**, 377; D. Swinnen, D. Hilvert, *Org. Lett.* **2000**, *2*, 2439; R. Quaderer, D. Hilvert, *Org. Lett.* **2001**, *3*, 3181; T. W. Muir, *Annu. Rev. Biochem.* **2003**, *72*, 249; T. Kawakami et al., *Tetrahedron Lett.* **2005**, *46*, 8805; J. A. Camarero, A. R. Mitchell, *Prot. Pept. Lett.* **2005**, *12*, 723].

C-type natriuretic peptide (CNP), GLSKGCF GLK¹⁰LDRIGSMSGL²⁰GC (pCNP, disulfide bond: C⁶–C²²), a 22-peptide that belongs to the → natriuretic peptides (ANP, BNP). The natriuretic activities of CNP are smaller compared with those of ANP and BNP. CNP does not occur practically in the blood circulation, but it has been detected in the vascular endothelium, kidney, intestinal tract and the cerebrospinal fluid, where it fulfills endocrine functions. Porcine prepro-CNP contains 126 residues. After cleavage, the Ala²³–Lys²⁴ bond results in proCNP (103 aa) that is converted proteolytically into the native 22-peptide CNP [T. Sudoh et al., *Biochem. Biophys. Res. Commun.* **1990**, *168*, 863; S. Suga et al., *Endocrinology* **1992**, *130*, 229; G. McDowell et al., *Eur. J. Clin. Invest.* **1995**, *25*, 291; R. C. Fowkes, C. A. McArdle, *Trends Endocrinol. Metab.* **2000**, *11*, 333; M. Forero McGrath et al., *Trends Endocrinol. Metab.* **2005**, *16*, 469].

Culicinins, a group of linear 10-peptides isolated from the fermentation broth of the entomopathogenic fungus *Culicino-mycetes claviformis* (strain LL-121252). Among the culicinins A–D, the major component *culicinin D* exhibits selective inhibitory activity against PTEN-negative MDA468 breast tumor cells versus PTEN-positive MDA468 cells. This antitumor peptaibol (→ peptaibols) contains eight known amino acids: Leu (2), Pro, 3-aminopropionic acid, 2-aminoisobutyric acid (3), and 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid [H. He et al., *J. Nat. Prod.* **2006**, *69*, 736].

Curtius, Theodor, (1857–1928), professor of chemistry at various German universities, last of all he succeeded Victor Meyer at the old university Heidelberg, where he started his studies of chemistry with Robert

Bunsen. Later, Curtius worked with Hermann Kolbe at Leipzig University and received his Ph.D in 1882 therein. During these studies he performed the first chemical synthesis of a protected peptide (Bz-Gly-Gly-OH), and in 1902 developed the \rightarrow acyl azide method. Together with Emil \rightarrow Fischer, he pioneered peptide synthesis.

Curvacin A, ARSYGNGVYC¹⁰NNKKCWVNRG²⁰EATQSIIGGM³⁰ISGWASGLAG⁴⁰M, a membrane-permeabilizing 41-peptide belonging to the pediocin-like peptides (class IIa bacteriocins). Curvacin A has anti-*Listeria* activity, and kills target cells by permeabilizing the cell membrane [P. S. Tichaczek et al., *Syst. Appl. Microbiol.* **1992**, *15*, 460; H. S. Haugen et al., *Biochemistry* **2005**, *44*, 16149].

Cy, cyclohexyl.

Cya, cysteic acid.

Cyanobacterial peptides, oligopeptides synthesized by cyanobacteria showing a high structural diversity. Until now, more than 600 peptides are known which can be classified based on the molecular structure, irrespective of the original source of individual congeners. The majority of these peptides are of non-ribosomal origin. Main classes of cyanobacterial peptides (selected synonyms in brackets) are \rightarrow *aeruginosins* (microcin, spumigin), \rightarrow *microginins* (cyanostatin, oscillaginin, nostoginin), \rightarrow *anabaenopeptins* (oscillamide, keramanide, konbamide, mozamide, schizopeptin), \rightarrow *cyanopeptolins* (aeruginopeptin, anabaenopeptilide, dolostatin, hofmannolin, nostopeptin), \rightarrow *microcystins* (motuporin, nodularin), \rightarrow *microviridins*, \rightarrow *cyclamides* (bistratamide, dendroamide, microcyclamide, nostocyclamide, obyanamide). A comprehensive review on the biosynthesis, the structural diversity within peptide classes and po-

tential functions has been published [M. Welker, H. von Döhren, *FEMS Microbial Rev.* **2006**, *30*, 530].

Cyanopeptolins, a family of cyclodepsipeptides (\rightarrow depsipeptides) and a main class of \rightarrow cyanobacterial peptides from *Microcystis*, *Planktothrix*, and *Nodularia*. *Cyanopeptolin S* was isolated from a water bloom of *Microcystis* sp. in the Auensee/Leipzig region of Germany. It contains, besides Arg, Thr, Ile, MePhe, a L-glutamic acid-delta-aldehyde ring system and a sulfated D-configured glyceric acid as a side chain. Cyanopeptolin S inhibits trypsin. *Cyanopeptolins A–D* were isolated from the cyanobacterium *Microcystis* sp. PCC 7806 containing Leu, Val, Thr, Asp, cyclic L-glutamic acid-gamma-aldehyde, hexanoic acid, and a variable basic amino acid (A: Arg; B: Lys; C: N^εMeLys; D: N^εMe₂Lys). *Hofmannolin* is a cyanopeptolin from *Scytonema hofmanni* PCC 7110. O-methylated tyrosine forming the sixth moiety from the amino terminus, and the blocked N-terminus by 2-hydroxy-3-methyl-valeric acid, are the two special features which distinguish hofmannolin from other members of this family. *Cyanopeptolin 963A* was isolated from an axenic strain of the toxic freshwater cyanobacterium *Microcystis* PCC 7808 acting as chymotrypsin inhibitor [M. C. Oberer et al., *J. Antibiot.* **1993**, *46*, 1550; C. Jakobi et al., *FEMS Microbiol. Lett.* **1995**, *129*, 129; U. Matern et al., *Phytochemistry* **2003**, *64*, 1061; B. Bister et al., *J. Nat. Prod.* **2004**, *67*, 1755].

Cyclamides, main class of \rightarrow cyanobacterial peptides. As verified in *nostocyclamide*, a typical peptide of this family, thiazole/oxazole units occur in alternation with unmodified amino acids forming a cyclic 6-peptide. The first peptides of this class are the \rightarrow bistratamides [A. K. Todorova et al., *Org. Chem.* **1995**, *60*, 7891; M. Welker, H.

von Döhren, *FEMS Microbiol. Rev.* **2006**, *30*, 530].

Cyclic peptides, *cyclopeptides*, macrocycles composed of amino acids occurring in different ring size. Formally, cyclic peptides are created upon formation of a peptide bond between the amino and carboxy termini of a linear peptide, and have been termed as homodetic cyclic peptides. However, cyclic peptides can also contain disulfide-, thioether-, ether- and amide-linked bridges of side-chain functionalities (\rightarrow bridged peptides, \rightarrow branched peptides). Cyclic peptides which contain ester (depside) bonds as part of the backbone, and also include the side-chain functionalities of Ser and Thr and the main backbone carboxyl functions (macrocyclic lactones), belong to the \rightarrow depsipeptides. Those cyclic peptides are also termed heterodetic cyclic peptides. Cyclic peptides have been found in many natural environments, and exhibit a wide spectrum of biological activity. The synthesis of cyclic peptides (\rightarrow cyclization reaction) has been initiated from the need for structural proof of natural compounds, and the synthesis of more active analogues. Furthermore, cyclization of the critical binding motifs of peptides has proven to be a useful strategy to gain information on the three-dimensional structure of a peptide ligand while bonded to its receptor [S. A. Kates et al., in: *Peptides: Design, Synthesis, and Biological Activity*, C. Basawa, G. M. Anantharamaiah (Eds.), Birkhäuser, Boston, **1994**, 39].

Cyclization reaction, approach to the synthesis of \rightarrow cyclic peptides. Cyclization reactions comprise backbone cyclization (head-to-tail cyclization), side chain-to-side chain ring closure, side chain-to-head and

tail-to-side chain cyclization. Head-to-tail cyclizations of small to mid-sized linear oligomers are usually not impeded by sequence-specific problems. They may be synthesized by solution- or solid-phase methods (or by a combination of these), where a linear sequence is synthesized on polymeric support and cyclization is performed in solution after cleavage from the resin. The side-chain-protecting groups are cleaved in the final step. The major obstacles of classical cyclization reactions in solution (cyclo-oligomerization and cyclo-dimerization) must be avoided by high dilution. A viable route towards cyclic peptides comprises the assembly and cyclization of a peptide while it is still bound to the resin. The so-called pseudo-dilution-, a kinetic phenomenon favoring intramolecular reactions of resin-bound peptides over intermolecular side reactions of resin-bound peptides, – presents a major advantage, provided that the resin loading is not too high. One precondition for on-resin cyclization is attachment of the first amino acid to the polymeric support via a side-chain functional group. Such types of cyclization reaction can be performed using orthogonal protecting groups such as Fmoc/*tert*-butyl/allyl type. Peptide cyclization with simultaneous cleavage from safety-catch resin experienced a further renaissance in this field. During the course of this process, the linker moiety is activated so that the bound peptide is able to undergo intramolecular aminolysis [U. Schmidt, *Pure Appl. Chem.* **1986**, *58*, 295; V. J. Hruby et al., *Biochem. J.* **1990**, *268*, 249; C. Blackburn, S. A. Kates, in: *Methods in Enzymology, Solid-Phase Peptide Synthesis*, G. B. Fields (Ed.), Academic Press, Orlando, **1997**, Volume 289, 175; J. N. Lambert et al., *J. Chem. Soc. Perkin Trans. I* **2001**, 471; J. S. Davies, *J. Peptide Sci.* **2003**, *9*, 471].

Cyclolithistide A, a cyclodepsipeptide (\rightarrow depsipeptides) isolated from the marine sponge *Theonella swinhoei*. It contains seven known amino acids beside the unique building blocks 4-amino-3,5-dihydroxyhexanoic acid, formyl-leucine, and chloroisoleucine. Cyclolithistide A exhibits potent antifungal activity [D. P. Clark et al., *J. Org. Chem.* **1998**, 63, 8757].

Cyclopeptides, \rightarrow cyclic peptides.

Cyclophilins, a highly conserved family of \rightarrow peptidyl prolyl *cis/trans* isomerases present in organisms from archaea to humans. Human cyclophilin 18 (also known as cyclophilin A) represents the prototypic enzyme that bears the catalytic activity. In other cyclophilins various functional domains complement the catalytic domain, leading to proteins with molecular masses up to 358 kDa. The cytosolic human Cyp18 is an abundant protein with about 18 μ g per mg total protein in kidney tubules. The alignment of amino acid sequences of cyclophilins defines residues that have a near-perfect conservation locating in the central region of the catalytic domain (-Phe-His-Arg-Ile/Val-Ile-(Xaa)₅-Gln-Gly-Gly- and -Met-Ala-(Xaa)₉₋₁₀-Gly-Phe-Phe/Tyr-Ile/Val-). The three-dimensional structure of Cyp18 shows an eight-stranded antiparallel β -sheet barrel capped by short α -helices. Cyclophilins have high affinity to \rightarrow cyclosporin A in the low nanomolar range of dissociation constants. Complex formation leads to inhibition of peptidyl prolyl *cis/trans* isomerase activity. In the cytosol, the complex made up from cyclophilin and cyclosporin A recruits protein phosphatase 2B (\rightarrow calcineurin). This interaction is inhibitory in a non-competitive manner for the protein phosphatase activity of calcineurin [J. Fanghanel, G. Fischer, *Front. Biosci.* **2004**, 9, 3453].

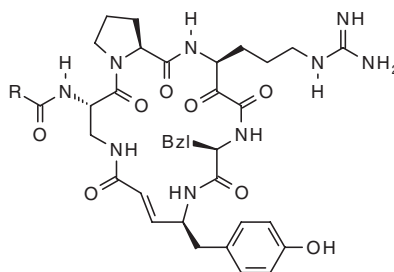
Cyclosporins, a group of homodetic cyclic peptide antibiotics with the representative member **cyclosporin A**, **CsA**, cyclo-(-MeBmt¹Abu-Sar-MeLeu-Val⁵-MeLeu-Ala-D-Ala-MeLeu-MeLeu¹⁰-MeVal-), produced by the fungus *Beauveria nivea* (previously named *Tolypocladium inflatum*). CsA exhibits a remarkable spectrum of various biological activities, including antifungal, antiviral, antiparasitic, anti-inflammatory, as well as immunosuppressive activities. It is a highly effective agent for the treatment of autoimmune disorders and for preventing organ-transplant rejection. Until now, CsA has been the main component of 25 naturally occurring cyclosporins that differ in the basic primary structure of CsA by amino acid substitutions in positions 1, 2, 4, 5, 7, and 11. In addition, unmethylated peptide bonds have been found in positions 1, 4, 6, 9, 10, and 11. The first total chemical synthesis was described by Wenger in 1984, but since then several hundred CsA analogues have been chemically synthesized. The biosynthesis in *Beauveria nivea* is accomplished by the multienzyme cyclosporin synthetase, which is the largest integrated enzyme structure so far known, catalyzing about 40 reaction steps including the final assembly of the undecapeptide chain of CsA and its cyclization. By *in-vitro* synthesis, many new analogues of CsA became available which exerted remarkable immunosuppressive activity *in vitro*. CsA inhibits the activity of the \rightarrow peptidyl prolyl *cis/trans* isomerase (PPIase) cyclophilin (M_r 17.7 kDa), a cytosolic CsA-binding protein. The immunosuppressive property of CsA is based on the ability of its complex with cyclophilin to prevent the expression of genes involved in the activation of T lymphocytes by interfering with the appropriate intracellular signaling pathways. In principle, the clinical use of CsA is

limited because of poor aqueous solubility, associated with very important adverse side effects. Since oral or parenteral formulation forms result in CsA being distributed widely throughout the body, the development of alternative dosage forms which deliver the drug specifically to the target site is needed. Water-soluble prodrugs of CsA with tailored conversion rates have been developed [R. M. Wenger, *Helv. Chim. Acta* **1984**, 67, 502; J. Kallen et al., *Cyclosporins: Recent Developments in Biosynthesis, Pharmacology and Biology, and Clinical Applications*, in: *Biotechnology, a Multi-Volume Comprehensive Treatise* (H.-J. Rehm et al., Eds.), **1997**, Volume 7, 535–591; C. J. Dunn et al., *Drugs* **2001**, 61, 1957; A. R. Hamel et al., *J. Peptide Res.* **2004**, 63, 147; H. Cho, Y. Chung, *Arch. Pharm. Res.* **2004**, 27, 662; A. R. Hamel et al., *J. Peptide Sci.* **2005**, 65, 364].

Cyclosporin synthetase, → cyclosporins.

Cyclotheonamides, cyclopeptides from the sponge *Theonella* with strong inhibitory activity against → thrombin and other serine proteases. They are members of the → vinylogous peptides. Cyclotheonamide A and B contain, beside vinylogous tyrosine, the non-proteinogenic amino acid β -amino- α -oxohomoarginine [N. Fusetani et al., *J. Am. Chem. Soc.* **1990**, 112, 7053; P. Wipf, *Chem. Rev.* **1995**, 95, 2115].

Cyclotides, a family of macrocyclic knotted peptides containing about 28–37 aa in length, characterized by well-defined secondary structures, and adopting a compact three-dimensional fold similar to large proteins. These so-called miniproteins contain three knotted disulfide bonds, a head-to-tail cyclized backbone, and show exceptional resistance against chemical, thermal, and proteolytic degradation. The cyclotides show a wide range of biological



Cyclotheonamide A (R = H)
Cyclotheonamide B (R = CH₃)

Cyclotheonamide

effects, including HIV inhibitory, antimicrobial, uterotonic, cytotoxic, hemolytic, neurotensin antagonistic, trypsin inhibitory, and insecticidal activities. The most potent hemolytic activity in cyclotides was described for → cycloviolacin H4. The leaf-specific Vhl-1 shows anti-HIV activity. Kalata B1 and B2 have shown to inhibit the growth and development of *Helicoverpa punctigera* and *H. armigera* larvae, which may have importance in plant defense. Cyclotides are present in plants from the Rubiaceae, Violaceae, and Cucurbitaceae families. More than 60 different cyclotides occur in the genus *Viola*, from which 500 species worldwide exist. The term cyclotide is derived from *cyclopeptide* as the class name of peptides and small proteins with cystine knots. [D. J. Craik et al., *J. Mol. Biol.* **1999**, 294, 1327; B. Chen et al., *J. Biol. Chem.* **2005**, 280, 22395; M. Trabi et al., *Plant Cell* **2004**, 16, 2204].

Cycloviolacin H4, cyclo-(-CAESCVWIPC¹⁰TVTALLGCSC²⁰SNNVCYNGIP³⁰-) [disulfide bonds: C¹–C¹⁸/C⁵–C²⁰/C¹⁰–C²⁵], a hydrophobic member of the → cyclotides from the Australian violet *Viola hederaceae*, exhibiting the most potent hemolytic activity in cyclotides reported so far. It is classified in the bracelet subfamily of cyclotides

due to the absence of a *cis*-Pro peptide bond [B. Chen et al., *J. Nat. Prod.* **2006**, 69, 23].

Cyp, cyclophilin.

Cys, cysteine.

Cystatin C, cys-C, a single-chain 120 aa protein (M_r 13,343 kDa, non-hydroxylated) belonging to the human \rightarrow cystatins. It shows amyloidogenic properties. Initially, cys-C was known as inter alia γ -trace, post- γ -globulin, and gamma-CSF. Cys-C contains two disulfide bonds ($C^{73}-C^{83}/C^{97}-C^{117}$). About 50% of cys-C contains a hydroxylated Pro^3 residue. It dimerizes through three-dimensional domain swapping. Cys-C seems to be produced by all human nucleated cells, and is used as a marker of the glomerular filtration rate (GFR). It has been reported that cys-C is at least equal, if not superior, to serum creatinine as a marker of GFR [A. Grub, H. Löfberg, *Proc. Natl. Acad. Sci. USA* **1982**, 79, 3024; R. Janowski et al., *Nature Struct. Biol.* **2001**, 8, 316; G. Filler et al., *Clin. Biochem.* **2005**, 38, 1].

Cystatins, a human superfamily of cysteine peptidase inhibitors. They are tight-binding reversible inhibitors of many cysteine proteases, and are not capable of inhibiting other proteases. Members of this superfamily contain at least two intrachain disulfide bonds and an α -helical structure over a distance of about 100 aa. This superfamily comprises: (i) *Family 1* (intracellular cystatins): cystatin A and cystatin B; (ii) *Family 2* (extracellular and/or transcellular cystatins): \rightarrow cystatin C, cystatin D, cystatin E, cystatin F, cystatin G, cystatin S, cystatin SA and cystatin SN; and (iii) *Family 3* (intravascular cystatins): LMW-kininogen and HMW-kininogen [A. J. Barret, *Trends Biol. Sci.* **1987**, 12, 193; S. Nagpal et al., *J. Invest. Dermatol.* **1997**, 109, 91; M. Zanatti,

J. Leukoc. Biol. **2004**, 75, 36; G. Filler et al., *Clin. Biochem.* **2005**, 38, 1].

Cysteine, (Cys, C), α -amino- β -mercapto-propionic acid, $HS-CH_2-CH(NH_2)-COOH$, $C_3H_7NO_2S$, M_r 121.16 Da, a proteinogenic amino acid.

Cysteine mimetics, nucleophilic residues that replace the *N*-terminal cysteine in the donor peptide or protein fragment in \rightarrow chemical ligation. Examples are homocysteine, thiaproline, selenocysteine, selenohomocysteine, glycine, and histidine [N. Budisa, *ChemBioChem* **2004**, 5, 1176].

Cysteine peptidases, *cysteine proteases*, *cysteine-type peptidases*, *thiol peptidases*, *sulfhydryl peptidases*, \rightarrow peptidases in which the attacking nucleophile is the sulfhydryl group of a cysteine residue (Cys²⁵ in the papain numbering system). The mechanism of catalysis is similar to that of \rightarrow serine peptidases because a covalent intermediate is formed. Beside the cysteine nucleophile a proton donor/general base is required which, in the majority of cysteine peptidases, is a His residue (His¹⁵⁹). Despite the fact that in some families of cysteine peptidases a third amino acid residue is required to orientate the imidazolium ring of the histidine moiety during the course of the catalytic process, in general, only a catalytic dyad is necessary. The archetype of cysteine peptidase is \rightarrow papain. A second group of cysteine peptidases which is very diverse in sequence are the "*papain-like*" *endopeptidases of RNA viruses* which contain only the catalytic dyad Cys/His, without additional residues involved in the catalytic mechanism. The same is true for \rightarrow caspases. A further important member of the cysteine peptidases is \rightarrow clostripain. The catalytic mechanism of the *adenovirus endopeptidase* is similar to that of papain, except that it involves four amino acids His,

Glu (or Asp) Gln and Cys [A. J. Barrett, N. J. Rawlings, *Arch. Biochem. Biophys.* **1995**, 318, 247].

Cystine bridges, disulfide bridges that are formed upon oxidative coupling of two thiol groups of cysteine residues, and frequently occur in peptides and proteins.

Cytokines, local mediator proteins regulating the differentiation, proliferation, and activities of the various types of blood cell. This general term for these intercellular signaling agents was introduced by S. Cohen in 1974. Cytokines play a critical role of the innate and adaptive immune responses. They control both the communication between immune cells and the proliferation and differentiation of leukocytes. Furthermore, they support the induction of immune reactions, and can both amplify and stop inflammation reactions. They are produced only in very small concentrations by many different cells, but the main producers are the immune cells themselves. The message of the highly active cytokines is mediated through receptors on the surface of the target cells. Examples of cytokines are → interferons (IFN), → interleukins (IL), → colony-stimulating factors (CSF), → tumor necrosis factor (TNF), → transforming growth factor- β (TGF- β), and → fibroblast growth factors.

The functions of the different factors overlap frequently. IL-1, IL-2, IL-4, IL-6, IFN- γ and TNF- α preferentially act in immune regulation. They promote the release of further cytokines, but also increase the effector function of mononuclear phagocytes, natural killer cells, and cytotoxic T cells (killer T cells). IFN- α and IFN- β are antivirally acting proteins that inhibit virus reproduction. As with TGF- β , these interferons suppress the reproduction of cells and play an important role in the inhibition of blood formation (hematopoiesis). TGF- β and IL-10 are engaged in suppressing cytokine production. IL-3 and CSF are hematopoietic growth factors causing the formation of blood in the spinal cord, supported by many interleukins. The increasing importance of cytokines in the therapy of many diseases is emphasized. IL-20, which is structurally related to IL-10, belongs to the newly discovered member of the cytokines, and appears to be an autocrine factor for keratinocytes that regulates their participation in inflammation processes [F. R. Balkwill, F. Burke, *Immunology Today* **1989**, 299; H. Kirchner et al., *Cytokine and Interferone: Botenstoffe des Immunsystems*, Spektrum Akademischer Verlag, Heidelberg, **1994**; H. Blumberg et al., *Cell* **2001**, 104, 9].

Cytolysine, → perforin.

CZE, capillary zone electrophoresis.

D

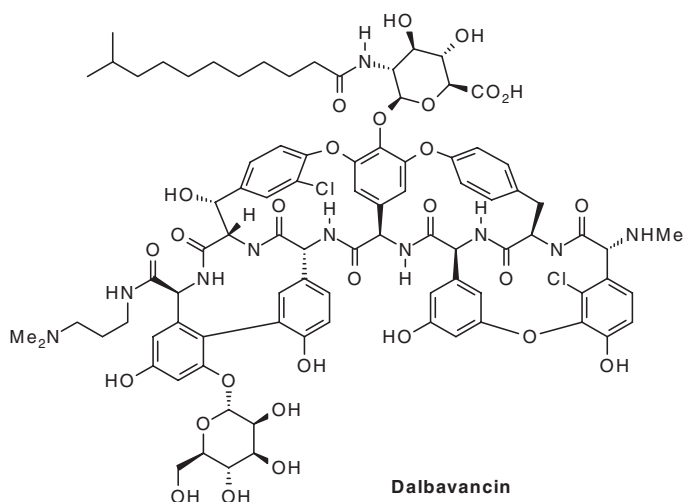
Dab α,γ -diaminobutyric acid.

Dalbavancin, a semi-synthetic derivative of the teicoplanin-related glycopeptide A40926 modified with an amide appendage at the C-terminus and an alteration of the hydrophobic acylglucosamine substituent. It is the most clinically advanced of the second-generation lipoglycopeptide antibacterials, and was derived from a rational design approach intended to improve both activity against coagulase-negative staphylococci and pharmacokinetic properties. Dalbavancin is active against both VanB enterococci and staphylococci and other important species [J. L. Pace, G. Yang, *Biochem. Pharmacol.* **2006**, 71, 968].

Dansyl method, an approach to determination of N-terminal amino acid residues in peptides and proteins. The reagent 1-dimethylaminonaphthalene-5-sulfonyl-

chloride (dansyl chloride) reacts with the target molecule to yield dansylated polypeptide. Acid hydrolysis liberates the N-terminal amino acid residue as fluorescent dansyl amino acid that can be determined chromatographically at the 100 pmol level [W. R. Gray, B. S. Hartley, *Biochem. J.* **1963**, 89, 59].

Daptomycin, Cubicin[®], N-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartyl-glycyl-D-seryl-threo-3-methyl-L-glutamyl-L-kynurenine ϵ_1 -lactone, a branched cyclic 13-peptide linked by an ester bond between the terminal kynurenine and the hydroxyl group of threonine bearing a lipophylic tripeptide tail. The cyclic lipopeptide antibiotic resembles structurally \rightarrow polymyxins, and is derived from the fermentation product of *Streptomyces roseosporus*. Daptomycin is active *in vitro*



against a wide array of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA). In 2003, daptomycin was approved in US for the treatment of skin and skin structure infections caused by Gram-positive pathogens. Daptomycin analogues containing polar functionality such as sulfonamides or polar spacers (e.g., piperazine) have been obtained by synthetic array technology or chemoenzymatic procedures [F. P. Tally et al., *Expert. Opin. Invest. Drugs* **1999**, *8*, 1223; J. Siedlecki et al., *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 4245; J. Gruenewald et al., *J. Am. Chem. Soc.* **2004**, *126*, 17025; C. A. Schriever et al., *Am. J. Health-Syst. Pharm.* **2005**, *62*, 1145; R. H. Baltz et al., *Nat. Prod. Rep.* **2005**, *22*, 717; K. S. Rotondi, L. M. Gierasch, *Biopolymers (Pept. Sci.)* **2005**, *80*, 374].

DAST, diethylaminosulfur trifluoride.

DBIP, diazepam-binding inhibitor peptide.

DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

Dcb, dichlorobenzyl.

DCC, *N,N'*-dicyclohexylcarbodiimide (also DCCI).

Dcha, dicyclohexylammonium salt.

DCHA, dicyclohexylamine.

DCM, dichloromethane.

Dcp, α,α -dicyclopropylglycine, also dipeptidyl carboxypeptidase.

DCU, *N,N'*-dicyclohexylurea (also DCHU).

DDAVP, [1-desamino-D-Arg⁸]vasopressin.

Dde, 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl.

DDz, 2-(3,5-dimethoxyphenyl)isopropoxy-carbonyl.

De novo protein design, approaches to design new proteins with native-like properties based on studying natural folds with natural sequences in order to make natural folds from unnatural sequences. Intensive studies at elucidating in which way proteins fold have improved confidence in protein design to a level that allows the design of helix bundle proteins, monomeric β -sheets, and mixed motifs for sequences in 100 aa size. The possibilities to design polypeptides which fold into structures that are pre-organized to form specific protein-protein interactions that control further assembly into even larger superstructures seems to be a realistic target, and opens fascinating perspectives for a better understanding of biocatalysis and biomolecular recognition in future [R. B. Hill et al., *Acc. Chem. Res.* **2000**, *33*, 745; L. Baltzer et al., *Chem. Rev.* **2001**, *101*, 3153].

de13a, a 32-peptide from the crude venom of the worm-hunting snail *Conus lessertii*, collected in the Yucatan Channel, Mexico. This novel member of the \rightarrow conotoxins contains post-translationally modified amino acids, including 6-bromotryptophan, 4-hydroxylysine, and 5-hydroxylysine. The eight cysteine residues are arranged in a pattern (C-C-C-CC-C-C-C) not found previously in conotoxins [M. B. Aguilar et al., *Biochemistry* **2005**, *44*, 11130].

DEAD-box proteins, a widely dispersed family of proteins found in all eukaryotes, and most prokaryotes. The name of the family was derived from the amino-acid sequence D-E-A-D of its Walker B motif. This motif have been found in more than 500 proteins, and RNA helicases. The DEAD-box proteins are associated with nearly all processes that are involved with RNA, from transcription to RNA decay.

Decorsin, APRLPQCQGD¹⁰DQEKCLCNKD²⁰ECPPGQCRFP³⁰RGDADPYCE, a 39-peptide crosslinked by three disulfide bridges (C⁷–C¹⁵/C¹⁷–C²⁷/C²²–C³⁸) originally isolated from the leech *Macrobdella decora*. Decorsin is a potent integrin $\alpha_{IIb}\beta_3$ antagonist, and one of the most powerful inhibitors of platelet aggregation. It contains six Cys as well as six Pro, and a RGD adhesion site recognition sequence, which is found in adhesive proteins such as \rightarrow fibrinogen, von Willebrand factor, and vitronectin. Purified recombinant decorsin has been found to be indistinguishable from the native peptide. The chemical synthesis of decorsin and analogues has been recently described [J. L. Seymour et al., *J. Biol. Chem.* **1990**, 265, 10143; A. M. Krezel et al., *Protein Sci.* **2000**, 9, 1428; E. Frare et al., *Prot. Eng. Design & Select.* **2005**, 18, 487].

β -Defensin-fold family, a peptide family consisting of a short helix or turn followed by a small twisted anti-parallel β -sheet. This fold is very similar to that of β -defensins (\rightarrow defensins). The six Cys are paired in a 1 \rightarrow 5, 2 \rightarrow 4, 3 \rightarrow 6 alignment. Members of this family include peptides with \sim 35–50 aa in sea anemones (\rightarrow anthopleurin A, \rightarrow ShI), snakes (\rightarrow crotamine), platypus (\rightarrow defensin-like peptides) and humans (β -defensins) possessing disparate activities, such as antimicrobial, myonecrotic, analgesic, and ion-channel-inhibiting [A. M. Torres, P. W. Kuchel, *Toxicon* **2004**, 44, 581].

Defensin-like peptides (DLP), peptides from platypus venom belonging to the \rightarrow β -defensin-fold family. These peptides have tertiary structures that resemble those of the mammalian antimicrobial β -defensins (\rightarrow defensins). DLP-2 is a 42-peptide that contains a D-amino acid residue, D-Met at position 2, while DLP-4 with an identical

amino acid sequence has all amino acids in the L-form. An isomerase in the platypus gland venom is responsible for the conversion of DLP-4 into DLP-2 [A. M. Torres et al., *Biochem. J.* **2005**, 391, 215].

Defensins, potent antimicrobial and proinflammatory peptides (\rightarrow antimicrobial peptides). Mammalian defensins are cationic peptides ($M_r \sim 3.5$ –4.5 kDa), rich in lysine and arginine containing six cysteine residues which form three characteristic disulfide bridges. According to the alignment of the disulfide bonds and the overall structure, defensins can be divided into three groups: α -defensins, β -defensins, and θ -defensins. Antimicrobial peptides of plants or insects have also been termed defensins, though they have different structural features in comparison to vertebrate defensins. α -Defensins consist of 29–35 aa and contain three disulfide bonds (C1 \rightarrow C6/C2 \rightarrow C4/C3 \rightarrow C5) that stabilize the triple-stranded β -sheet. Until now, six different human α -defensins (HD) have been described. HD-5 and HD-6 are constitutively expressed in Paneth cells of the small intestine. The human neutrophil peptides (HNP) are localized in azurophilic granules of neutrophil granulocytes. The latter are HNP-1, DCYCRIPACI¹⁰AGERRYGTCI²⁰YQGRLWAFCC³⁰ (disulfide bonds: C²–C³⁰/C⁴–C¹⁹/C⁹–C²⁹), HNP-3, and HNP-4, whereas the peptide termed HNP-2 is a truncated HD that associates as amphiphilic dimers. Human α -defensins are synthesized as 93–100 aa prepropeptides bearing a 19 aa signal sequence and a 41–51 aa anionic pro segment. α -Defensins, present in seeds or leaves, are characterized by complex structures containing disulfide-linked cysteines in triple-stranded antiparallel β -sheets with only one α -helix. Plant α -defensins do not form ion-permeable

pores in artificial membranes, but may act through a receptor-mediated mechanism. β -Defensins consist of 29–35 aa with a disulfide alignment C1→C5/ C2→C4/ C3→C6, and have been isolated from different sources. Human β -defensins (HBD) are expressed predominantly in epithelial tissues. The first member of this class, HBD-1, was originally isolated as a 36 mer from a human hemofiltrate obtained from patients with end-stage renal disease. HBD-1 and HBD-2 are synthesized as 64–68 aa prepropeptides [R. I. Lehrer et al., *Cell* **1991**, 64, 229; H.-G. Sahl et al., *J. Leukocyte Biol.* **2005**, 77, 466; C. Beisswenger, R. Bals, *Curr. Prot. Pept. Sci.* **2005**, 6, 255; J. J. Schneider et al., *J. Mol. Med.* **2005**, 83, 587; A. J. De Lucca et al., *Can. J. Microbiol.* **2005**, 51, 1001].

Deg, C $^{\alpha,\alpha}$ -diethylglycine.

Delivery peptide vectors, → cell-penetrating peptides.

Delta sleep-inducing peptide (DSIP), H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-OH, a 9-peptide first isolated from cerebral venous blood of sleeping rabbits, in 1977. It is widely distributed in the brain and other tissues. The concentration in the brain increases during hibernation. DSIP and appropriate analogues mediate sleep-like states (δ -slow-wave sleep) after intraventricular application into the rabbit brain. From various studies it can be concluded that DSIP passes the blood-brain barrier. DSIP causes a prolonged time of sleep in patients suffering from disturbed sleep. Phosphorylation of the hydroxyl group of Ser⁷ results in a more potent and more proteolytically stable analogue. DSIP was initially regarded as a candidate sleep-promoting factor. However, in part due to the lack of isolation of the DSIP gene, protein and related receptor, the link be-

tween DSIP and sleep has never been further characterized. Nowadays, the hypothesis regarding DSIP as a sleep factor is not well documented and remains weak. Despite this fact, DSIP itself presented a focus of investigations for a number of research teams. However, the existence of a DSIP-like peptide (or peptides) responsible for DSIP-like immunoreactivity and DSIP biological activity has been hypothesized [G. A. Schoenenberger, *Eur. Neurol.* **1984**, 23, 321; M. V. Graf, A. J. Kastin, *Peptides* **1986**, 1165; V. M. Kovalzon, T. V. Strekalova, *Neurochemistry* **2006**, 97, 303].

Deltorphins, a class of highly selective δ -opioid 7-peptide amides isolated from the skin of the South American frog *Phyllomedusa bicolor* and *P. sauvagei*. Deltorphins contain D-Met or D-Ala, respectively, in position 2, and together with → dermorphin they are the first naturally occurring regulatory peptides that contain D-amino acids. *Deltorphin (DT, Dermenkephalin)* H-Tyr-D-Met-Phe-His-Leu-Met-Asp-NH₂, is released from a biosynthetic precursor additionally containing four copies of dermorphin. A propeptide from *Phyllomedusa bicolor* contains three copies of [D-Ala²]deltorphin I, H-Tyr¹-D-Ala-Phe-Asp-Val⁵-Val-Gly-NH₂, and one copy of [D-Ala²]deltorphin II, H-Tyr¹-D-Ala-Phe-Glu-Val⁵-Val-Gly-NH₂. However, in all cases the D-amino acids in position 2 are formed in a post-translational reaction. In contrast to dermorphin, DT binds to δ -receptors. The varying selectivity for the opioid receptors can be explained by charge effects and differences in the hydrophobicity of the C-terminal part of the peptides. The synthesis of analogues of deltorphins A, B, and C have provided useful data for their potential application in clinical and therapeutic settings [V. Erspamer et al.,

Proc. Natl. Acad. Sci. USA **1989**, 86, 5188; L. H. Lazarus et al., *Prog. Neurobiol.* **1999**, 57, 377].

Denmotoxin, a monomeric 77-peptide containing five disulfide bridges isolated from the venom of the mangrove catsnake *Boiga dendrophila* with bird-specific activity. It is a member of the three-finger toxins (3FTXs). The peptide toxin has been chemically synthesized, crystallized and its crystal structure is solved at 1.9 Å. Denmotoxin caused a virtually irreversible blockade of chick muscle $\alpha_1\beta\gamma\delta$ -nAChRs [J. Pawlak et al., *J. Biol. Chem.* **2006**, 281, 29030].

De novo sequencing by MS, → MS *de novo* sequencing.

DEPBT, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazine-4(3H)-one.

DEPC, diethyl pyrocarbonate.

Depsipeptides, heterodetic peptides in which some of the peptide bonds are replaced by ester bonds. The bond replacement is almost isosteric. Since the dipolar characteristics are also comparable, similar conformational preferences can be expected. However, the ester bond cannot be a donor in a hydrogen bond. Depsipeptides include homomeric *O-peptides* and *peptide lactones* (→ actinomycins, → etamycin) of hydroxyamino acids such as Ser, Thr, etc., and heteromeric peptides characterized by the replacement of some peptide bonds by ester (depside) bonds as part of the backbone, also called *peptolides*. Nature is a rich source of cyclodepsipeptides containing alternating residues of α -amino and α -hydroxy acids, e.g., the ion-selective antibiotics → valinomycin and the closely related → enniatin family. Highly symmetric cyclodepsipeptides containing α - and β -amino and hydroxy acids are the → onchidins. Further

prominent and important depsipeptides are → vancomycin, → actinomycins, → destruxins, → didemnins, discodermins, quinoxaline antibiotics, → arenastatin A, FR901228, → dolastatins, polydiscamides, → theonellapeptolides, and discokiolides. A huge number of depsipeptides show very promising biological activities including anticancer, antifungal, antiviral, antibacterial, anti-inflammatory, and anticlotting properties. However, their extreme toxicity has limited their success in clinical trials. Therefore, suitable structural analogues identified by structure–activity investigations and mode-of-action studies should have more strong potential for therapeutic use. One of the most potent antineoplastic agents known is dolastatin 10. Further potent anticancer compounds are didemnin B, dehydrodidemnin B (DDB, aplidine), and FR901228. Some depsipeptides, such as → vinylamycin, fusaricidins, → theonellapeptolides, and WAP-8294A₂ inhibit the growth of various bacteria. The callipeltins and quinoxapeptins have been discovered as inhibitors of → HIV protease and may be developed as AIDS drugs. Antifungal depsipeptides include glomospirin, → jaspamides, → viscosinamide, → cyclolithistide A, and the LI-F antibiotics. Despite several attempts by the IUPAC-IUB nomenclature commission, the literature does not clearly display rules for the nomenclature of depsipeptides. A contribution to the nomenclature of depsipeptides, and especially to transcribe drawn depsipeptide structures in one-line text, was published in 2004. In chemical synthesis, the depside bond is known as being more difficult to incorporate into the backbone than peptide bonds. Therefore, it tends to be pre-formed in the linear precursor prior to cyclization at a amide bond to form the cyclic depsipeptide. An excellent review on recent developments

in depsipeptide research was published in 2004 [O. Kuisle et al., *J. Org. Chem.* **1999**, 64, 8063; F. Sarabia et al., *Curr. Med. Chem.* **2004**, 11, 1309; J. S., Davies, *J. Peptide Sci.* **2003**, 9, 471; S. V. Filip, F. Cavelier, *J. Peptide Sci.* **2004**, 10, 115].

Depsipeptide SPSS methodology, a method for \rightarrow SPSS applicable to \rightarrow difficult sequences arising from aggregation phenomena. It relies on the synthesis of Ser or Thr isopeptide intermediates with a final O-N acyl migration step. The principle is identical to the \rightarrow O-acyl isopeptide method, also termed \rightarrow click peptide or \rightarrow switch peptide method that were developed independently by different groups. It was, for example, successfully employed to synthesize the extremely difficult WWDomain FBP28 [I. Coin et al., *J. Org. Chem.* **2006**, 71, 6171].

Dermaseptins, a family of non-hemolytic antifungal peptides produced by the South American arboreal frog *Phyllomedusa sauvagei*. They are linear cationic, lysine-rich peptides, 27–34 aa in chain length, and are believed to lyse microorganisms by interacting with lipid bilayers. *Dermoseptin* S4, ALWMTLLKKV¹⁰LKA AAKAALN²⁰AVLVGANA, a 28-peptide, adopts an amphipathic α -helical conformation upon association with lipid bilayers, leading to membrane permeabilization and microbe death. It displays a broad spectrum of activity against Gram-negative and Gram-positive bacteria, yeast, filamentous fungi, *Plasmodium falciparum*, and the developed herpes simplex virus type 1 (HSV-1). It has been reported that Dermaseptin S4 inhibits HIV-1 infectivity *in vitro*. While \rightarrow phylloxin was a truly novel prototype peptide, \rightarrow dermatoxin sequences were predicted from cDNA clones generated from skin libraries of phyllomedusine frogs [A. Mor et al., *Biochemistry* **1991**, 30, 8824; C. Lorin et al., *Virology* **2005**, 334, 264].

Dermatoxin, SLGSFLKGVG¹⁰TTLASVGK VV²⁰SDQPGKLLQA³⁰GQ, a 32-peptide isolated from the skin of a single specimen of the tree frog *Phyllomedusa bicolor*. Dermatoxin proved to be bactericidal towards mollicutes (wall-less eubacteria) and Gram-positive eubacteria, and, additionally, to a lesser extent, towards Gram-negative eubacteria. *Dermatoxin-s*, ALGTLLKG VG¹⁰SAVATVGKMV²⁰ADQFGKLLQA³⁰a, from the waxy monkey frog, *Phyllomedusa sauvagei* differs in the sequence from that of *P. bicolor* [M. Amiche et al., *Eur. J. Biochem.* **2000**, 267, 4583; T. Chen et al., *Regul. Pept.* **2005**, 129, 103].

Dermorphins, besides the \rightarrow deltorphins the first examples of D-amino acid-containing peptides found in animals. *Dermorphin*, H-Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH₂, was first isolated in 1981 from the skin of the South American frog *Phyllomedusa sauvagei*. A similar peptide, [Hyp⁶]dermorphin, was discovered in the skin of *Phyllomedusa rhodai* and *Phyllomedusa burmeisteri*. Dermorphin is released from a biosynthetic precursor containing several copies of dermorphin with the L-isomer only. The conversion of L-Ala into D-Ala occurs post-translationally. Dermorphin binds preferably to the μ -receptors. In the guinea pig ileum test, dermorphin is 57 times as active as Met-enkephalin and, when given intravenously, it shows a significantly higher analgesic activity than morphine. With [Lys⁷]dermorphin, [Trp⁴, Asn⁷]dermorphin, and [Trp⁴, Asn⁷]dermorphin-(1–5), three additional dermorphin analogues were found in the skin of *Phyllomedusa bicolor*. The dermorphins are potent analgesics in rodents and primates, including humans [P. C. Montecuchi et al., *Int. J. Pept. Protein Res.* **1981**, 17, 275; P. Melchiorri, L. Negri, *Gen. Pharmacol.* **1996**,

27, 1099; A. B. Usenko et al., *Biol. Bull.* **2002**, 29, 2002].

Desirudin®, → Lepirudin®.

Destruxins, cyclodepsipeptides (→ depsipeptides) first isolated from the entomopathogenic fungus sp. *Oospora destructor* in 1961, from which the name “destruxin” is derived. The destruxins are composed of five amino acids and an α -hydroxy acid. The more than 20 structurally related destruxins differ on the hydroxy acid, *N*-methylation and the side chain of the amino acid residues. The destruxins show a wide variety of biological activities, especially phytotoxic and insecticidal activities. [S. Gupta et al., *J. Chem. Soc., Perkin Trans. 1* **1989**, 2347; M. S. Pedras et al., *Phytochemistry* **2002**, 59, 579].

DFIH, 2-fluoro-4,5-dihydro-1,3-dimethyl-1*H*-imidazolium hexafluorophosphate.

Dha, α,β -didehydroalanine (more commonly: α,β -dehydroalanine).

Dhbt, 3,4-dihydro-4-oxobenzotriazin-3-yl.

Diabetes mellitus, a chronic metabolic disease caused by insulin deficiency. This disease results from either insufficient → insulin secretion or decreased sensitivity of the → insulin receptor in the target cells. Two types of diabetes mellitus are known, → *insulin-dependent (type I) diabetes mellitus (IDDM)*, also termed juvenile-onset diabetes mellitus, caused by a deficiency of pancreatic β cells and often strikes suddenly in childhood, and → *non-insulin-dependent (type II) diabetes mellitus (NIDDM)*, that may be associated with loss of fully active insulin receptors on normally insulin-responsive cells and is strongly correlated with obesity. Although more than 80 years have passed since the discovery of insulin, the molecular actions of insulin have only begun to be investigated

over the past 25 years, based on cloning of the insulin receptor, the advent of transgenic technology, and the development of phosphotyrosine-specific antibodies. The diabetes epidemic has reached ~200 million people worldwide, and global prevalence is expected to reach more than 300 million during the next 20 years [M. Harris et al., *Diabetes Care* **1998**, 21, 518].

Diabetes-associated peptide, → amylin.

Dialkylamino acids, *C α -dialkylamino acids*, amino acids bearing two alkyl substituents at the α -carbon atom. Examples are the naturally occurring amino acids diethylglycine (Deg), α -aminoisobutyric acid (Aib), or isovaline (Iva, 2-amino-2-methylbutyric acid). Such amino acids are often incorporated into peptides to study the conformational requirements of receptors, and are used as building blocks for the stabilization of short peptides in a well-defined conformation, depending on the nature of the two substituents attached to the *C α* -carbon. 3_{10} -Helices are stabilized by the incorporation of Aib and other *C α* -dialkyl-substituted building blocks [P. Balaram, T. S. Sudha, *Int. J. Pept. Protein Res.* **1983**, 21, 381; I. L. Karle, *Biopolymers* **1996**, 40, 157; B. Pispisa et al., *Biopolymers* **2000**, 53, 169].

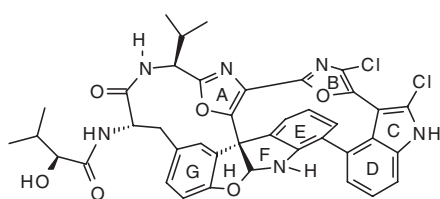
Dialysis, a concentration gradient-driven separation process on the basis of molecular diffusion through a membrane. Dialysis is a suitable technique to exchange the buffer in which a protein of interest is dissolved or to decrease the salt concentration of a protein solution.

Dianthins, cytotoxic cyclic peptides isolated from the methanol extract of the traditional Chinese medical plant *Dianthus superbus*. Beside *dianthin C*, cyclo-(-Gly-Pro-Phe-Tyr-Val-Ile-), the dianthins D–F with similar

structures have been identified [P.-W. Hsieh et al., *J. Nat. Prod.* **2004**, 67, 1522].

Diazepam-binding inhibitor peptide (DBIP), *anxiety peptide*, *octadecaneuropeptide*, ODN, QATVGDVNTD¹⁰RPGLDLK, an 18-peptide isolated from human and rat brain extracts besides other neuroactive peptides. DBIP is a bioactive fragment of the diazepam-binding inhibitor (DBI), and shows a number of behavioral and neurophysiological activities. It interacts with the benzodiazepine receptor and appears to increase anxiety [P. Ferrero et al., *Neuropharmacology* **1984**, 23, 1359; P. W. Gray et al., *Proc. Natl. Acad. Sci. USA* **1986**, 83, 7547; P. De Stefanis et al., *Regul. Pept.* **1995**, 56, 153; J. Leprince et al., *Peptides* **2006**, 27, 1561].

Diazonamide A, a marine natural product isolated from the colonial ascidian *Diazona angulata*. The revised structure was confirmed by total synthesis in 2002. It shows cytotoxicity against several tumor cell lines with IC₅₀ values <15 ng mL⁻¹ [N. Lindquist et al., *J. Am. Chem. Soc.* **1991**, 113, 2303; K. C. Nicolaou et al., *Angew. Chem. Int. Ed.* **2002**, 41, 3495].



Diazonamide A

DIC, *N,N'*-diisopropylcarbodiimide (also DIPCI).

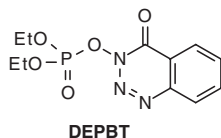
Dichotomins, cyclic peptides from the *n*-BuOH-soluble fractions of the roots of *Stellaria dichotoma* L. var. *lanceolata* Bge., which has been used as an anti-febrile. The latest-discovered members of

the dichotomins A–K were dichotomin J, cyclo-(Gly-Ile-Phe-Leu-Tyr-Ala-) and dichotomin K, cyclo-(Tyr-Tyr-Val-Ile-Pro-Ala-Val-Ile-Pro-), which inhibited vasoconstriction induced by norepinephrine on rat aorta [H. Morita et al., *J. Nat. Prod.* **2005**, 68, 1686].

Didemnins, a class of \rightarrow depsipeptides isolated from a Caribbean tunicate of the family *Didemnidae*. The first-discovered didemnins A–C inhibit the growth of both RNA and DNA viruses, are highly cytotoxic to L1210 leukemic cells, and protect mice against P388 leukemia and B16 melanoma. *Didemnin A*, MeLeu¹ \rightarrow Thr \rightarrow Sta \rightarrow Hip \rightarrow Leu⁵ \rightarrow Pro \rightarrow Me₂Tyr \rightarrow O (ester bond: Me₂Tyr⁷ \rightarrow Thr²) contains beside the proteinogenic amino acids (Thr, Leu, Pro), *N,O*-dimethyltyrosine (Me₂Tyr) and \rightarrow statine (Sta). Later, the didemnins D and E, nordidemnins A and B and the formaldehyde adduct methylenedidemnin A, as well as didemnin G, were isolated from *Trididemnum solidum*. In 1995, seven new didemnins – M, N, X, and Y, as well as nordidemnin N, epididemnin A₁ and acylodidemnin A – were described. Due to their remarkable antitumor, antiviral, and immunosuppressive activities details of numerous chemical, structural and biological investigations have been published [K. L. Rinehart et al., *J. Am. Chem. Soc.* **1981**, 103, 1857; R. Sakai et al., *J. Am. Chem. Soc.* **1995**, 117, 3734; A. A. Geldof et al., *Cancer Chemother. Pharmacol.* **1999**, 44, 312; K. L. Rinehart, *Med. Res. Rev.* **2000**, 20, 1].

3-(Diethoxyphosphoryloxy-1,2,3-benzotriazin-4(3H)-one (DEPBT), an effective coupling agent for the synthesis of linear and cyclic peptides, both in solution and on solid support. Beside its remarkable resistance to racemization in peptide bond formation, it is not necessary to protect the

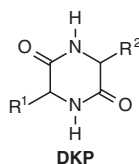
hydroxy functions of Tyr, Ser, Thr and the imidazole group of His if these residues are located in the amino component [Y.-H. Ye et al., *Biopolymers (Pept. Sci.)* **2005**, 80, 172].



Difficult sequences, *difficult sequence-containing peptides*, peptides often obtained in low yield and purity in stepwise \rightarrow SPPS. Despite all the improvements made in solid-phase technique since the pioneering studies of Merrifield, problems still occur; these are characterized by low elongation yields of successive amino acid couplings accompanied by a changes in the resin structure. Especially, a loss of the gel-like character of the resin and the appearance of a macroscopic shrinking of the support material have been observed. These problems can be attributed to peptide aggregation mediated by hydrophobic interactions promoted by sequence-containing hydrophobic building blocks and hydrogen bond networks among resin-bound peptide chains. Consequently, secondary structures such as β -sheets are stabilized, which leads to both an ineffective solvation of the peptide chain and the polymeric matrix. The use of chaotropic salts, different solvents, polar matrices, solubilizing protecting groups, \rightarrow amide-protecting groups within the peptide chain (\rightarrow backbone-amide protecting groups), elevated coupling temperature, reduced resin loading, and last – but not least – the application of special methods such as the dipeptide incorporation of \rightarrow pseudo-prolines, the \rightarrow O-acyl isopeptide method, \rightarrow depsipeptide SPPS methodology, and the \rightarrow peptoid methodology have been described to overcome these prob-

lems of ineffective solvation of the peptide chain and the polymeric matrix. [M. W. Pennington, M. E. Byrnes, in: *Methods in Molecular Biology: Peptide Synthesis Protocols*, Volume 35, M. W. Pennington, B. M. Dunn (Eds.), Humana Press, Totowa, New Jersey, USA, **1994**, 1; M. Quibell, T. Johnson, in: *Fmoc Solid Phase Peptide Synthesis, a Practical Approach*, W. C. Chan, P. D. White (Eds.), Oxford University Press, **2000**, 115; G.-A. Cremer et al., *J. Peptide Sci.* **2006**, 12, 437].

Diketopiperazine (DKP), a cyclic dipeptide easily formed by the cyclodimerization of amino acid esters. The formation of diketopiperazines is an undesired cyclization reaction by incorporation of the third amino acid by stepwise \rightarrow SPPS. The free amino group of the resin-bound dipeptide can attack the peptide-resin anchorage intramolecularly, resulting in the formation of diketopiperazine [J. R. Spencer et al., *Int. J. Pept. Protein Res.* **1992**, 40, 282].



β -2,4-dimethyl-3-pentyl ester, a side-chain protecting group for aspartic acid in \rightarrow SPPS [A. H. Karlström, A. E. Uden, *Tetrahedron Lett.* **1995**, 36, 3909].

Dinitrophenyl method (DNP method), a method for N-terminal end group analysis of peptides and proteins introduced by Sanger. After labeling the N-terminus of the peptide chain with the reagent 2,4-dinitrofluorobenzene, complete hydrolysis liberates the DNP amino acid that can be identified by chromatography [F. Sanger, *Biochem. J.* **1945**, 39, 507].

Diosynth Rapid Solution Synthesis of Peptides (DioRaSSP), a method for repetitive peptide synthesis in solution without isolation of intermediates. Especially developed for the large-scale manufacture of peptides consisting of repetitive cycles of coupling by \rightarrow water-soluble carbodiimides and deprotection in a permanent organic phase [I. F. Eggen et al., *J. Peptide Sci.* **2005**, *11*, 633; I. F. Eggen et al., *Org. Process Res. & Dev.* **2005**, *9*, 98].

DIPEA, diisopropylethylamine (also DIEA).

Dipeptidyl carboxypeptidase (Dcp), a 680 aa cytoplasmic peptidase (M_r 77.5 kDa) from *E. coli*. Dcp shows a strict carboxypeptidase activity and belongs to the M3 family of mono zinc peptidases. This membrane-anchored enzyme shares its substrate specificity with the mammalian \rightarrow angiotensin-converting enzyme. The crystal structure was determined in 2005 [B. Heinrich et al., *J. Bacteriol.* **1993**, *175*, 7290; M. Comellas-Bigler et al., *J. Mol. Biol.* **2005**, *349*, 99].

Dipeptidyl peptidase IV (DP IV), EC 3.4.14.5 (CD26), a plasma membrane glycoprotein ectopeptidase ($M_r \sim 110$ kDa) belonging to the prolyl oligopeptidase family. In mammals, it is expressed ubiquitously on the surface of endothelial and epithelial cells. DP IV splits selectively *N*-terminal dipeptides from oligopeptides with a strong preference for Pro > Ala > Ser as the penultimate amino acid. Homodimerization is necessary for DP IV to act as a serine protease. DP IV is established as the primary inactivating enzyme of the incretin hormone glucagon-like peptide 1 (\rightarrow glucagon-like peptides). Since several new approaches to diabetes therapy are undergoing clinical trials, including those involving stimulation of the pancreatic β -cell with the \rightarrow incretins GIP

and GLP-1, dipeptidyl peptidase IV inhibitors may be useful as new antidiabetic agents for the treatment of type 2 diabetes [A. M. Lambeir et al., *Crit. Rev. Clin. Lab Sci.* **2003**, *40*, 209; M. Engel et al., *J. Mol. Biol.* **2006**, *355*, 768; Z. Pei et al., *J. Med. Chem.* **2006**, *49*, 3520].

Diptericin, an antibacterial 82-peptide amide consisting of an *N*-terminal proline-rich domain and a central and C-terminal glycine-rich domain carrying two Glc-Gal-GalNAc threonine side-chain substitutions (Thr¹⁰ and Thr⁵⁴). This anti-Gram negative polypeptide was first isolated from the blood of bacteria-challenged larvae of the dipteran insect *Phormia terranova*. Treatment of diptericin with O-glycosidase led to removal of the O-glycan moieties, and abolished the antibacterial activity. However, it has been reported that synthetic unglycosylated diptericin possesses antibacterial activity against a range of Gram-negative bacteria [J.-L. Dimarcq et al., *Eur. J. Biochem.* **1988**, *171*, 17; P. Bulet et al., *Biochemistry* **1995**, *34*, 7394; M. Cudic et al., *Eur. J. Biochem.* **1999**, *266*, 549].

Discontinuous epitope, a peptide sequence used in epitope mapping where the crucial amino acids are located in different positions within the sequence.

Discrepin, a 38-peptide with a pyroglutamic acid as *N*-terminal residue isolated from the venom of the Venezuelan scorpion *Tityus discrepans*. It is the most distinctive member of the α -KTx15 subfamily of scorpion toxins. Discrepin blocks preferentially the I_A currents of the voltage-dependent K⁺ channel of rat cerebellum granular cells in an irreversible way. From the solution structure analysis it follows that discrepin displays the α/β scaffold, characteristic of scorpion toxins [G. D'Suze et al., *Arch. Biochem. Biophys.* **2004**, *430*,

256; A. Prochnicka-Chalufour et al., *Biochemistry* **2006**, 45, 1795].

Disulfide bond, a bond between two thiol groups of cysteine residues normally formed upon oxidation.

DKP, diketopiperazine.

DLP, defensin-like peptides.

Dmbab, 4-[[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl] amino}benzyl

DMF, dimethylformamide.

DMSO, dimethylsulfoxide.

DNA, desoxyribonucleic acid.

DNA template-controlled ligation, formation of a peptide bond between two \rightarrow peptide nucleic acid (PNA) precursors that associate in a sequence-specific manner with a DNA template. The connection is formed during the course of a thioester ligation reaction (\rightarrow chemical ligation) between one PNA molecule with a C-terminal glycyl thioester and a second PNA molecule with an N-terminal cysteine residue [C. Dose et al., *Angew. Chem. Int. Ed.* **2006**, 45, 5369].

DnaK, (hsp70, BiP), \rightarrow molecular chaperones.

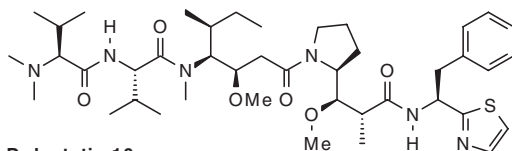
Dnp, 2,4-dinitrophenyl.

Dns, 5-dimethylaminonaphthalene-1-sulfonyl (dansyl).

Dolastatins, antitumor pseudopeptides isolated from the Indian Ocean sea hare *Dolabella auricularia*. Among all the members

dolastatin 10 and dolastatin 15 exhibit the most promising antiproliferative properties, and are currently under evaluation in clinical trials. Dolastatin 10 causes the formation of a cold-stable tubulin aggregate at higher drug concentrations, and seems to exert activity by interacting with tubulin and inducing apoptosis. Dolastatin 10 exists in two different conformations corresponding to a *cis/trans* isomerization of a central amide bond, but this finding could not be demonstrated for dolastatin 15. The potently cytotoxic dolastatin 15 is a relatively weaker inhibitor of tubulin assembly. One possible explanation for its potent cytotoxicity is that intracellularly formed metabolites show an increased affinity for tubulin. Other members of this family are dolastatins 11 and 12, both of which show high cytotoxicity against human cancer cells. Dolastatin 10 has been expected to be developed into an anticancer agent [G. R. Pettit et al., *J. Am. Chem. Soc.* **1987**, 109, 6883; M. Jaspars, *Chem. Ind.* **1999**, 51; G. R. Pettit, M. P. Grealish, *J. Org. Chem.* **2001**, 66, 8640; T. Shioiri, Y. Hamada, *Synlett* **2001**, 184; M. A. Ali et al., *Bioorg. Med. Chem.* **2005**, 13, 4138].

Dolichin, an antifungal protein ($M_r \sim 28$ kDa) isolated from the seeds of the field bean *Dolichos lablab*. It shows structural resemblance to chitinases, which also exhibit antifungal activity. Dolichin shows antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, and *Coprinus comatus*. Furthermore, dolichin is able to inhibit HIV reverse transcriptase, and α - and β -glucosidases associated with HIV infection



Dolastatin 10

[X. Y. Ye et al., *Biochem. Biophys. Res. Commun.* **2000**, 269, 155].

DOPA, 3,4-dihydroxyphenylalanine.

Double-His₆ tag, a sequence comprising of two His₆ separated by a 11 aa spacer showing at least one order of magnitude stronger binding to Ni-NTA-modified surfaces than a single-His₆ tag (\rightarrow His tag). Over the past few years the conventional His₆ tag has been widely used as a powerful and universal tool for the affinity purification of recombinant proteins. The His₆ sequence tags to transition metal chelates of nitrilotriacetic acid (NTA), forming a tetradentate chelate preferentially not only with Ni²⁺ but also with Co²⁺, Cu²⁺, and Zn²⁺ ions. It has been reported that the double-His₆ tag has the potential as a universal tag for protein immobilization and detection on arrays and single-step purification of proteins from crude mixtures [E. Hochuli et al., *BioTechnology* **1988**, 6, 1321; F. Khan et al., *Anal. Chem.* **2006**, 78, 3072].

DP IV, dipeptidyl peptidase IV.

Dpg, C ^{α} , α -dipropylglycine.

Dpm, diphenylmethyl (also Bzh, benzhydryl).

DPPA, diphenylphosphoryl azide (diphenyl phosphorazidate).

Dpr, 2,3-diaminopropionic acid.

DPTU, N,N'-diphenylthiourea.

Drm-NPF peptide, SNSRPPRKND¹⁰VNTMADAYKF²⁰LQDLDTYYGD³⁰RARVRFa, a 36-peptide amide from the fruitfly related to the \rightarrow neuropeptide Y family. It is expressed in larval and adult brain and gut [M. R. Brown et al., *Peptides* **1999**, 20, 1035].

Dromyosuppressin (DMS), \rightarrow FMR-Famide-related peptides.

Drosomycin, a 44-peptide produced from *Drosophila melanogaster* that belongs to the insect \rightarrow defensins. It shows significant homology with plant antifungal peptides from seeds of members of the family Brassicaceae. It is similar in structure to the radish antifungal peptide, Rs-AFP₁. Drosomycin is particularly effective against *F. oxysporum* isolates [P. Fehlbaum et al., *J. Biol. Chem.* **1994**, 269, 33159; L. Michaut et al., *FEBS Lett.* **1996**, 395, 6].

Drosocin, KRPYSPRPT¹⁰SHPRPIR, a P-rich cationic 17-peptide (\rightarrow antimicrobial peptide) from the fruit fly (*Drosophila melanogaster*).

Drosulfakinins (DSK), \rightarrow RFamide peptides.

Drug-polymer conjugates, \rightarrow polymer therapeutics.

DSA safety-catch linker, a sulfoxide-containing safety-catch linker. DSA is stable against treatment with acid, but undergoes acidolysis after reduction of the sulfoxide group [T. Kimura et al., *Chem. Pharm. Bull.* **1997**, 45, 18].

DSC, di(N-succinimidyl)carbonate.

DSIP, delta sleep-inducing peptide.

DSK, drosulfakinin.

Dsu, (2S,7S)-2,7-diaminosuberlic acid.

Dts, dithiasuccinoyl.

DTT, dithiothreitol.

Duramycins, lanthionine-containing antibiotics, especially, analogues of B-type lantibiotics of the prototype \rightarrow cinnamycin, exemplified by duramycin, duramycin B, and duramycin C. The latter two peptides have been isolated from *Streptoverticillium* strain R2075 and *Streptomyces griseoluteus* (R2107). All antibiotics of this group inhibit

human phospholipase A2 [A. Fredenhagen et al., *J. Antibiot. (Tokyo)* **1990**, 43, 1403].

du Vigneaud, Vincent (1901–1978), American biochemist and winner of the Nobel Prize in Chemistry 1955 for outstanding achievements in peptide and protein research. The establishment of the structure of \rightarrow oxytocin and \rightarrow vasopressin, including the first chemical synthesis of a peptide hormone, had opened the door for a better understanding of these hormones and was a “breakthrough” in natural sciences. In 1932, he became head of the biochemistry department at the George Washington University School of Medicine, Washington D.C., in 1938 he headed the department of biochemistry at the Cornell University Medical College New York City, and from 1967 to 1975 he was Professor of Chemistry at Cornell University, Ithaca, New York. The main topics of de Vigneaud’s researches were mainly sulfur-containing compounds of biochemical importance, particularly insulin and the neurohypophyseal hormones, but his interest was also focused on intermediary metabolism, transmethylation, and the metabolism of one-carbon compounds, trans-sulfuration, penicillin, and biotin [U. Ragnarsson, *The Nobel trail of Vincent du Vigneaud*, *J. Peptide Sci.* **2007**, 13, 431].

DVD, divinylbenzene.

Dyn, dynorphin.

Dynamin 1, a member of the dynamin family of large GTPases. Mammalian dynamin 1 forms ring-like assemblies around the necks of budding synaptic vesicles. Structurally, it can be subdivided into five domains. The high-resolution X-ray structure of the GTPase domain from *Rattus norvegicus* was described in 2005 [K. Takei et al., *Nature* **1995**, 374, 186;

T. R. Reubold et al., *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13093].

Dynorphins (Dyn), opioid peptides released from the precursor protein prepro-dynorphin, (prepro-enkephalin B). *Dynorphin A (Dyn A)*, YGGFLRRIRP¹⁰ KLKWDNQ, *dynorphin B (Dyn B)*, YG GFLRRDFK¹⁰VVT, α -neoendorphin (\rightarrow neoendorphins), prodynorphin-derived peptides, e.g., *Big dynorphin (Big Dyn)*, GGFLRRIRP¹⁰KLKWDNQKRY²⁰GGFLRRDFKV³⁰VT, comprise the family of dynorphins. The sequence of Big Dyn [human pro-dynorphin-(207–238)] contains Dyn A [Big Dyn-(1–17)], and Dyn B [Big Dyn-(20–32)]. Dynorphins are putative endogenous ligands for the κ -opioid receptor (KOR). They are synthesized in several brain areas, including the striatum, hippocampus, basal ganglia, cerebral cortex, and spinal cord. The dynorphins interact preferentially with KOR, and are critical for regulation of nociceptive transmission, stress-induced responses, and substance dependence. In humans, the dynorphins may be involved in the development of various neuropsychiatric disorders. It has been reported that pro-dynorphin expression is altered in the brain of drug abusers and psychiatric patients. Furthermore, from KOR-mediated effects of salvinorin A it has been suggested that dynorphins may contribute to perceptual distortions in dementia, schizophrenia, and bipolar disorders. The longer dynorphins were first detected in the hypothalamus, hypophysis, and duodenum of the pig. Later, they were isolated from adrenal medulla, guinea pig heart, and rat duodenum [A. Goldstein et al., *Proc. Natl. Acad. Sci. USA* **1979**, 76, 6666; J. P. Pierce et al., *Hippocampus* **1999**, 9, 255; Y. L. Hurd et al., *Mol. Psychiat.* **2002**, 7, 75; D. J. Sheffler, B. L. Roth, *Trends Pharmacol. Sci.* **2003**, 24, 107; F. Merg et al., *J. Neurochem.* **2006**, 97, 292].

E

<E, single-letter code for pGlu.

EC, enzyme commission (enzyme nomenclature).

Ecdysis-triggering hormones (ETH), peptide hormones involved in the ecdysis motor behavior that leads to shedding of the old cuticle at the end of each molt. This pathway was first elucidated in the moth *Manduca sexta*. *Mas-ETH*, SNEA ISPF¹⁰DQ¹⁰GMMGYVIKTN²⁰KNIPRMa, a 26-peptide hormone, triggers ecdysis in developing insects. Ecdysis in insects requires the exact coordination of behavior with the development changes that occur late in a molt. Two sets of endocrine cells, the peripherally located Inka cells, that release ETH, and the centrally located VM neurons responsible for release of the → eclosion hormone – are involved in the coordination. Besides the eclosion hormone, the → crustacean cardioactive peptide (CCAP), and *Drm-ETH* appear to be involved in this neuronal pathway. After gene encoding of the precursor for ETH-like peptides in *Drosophila*, both *Drm-ETH-1*, DDSSPGF FLK¹⁰ITKNVPRLa, and *Drm-ETH-2*, GENFAIKNLK¹⁰TIPRIa, have been found to induce premature eclosion after injection [J. Ewer et al., *J. Exp. Biol.* **1997**, 200, 869; D. Zitnan et al., *Science* **1996**, 271, 88; Y. Park et al., *FEBS Lett.* **1999**, 463, 133; J. V. Broeck, *Peptides* **2001**, 22, 241; D. Zitnan et al., *J. Exp. Biol.* **2003**, 206, 1275].

ECE, endothelin-converting enzyme.

ECGF, endothelial cell growth factor.

Echinocandins, a diverse family of lipopeptides including echinocandins, cilofungin, pneumocandins, → aculeacins, mulundocandin, and WF 11899. They are non-competitive inhibitors of (1,3)-β-D-glucan synthase. The name of the family was originally applied to a small family of cyclic lipopeptide antifungal natural products with the same cyclic peptide moiety but different fatty acid side chains. Echinocandins show antimicrobial activity against *Pneumocystis carinii* and *C. albicans* [W. W. Turner, W. L. Current, in: *Biotechnology of Antibiotics*, W. R. Strohl (Ed.), 2nd edn., Marcel Dekker, New York, **1997**, 315].

Echinomycin, beside → triostin A, a parent member of a family of antitumor antibiotics that have advanced into clinical trials [M. J. Waring, *Path Biol. (Paris)* **1992**, 1022; W. J. Gradishar et al., *Invest. New Drugs* **1995**, 13, 171].

Echistatin, ECESGPCCRN¹⁰CKFLKEGTIC²⁰KRARGDDMD³⁰YCNGKTCDCP⁴⁰RNP HKGPAT (disulfide bonds: C²–C¹¹ / C⁷–C³² / C⁸–C³⁷ / C²⁰–C³⁹), a RGD-containing 49-peptide originally isolated from the venom of the saw-scaled viper *Echis carinatus*. It has been shown that echistatin is a potent inhibitor of bone resorption by isolated osteoclasts. It inhibited the excavation of bone slices by rat osteoclasts. It has been demonstrated that osteoclasts bind to bone via a RGD sequence as an obligatory step in bone resorption. This RGD-binding integrin is present in adhesion structures and co-localizes with vinculin and an α-like subunit. Structure–activity relationship studies led to the conclusion that shorter

and more potent antagonists of the β_3 integrin receptor may find clinical application in the blockade of bone reabsorption [M. Sato et al., *J. Bone Miner. Res.* **1994**, *9*, 1441].

Eclosion hormone (EH), a 62-peptide hormone produced in the nervous system and involved in eclosion behavior. EH plays an integral role in triggering ecdysis behavior at the end of each molt. Target cells for EH are believed to include two pairs of neurons in each of the ganglia of the ventral nerve cord that contain the \rightarrow crustacean cardioactive peptide, the Inka cells of the peripheral epitracheal glands, and intrinsic non-neuronal cells in the abdominal transverse nerves. EH provides a link between the \rightarrow ecdysis-triggering hormone and crustacean cardioactive peptide in the neuroendocrine cascade controlling ecdysis behavior [F. M. Horodyski et al., *Eur. J. Biochem.* **1993**, *215*, 221; S. C. Gammie, J. W. Truman, *J. Exp. Biol.* **1999**, *202*, 343; D. B. Morton, P. J. Simpson, *J. Insect. Physiol.* **2002**, *48*, 1].

ED₅₀, median effective dose.

EDC, *N*-ethyl-*N'*-(3-dimethylaminopropyl) carbodiimide.

Edestin, a legumin class reserve hexameric protein ($M_r \sim 300$ kDa) from hemp seeds (*Cannabis sativa*) belonging to the \rightarrow globulins. Each of the six identical subunits consists of two non-identical peptide chains linked by disulfide bridges. The crystallographic characterization of edestin has been described [S. Patel et al., *J. Mol. Biol.* **1994**, *235*, 361].

EDF, epidermal growth factor or erythrocyte differentiation factor.

EDFR, epidermal growth factor receptor.

Edman degradation, an important method of *N*-terminal \rightarrow sequence analysis using phenyl isothiocyanate (PITC), a reagent introduced by Pehr Edman in 1949. This cyclic process consists of three steps: coupling, degradation, and conversion. Coupling with PITC provides phenylthiocarbamoyl (PTC) peptide, followed by degradation and formation of 2-anilino-5(4*H*)-thiazolone. The latter undergoes rearrangement in hot trifluoroacetic acid to give the more stable 3-phenyl-2-thiohydantoin (PTH), which can be identified by different methods. The Edman degradation has been improved by the development of the spinning-cup or \rightarrow liquid-phase sequencer, the \rightarrow gas-phase sequencer and the pulsed liquid sequencer [P. Edman, *Arch. Biochem.* **1949**, *22*, 475; P. Edman, G. Begg, *Eur. J. Biochem.* **1967**, *1*, 80].

Edman, Pehr Victor (1916–1977), a pioneer in the field of peptide and protein chemistry. Already for his Ph.D he had isolated and purified \rightarrow angiotensin. In 1947, he accepted an associate professorship at the University of Lund (Sweden), and in 1957 Edman came to Melbourne as the first John Holt director of research at St. Vincent's School of Medical Research. In 1972, he moved to Germany, having been appointed Professor at the Max-Planck-Institute for Biochemistry at Martinsried. He is the inventor of an important method for protein structure determination, named the \rightarrow Edman degradation [F. J. Morgan, *Edman, Pehr Victor (1916–1977)*, *Austr. Dict. Biograph.* **1996**, Volume 14, pp. 78–79].

EDT, ethanedithiol.

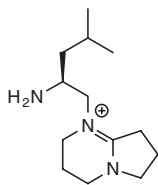
EDTA, ethylenediamine tetraacetic acid.

ee, enantiomeric excess.

EEDQ, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydrochinoline.

EEL, expressed enzymatic ligation.

Efrapeptins, a mixture of peptide antibiotics isolated from fungi of the species *Tolypocladium*. Efrapeptin C has the sequence Ac-Pip-Aib-Pip-Aib-Aib-Leu- β -Ala-Gly-Aib-Aib¹⁰-Pip-Aib-Gly-Leu-Aib-X. The efrapeptins are rich in pipecolic acid (Pip), aminoisobutyric acid (Aib) and isovaline (Iva), and share at the C-terminus a quite unique head group X derived from leucinol and a bicyclic cationic ring (2,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrimidin-1-ium system). The spermidine head group of the elvapeptins has been proposed to be the reduced biosynthetic precursor of this head group. The efrapeptins are active against the malaria pathogen *Plasmodium falciparum*, exhibit strong insecticidal activity as well as antiproliferative properties, and display strong sequence similarities to the \rightarrow neo-efrapeptins. Furthermore, they are inhibitors of the mitochondrial ATPase and have been used in the crystallographic structure determination of F₁-ATPase [S. Gupta et al. *J. Am. Chem. Soc.* **1991**, 113, 707; M. Jost et al., *Chem. Biodiv.* **2007**, 4, 1170].



Cationic head group X
of the efrapeptins

Efrapeptins

EGF, epidermal growth factor.

EGF family, *epidermal growth factor family*, a member of the gastroenteropancreatic peptide families. This family comprises

\rightarrow epidermal growth factor (EGF), \rightarrow transforming growth factor- α (TGF- α), \rightarrow amphiregulin (AR), heparin binding EGF-like growth factor (HB-EGF), \rightarrow betacellulin (BTC), neuregulin 1, neuregulin 2, neuroregulin 3, and \rightarrow epieregulin (ER). The members of this family share six conserved Cys residues, have one or more EGF domains, and a transmembrane domain. According to their receptor affinities, the members of the EGF family are divided into two groups. EGF, HB-EGF, TGF- α , AR, BTC and ER bind to erbB1, whereas HB-EGF, ER, and BTC bind to erbB4 as well as to erbB1. The remaining members are ligands for ErbB3 and ErbB4 [D. Zhang et al., *Proc. Natl. Acad. Sci. USA* **1997**, 94, 9562].

Egg-laying hormone (ELH), ISINQDLK AI¹⁰TDMLLTEQIR²⁰ERQRYLADLR³⁰QRL LEKa, a 36-peptide amide from *Aplysia californica*. ELH is synthesized by the bag cell neurons, and acts as a hormone facilitating expulsion of the egg string, and as a neurotransmitter on cells of the abdominal ganglion [A. Y. Chiu et al., *Proc. Natl. Acad. Sci. USA* **1979**, 76, 6656; R. H. Scheller et al., *Cell* **1983**, 32, 7].

Eglin c, a small thermostable single-chain protein (70 aa) isolated from the leech *Hirudo medicinalis*. It belongs to the eglin family of serine protease inhibitors, and inhibits effectively subtilisin, chymotrypsin, cathepsin G and leukocyte elastase. The potential therapeutic value of eglin c might lie in inflammatory processes. The crystal structure at 2 Å resolution with hydrolyzed reactive center of eglin c has been described [J. Dodt et al., *Biol. Chem. Hoppe Seyler* **1987**, 368, 1447; C. Betzel et al., *FEBS Lett.* **1993**, 317, 185].

EH, eclosion hormone.

Eisenin, pGlu-Gln-Ala-OH, a tripeptide extracted from the brown Japanese marine alga *Eisenia bicyclis* Setchell. It shows the immunological activity to augment natural cytotoxicity of peripheral blood lymphocytes in humans [R. Katakai, M. Oya, *J. Org. Chem.* **1974**, 39, 1974; T. Kojima et al., *J. Immunother.* **1993**, 13, 36].

ELAM, endothelial leukocyte adhesion molecule.

Elastin, a structural protein with rubber-like elastic properties. It is the main component of the elastic yellow connective tissue occurring, e.g., in the lungs and aorta. The amount of elastin is rather low in the inelastic white connective tissue of tendons. Elastin consists of 850–870 aa with a high content of Gly (27%), Ala (23%), Val (17%), and Pro (12%). It forms a three-dimensional network of fibers crosslinked by desmosine, lysinonorleucine, and isodesmosine. It has been reported that elastin has an unanticipated regulatory function during arterial development, controlling the proliferation of smooth muscle and stabilizing arterial structure [L. Robert, W. Hornebeck (Eds.), *Elastin and Elastases*, Volume 1, CRC Press, Boca Raton, FL, **1989**; D. R. Eyre et al., *Annu. Rev. Biochem.* **1984**, 53, 717; D. Y. Li et al., *Nature* **1998**, 393, 276].

Elcatonin (eCT), carbocalcitonin, a synthetic analogue of eel \rightarrow calcitonin.

Eledoisin, <EPSKDAFIGL¹⁰Ma, an 11-peptide amide from the salivary glands of the cephalopod (*Eledone moschata* and *E. aldrovandi*) belonging to the \rightarrow tachykinin family. Its biological activities *in vitro* are similar to those of \rightarrow substance P. The solution structure has been studied by two-dimensional NMR spectroscopy and distance geometry calculations [V. Erspamer,

A. Anastasi, *Experientia* **1962**, 18, 58; R. C. R. Grace et al., *Biophys. J.* **2003**, 84, 655].

ELH, egg-laying hormone.

ELISA, enzyme-linked immunosorbent assay.

Enalapril, (S)-1-[N-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline, an orally active inhibitor of the \rightarrow angiotensin-converting enzyme (ACE). After oral administration, the prodrug enalapril ($IC_{50} = 1.2 \times 10^{-6}$ M) is primarily bioactivated in the liver by hydrolysis of the ethyl ester to yield *enalaprilat* ($IC_{50} = 1.2 \times 10^{-9}$ M), which is one of the most active \rightarrow ACE inhibitors. Enalaprilat causes a drop in blood pressure, as does \rightarrow captopril. Enalapril is widely used to treat hypertension and congestive heart failure, and is available alone and in combination with hydrochlorothiazide. Enalapril was approved for marketing by the FDA in December 1985 [A. A. Patchett et al., *Nature* **1980**, 288, 280; E. H. Ulm, *Drug Metab. Rev.* **1983**, 14, 99].

End group analysis, determination of N-terminal (\rightarrow dinitrophenyl method, \rightarrow dansyl method, \rightarrow Edman degradation) and C-terminal (\rightarrow C-terminal end group analysis, \rightarrow Akabori method) amino acid residues in the primary structure analysis of peptides and proteins.

Endogenous opioid peptides, endogenous peptides that exert their effects through opioid receptors (\rightarrow enkephalins, \rightarrow endorphins, \rightarrow dynorphins, \rightarrow endomorphins). Early studies on morphine and related compounds concluded that opioids interact with a specific receptor. It was assumed that more than one type of opioid receptor existed because nalorphine is an antagonist of morphine but also displays analgesic activity. Three opioid receptors

(μ , κ , σ) were postulated even before the discovery of the first endogenous opioids. The isolation of the first opioid peptides led to the characterization of the δ -receptor. There is pharmacological evidence for subtypes of each receptor, and other types of novel, less well-characterized opioid receptors (ϵ , λ , ι , ξ) have also been postulated. The σ -receptor, however, is no longer regarded to be an opioid receptor. All cloned opioid receptors share the general structure of G protein-coupled receptors (GPCR), with an extracellular N-terminal region, seven transmembrane domains and intracellular C-terminal tail structure. An enormous number of opioid actions mediated via the different opioid receptor types has been elucidated. They are involved in analgesia, learning and memory, eating and drinking, pregnancy, development and endocrinology, mental illness and neurologic disorders as well as locomotion, respiration, and thermoregulation. An enormous number of opioid actions mediated via the different opioid receptor types has been elucidated since 1975. Recently, the 28th installment of the annual review of research concerning the endogenous opioid system that summarizes published papers during 2005 (e.g., on behavioral effects of molecular, pharmacological and genetic manipulations of opioid peptides, opioid receptors, opioid agonists and opioid antagonists) has been published. This excellent volume continues the tradition initiated by Abba Kastin, Gayle Olson, Richard Olson, David Coy, Anthony Vaccarino, and continued by Richard J. Bodnar and colleagues in the reviews spanning from 1978 through 2005 [R. J. Bodnar, M. M. Hadjimarkou, *Peptides* **2002**, 23, 2307; R. J. Bodnar, M. M. Hadjimarkou, *Peptides* **2003**, 24, 1241; R. J. Bodnar, G. E. Klein, *Peptides* **2004**, 25, 2205; R. J. Bodnar, G. E. Klein, *Peptides* **2005**, 26, 2629; R.

J. Bodnar, G. E. Klein, *Peptides* **2006**, 27, 3391].

Endokinins (EK), human \rightarrow mammalian tachykinins with cardiovascular activity encoded on the human TAC4 gene. The EK A–D are mainly distributed in the adrenal glands and in the placenta. The occurrence in the placenta suggests that EK may be involved in controlling blood flow during pregnancy. EK A, DGGEQTLST¹⁰EAETWVIVAL²⁰EEGAGPSIQL³⁰QLQEVKTGKA⁴⁰SQFFGLMa, and EK B, DGGEQTLST¹⁰EAETWEGAG²⁰PSIQLQLQEV³⁰KTGKASQFFG⁴⁰LMa, are significantly longer than the 14-peptide amides EK C, KKAYQLEHTF¹⁰QGLLa, and EK D, VGAYQLEHTF¹⁰QGLLa. EK A/B 10-mers show equivalent affinity for the three tachykinin receptors as \rightarrow substance P. EK C and EK D contain the previously uncharacterized tachykinin motif Phe-Gln-Gly-Leu-Leu-NH₂ and display only low potency. It has been reported that EK A/B might act as endocrine/paracrine agonists at peripheral substance P receptors [M. M. Kurtz et al., *Gene* **2002**, 296, 205; M. N. Page et al., *Proc. Natl. Acad. Sci. USA* **2003**, 100, 6245].

Endomorphins, H-Tyr-Pro-Xaa-Phe-NH₂, 4-peptide amides with the highest known affinity and specificity for the μ -opioid receptor. *Endomorphin-1* (Xaa = Trp) shows 4000- and 15 000-fold preference over the δ - and κ -receptors, respectively, and may be a natural ligand for this receptor. *Endomorphin-2* (Xaa = Phe) shows potent μ -selective activity, including analgesia. They play a potential endogenous role in many major physiological processes, including the perception of pain, responses related to stress, and complex functions such as reward, arousal, and vigilance, as well as autonomic, cognitive, neuroendocrine, and limbic homeostasis [J. E.

Zadina et al., *Nature* **1997**, 386, 499; H. C. Champion et al., *Peptides* **1997**, 18, 1393; J. Fichna et al., *Pharmacol. Rev.* **2007**, 59, 88].

Endorphins, generic term for \rightarrow endogenous opioid peptides. They are opiate-like endogenous peptides with morphine-like activity. The name is related to *endogenous morphine*. These morphinomimetic peptides were identified in the mid-1970s after the discovery of the receptors responsible for binding opioid peptides in a stereoselective manner. There are at least three multiple receptor subtypes: μ , δ and κ ; the existence of other receptors, such as ϵ and σ , have been suggested, but have not yet been confirmed. Opioid receptors have been discovered throughout the mammalian CNS and peripheral nerve tissues such as guinea pig ileum, the mouse *vas deferens* and human gastrointestinal tract. Based on their differing pharmacology, the following subclasses of receptors – δ_1 , δ_2 , κ_1 , κ_2 and κ_3 – have been proposed and, due to their differing location, also the subclasses μ_1 and μ_2 . The first endogenous peptides with morphine-like activity were the pentapeptides Met-enkephalin and Leu-enkephalin (\rightarrow enkephalins) discovered by Kosterlitz in 1975. Later, partial fragments of $\rightarrow \beta$ -lipotropin, e.g. α -endorphin., YGGFMTSEKS¹⁰QTPLVT, β -endorphin., TGGFMTSEKS¹⁰QTPLVTL FKN²⁰-AIIKNAYKKG³⁰E, γ -endorphin, YGGFMTSEKS¹⁰QTPLVTL, and δ -endorphin, YGGFMTSEKS¹⁰QTPLVTLFKN²⁰AIIKN AY, were isolated from pituitary material. All endorphins bear a common initial sequence, which corresponds to the primary structure of [Met]enkephalin. β -Endorphin is derived from \rightarrow pro-opiomelanocortin (POMC), and is secreted in the hypophysis in response to stress and other stimuli. It has analgesic and lipolytic

activity. The analgesic effect in the body is based on the secretion of β -endorphin. Acupuncture, for example, activates the central nervous endorphin system to cause an increase in the concentration of endorphins, which in turn leads to the elimination of sensitivity to pain. The hope that endorphins would allow analgesia to be separated from the development of addiction and dependence has not yet been realized. Furthermore, the enkephalins and other opioid peptides did not penetrate the blood-brain barrier (BBB), and had very short half-lives in the bloodstream. However, as a result of structure–activity (SAR) studies in many laboratories, potent and selective opioid agonists and antagonists could be obtained. Interestingly, effective BBB transport of glycosylated enkephalins has been demonstrated in the meantime. The term endorphin is used in the narrower sense not for all peptides with opiate-like effects (\rightarrow endogenous opioid peptides), but rather more preferentially to fragments of β -lipotropin. Therefore, $\rightarrow \alpha$ -neoendorphin, \rightarrow dynorphin, and enkephalin would not fit this narrower definition [M. J. Brownstein, *Proc. Natl. Acad. Sci. USA* **1993**, 90, 5391; L. Lazarus et al., *Proc. Natl. Acad. Sci. USA* **1976**, 73, 2156; C. H. Li, in *Central and Peripheral Endorphins: Basis and Clinical Aspects*, E. Mueller, A. R. Genazzani (Eds.), p. 17, Raven Press, New York, **1984**; R. Polt et al., *Med. Res. Rev.* **2005**, 25, 557].

Endothelin-converting enzymes (ECE), membrane-bound metalloproteases, ECE-1 and ECE-2, which catalyze the cleavage of human prepro-endothelin-1 into endothelin-1 (\rightarrow endothelin).

Endothelin-like peptides, designation for \rightarrow sarafotoxins (SRTX) consisting of 21 aa from snake venoms as their structural and pharmacological properties are

clearly those of \rightarrow endothelins. They differ from several new SRTX isopeptides that are shorter in sequence or bearing C-terminal extensions isolated from various snake species within the Atractaspididae family [F. Ducancel, *CMLS, Cell. Mol. Life Sci.* **2005**, 62, 5286].

Endothelin (ET), human *hET-1*: CSC-SSLMD KE¹⁰CVYFCHLDII²⁰W (disulfide bonds: C¹–C¹⁵/C³–C¹¹), a family of structurally related, strongly vasoactive peptides formed in the endothelial cells that exerts a great number of physiological functions in many tissues. Besides ET-1, which was first detected in the culture of endothelial cells, two other endothelins were found in humans after subsequent analysis of the endothelin encoding genes, named *ET-2* ([Trp⁶,Leu⁷]ET-1) and *ET-3* ([Thr^{2,5},Phe⁴,Tyr^{6,14},Lys⁷]ET-1), respectively. ET shows a great number of physiological effects, notably in development and vascular homeostasis. ET-1 is formed only in endothelial cells, and is the most abundant member of the family. ET-1 acts in an autocrine or paracrine manner as a vasoconstrictor on the vasculature. It is involved in many physiological and pathological processes, including vascular changes associated with pulmonary hypertension and sepsis. ET-2 is released in the epithelial cells of the kidney and intestine, while ET-3 is found in the brain. The biosynthetic precursor of hET-1, named *prepro-ET-1*, consists of 212 residues and provides (after proteolytic processing) the *big h-ET-1*, which consists of 38 residues bearing the ET-1 sequence in the N-terminal part of the molecule. Big ET-1 shows a 100-fold lower *in-vitro* activity compared to ET-1. In human brain, big hET-1 is specifically converted by the \rightarrow endothelin-converting enzyme into the fully active peptide by cleavage of the

Trp²¹–Val²² bond. All types of smooth muscle are contracted by ETs via the activation of specific receptors. The ETs can also relax the muscles, in some cases either by direct receptor activation or indirectly by releasing *endothelium-derived relaxing factors*, such as NO or eicosanoids. The receptors selective for ET-1 were designated ET-RA, with agonist potency ET-1 > ET-2 >> ET-3, whereas the non-selective receptor (ET-1 = ET-2 = ET-3) was named ET-RB. Generally, the ET-RA reside on smooth muscle cells and mediate vasoconstrictor responses, whereas the endothelial cells express the ET-RB. The latter mediate vasodilatory effects via the ET-induced release of endothelium-derived relaxing factors. Despite the low plasma concentration of ET, it behaves as a circulating mediator and can locally influence cells which are close to the ET-producing tissues. ET modulates chronotropy, ionotropy, bronchoconstriction, and neurotransmission. Furthermore, they act as regulators for other hormones and neurotransmitters. Intravenous application results in the regulation of blood pressure (both pressor and depressor effects), local blood flow, and kidney function. The sequence of hET-1 is identical with p-ET-1, originally isolated from porcine aorta, and with dog, rat, and mouse ET-1. Furthermore, hET-2 is identical in sequence with dog ET-2, and hET-3 with rat ET-3, respectively. Structural similarities exist also between ET and the 21-mer \rightarrow sarafotoxins (SRTX) from the genus *Atractaspis* of the Atractaspididae family, nowadays designated \rightarrow endothelin-like peptides, and other peptide neurotoxins, such as the bee venom \rightarrow apamin or α -scorpion toxin. Furthermore, the vasoactive intestinal contractor, VIC, known as *endothelin- β* , belongs to the ET-SRTX group. ET shows a high affinity to receptors, and is the strongest

vasoconstrictor presently known. Based on the properties of ET, it can be concluded that it may also play a role in chronic diseases, such as hypertension. For this reason, the development of suitable ET antagonists for medical applications is of major importance. A cyclic pentapeptide isolated from the cultured broth of *Streptomyces misakiensis*, cyclo-(D-Trp-D-Glu-Ala-D-Val-Leu-), has been found to be a potent endothelin antagonist with selectivity for the ET_A receptor subtype. Starting from this natural lead compound, a synthetic analogue (BQ-123) has been obtained where the inhibitory potency is improved by more than two orders of magnitude. Human chymase specifically converts big ETs to novel smooth muscle-contracting 31-peptide ETs that may play a role in allergies and vascular diseases [M. Yanagisawa et al., *Nature* **1988**, 332, 411; A. M. Doherty et al., *J. Med. Chem.* **1993**, 36, 2587; K. Ishikawa et al., *J. Med. Chem.* **1992**, 35, 2139; J. Hlavacek, R. Marcova, *Collect. Czech. Chem. Commun.* **1999**, 64, 1211; H. Kido et al., *Biol. Chem.* **1998**, 379, 885; J. Struck et al., *Peptides* **2005**, 26, 2482; F. L. Marasciulo et al., *Curr. Med. Chem.* **2006**, 13, 1655].

Endothelin- β , designation for the *vasoactive intestinal contractor* (VIC), a member belonging to the group of \rightarrow endothelin, and \rightarrow sarafotoxins.

Endothelium-derived relaxing factor, \rightarrow endothelin.

Enfuvirtide, \rightarrow T20.

Enkephalins (ENK), naturally occurring 5-peptides showing a strong antinociceptive effect *in vivo*, comparable to that of the most potent opioids used in medicine such as morphine, fentanyl, and sufentanyl. They act as the endogenous ligands of the μ , δ and κ opiate receptors in the brain. *Methionine-enkephalin*

([Met]enkephalin), H-Tyr-Gly-Gly-Phe-Met-OH, and *leucine-enkephalin* ([Leu]enkephalin), H-Tyr-Gly-Gly-Phe-Leu-OH, are released by limited proteolysis from the precursor proteins prepro-enkephalin, that contains six copies of Met-enkephalin and one copy of Leu-enkephalin, and preprodynorphin (also named prepro-enkephalin B) which contains only three copies of Leu-enkephalin, but also \rightarrow dynorphin and \rightarrow neoendorphin. Enkephalin acts both as neurotransmitter and neuromodulator. The application of enkephalins as analgesics has been retarded by their poor stability *in vivo* and by their inability to effectively penetrate the blood-brain barrier (BBB). An effective BBB transport of glycosylated enkephalins has been described by several groups. Many analogues have been synthesized in an attempt to develop new anodynes that would be more potent and less addictive (\rightarrow endorphins), but until now no definitive alternatives to the application of classical analgesics for pain treatment have been identified [J. Hughes et al., *Nature* **1975**, 258, 577; M. Comb et al., *Nature* **1982**, 295, 663; G. Cardillo et al., *J. Med. Chem.* **2002**, 10, 2755; R. Polt et al., *Med. Res. Rev.* **2005**, 25, 557].

Enniatin family, cyclic \rightarrow depsipeptides produced by strains of *Fusarium*. Members are *enniatin A*, cyclo-(D-Hiv-Me-Ile)₃, *enniatin B*, cyclo-(D-Hiv-Me-Val)₃, and *enniatin C*, cyclo-(D-Hiv-Me-Leu)₃, *enniatin D*, cyclo-(D-Hiv-Me-Leu-D-Hiv-Me-Val-D-Hiv-Me-Val-), *enniatin E*, cyclo-(D-Hiv-Me-Ile-D-Hiv-Me-Leu-D-Hiv-Me-Val-), and *enniatin F*, cyclo-(D-Hiv-Me-Leu-Me-Ile-D-Hiv-Me-Ile-) which all contain D- α -hydroxyisovaleric acid (D-Hiv) besides various L-methylamino acids. Enniatins act as ionophores to form complexes with K⁺ ions which allow their transport across membranes.

ENOD40 peptides, oligopeptides with 10 to 13 aa exhibiting mitogenic activity and acting as plant growth regulators. They are encoded by the *enod40* gene and characterized by a central Trp residue and the C-terminal sequence -Ile-His-Gly-Ser-OH. For example, the ENOD40 peptide of the pea (*Pisum sativum*) has the sequence: MKFLCWQKSI¹⁰HGS. These peptides are believed to affect cell division by modulation of cellular responses to auxin. It has been suggested that, in legumes, the ENOD peptides function as signal molecules in the formation of the nodule primordium [A. Schaller, *Plant Mol. Biol.* **1999**, *40*, 763; B. Compain et al., *Plant & Soil* **2001**, *230*, 1573].

Entactin, → laminin.

Enteropeptidase, EC 3.4.21.9, originally named *enterokinase*, a → serine peptidase belonging to clan SA, family S1. Enteropeptidase cleaves internal peptide bonds at sites closely resemble the cleavage site -Asp-Asp-Asp-Asp-Lys↓Ile- of cattle trypsinogen (→ trypsin). The latter is highly conserved among vertebrate trypsinogens (A. Light, H. Janska, *Trends Biochem. Sci.* **1989**, *14*, 110).

Enzymatic peptide synthesis, *enzyme-catalyzed synthesis*, the application of enzymes for peptide bond formation. The very complex ribosomal → peptidyl transferase center is not suitable as a catalyst for simple practical peptide synthesis. However, enzymes which usually act as hydrolases, catalyzing the cleavage of peptide bonds, should be considered as peptide ligases due to the principle of microscopic reversibility. The → protease-catalyzed peptide synthesis has been developed as a useful tool in the new catalytic synthetic approach based on protease-engineering and the develop-

ment of non-conventional enzymatic synthesis strategies. Interestingly, even → zymogens are capable of catalyzing peptide bond formation, as was demonstrated during the mid-1990s. The application of → non-ribosomal peptide synthesis (NRPS) displays certain advantages in biotechnological processes, including peptide bond formation in water, a lack of any protection needs for the amino acid building blocks, epimerization domains that enable selective incorporation of D-amino acids into the growing peptide chain, ultimately to obtain cyclic peptides. From a scientific point of view, the → abzyme-catalyzed peptide synthesis represents a very interesting approach which may have practical potential in the future [H.-D. Jakubke et al., *Biol. Chem.* **1996**, *377*, 455; H.-D. Jakubke, Peptide ligases – Tools for peptide synthesis, in: *Organic Synthesis Highlights III*, J. Mulzer, H. Waldmann (Eds.), Wiley-VCH, Weinheim, **1998**, 167].

Enzyme-labile protecting groups, protecting groups in peptide synthesis cleavable under very mild conditions using enzymes. Most commonly, the applied enzymes are hydrolases that directly attack carbonyl groups of esters and/or amides. Bz-Phe was the first enzyme-labile protecting group to be cleaved with chymotrypsin, in 1955. Subsequently, the development of enzyme-labile blocking groups has experienced a logical progression from the early specialized application to most sophisticated synthetic strategies. A special approach is the application of a different enzymatic transformation in a two-step procedure during which an otherwise stable precursor is converted enzymatically into a labile intermediate that subsequently hydrolyzes spontaneously under the reaction conditions [R. W. Holley, *J. Am. Chem. Soc.* **1955**, *77*, 2552; H. Waldmann, D. Sebastian, *Chem. Rev.*

1994, 94, 911; K. M. Koeller, C.-H. Wong, *Nature* **2001**, 409, 232].

Epidermal growth factor (EGF), *urogastron*, hEGF, ESYPGCPSSY¹⁰DGYCLN GGVC²⁰MHIESLDSYT³⁰CNCVIGYSGD⁴⁰RCQTRDLRW⁵⁰ELR (disulfide bonds: C⁶-C²⁰/C¹⁴-C³¹/C³³-C⁴²), a hormone-like polypeptide growth factor stimulating cell proliferation. EGF is an effective mitogen for a wide variety of epidermal and epithelial cells *in vivo* and *in vitro*. A homologous polypeptide was isolated from human urine and named urogastron; this may play a role in the maintenance of gastrointestinal homeostasis *in vivo*. EGF is also used in wound healing. EGF from mouse submaxillary gland forms a complex that contains two molecules of EGF and two molecules of EGF binding protein ($M_r \sim 29$ kDa). Mouse EGF is first synthesized as a large precursor protein (1168 aa). Analogously to many other protein growth factors, EGF stimulates the proliferation and differentiation of their target cells by binding to their receptor tyrosine kinase consisting of a C-terminal cytoplasmic tyrosine kinase domain, a helical single-pass transmembrane segment, and an extracellular cysteine-rich domain. The EGF receptor (EGFR) was identified as a downstream element in different signaling pathways. This function expanded its classical function as a receptor for EGF-like ligands to a role as mediator of various signaling system [S. Cohen, *J. Biol. Chem.* **1962**, 237, 1555; H. Gregory, *Nature* **1975**, 257, 325; J. A. Downie et al., *Annu. Rev. Biochem.* **1979**, 48, 103; S. Tomic et al., *J. Biol. Chem.* **1995**, 21277; P. O. Hackel et al., *Curr. Opin. Cell Biol.* **1999**, 11, 184].

Epidermin, a member of the Type-A family of \rightarrow lantibiotics. Epidermin is a tetracyclic peptide ($M_r \sim 2.2$ kDa) isolated from *Staphylococcus epidermidis* with anti-

crobial activity against *Propionibacterium acnes*, which is one of the causative factors of acne. Epidermin and its analogues, e.g., [Leu⁶]epidermin (*gallidermin*), [Phe¹,Lys²,Trp⁴,Dha⁵,Phe⁶]epidermin (*mutacin B-Ny266*) are much shorter and differ at the C-terminus, but their 12 N-terminal residues are highly related to \rightarrow nisin and \rightarrow subtilin. Gallidermin produced by a *Staphylococcus gallinarum* strain has similar properties to epidermin, but shows slightly better antimicrobial activity against *Propionibacterium acnes*. Therefore, it is an interesting therapeutic agent for the treatment of acne [R. W. Jack, G. Bierbaum, H.-G. Stahl, *Lantibiotics and Related Peptides*, Springer, Berlin, Heidelberg, New York, **1998**].

Epiregulin (ER), an epidermal growth factor-related growth regulating peptide purified from conditioned medium of the mouse fibroblast-derived tumor cell line NIH3T3/clone T7. ER is a single-chain 46-peptide exhibiting 24–50% sequence identity with sequences of other EGF-related growth factors. It belongs to the \rightarrow EGF family. Epiregulin exhibited bifunctional regulatory properties – that is, it inhibited the growth of various epithelial tumor cells and stimulated the growth of fibroblasts and several other cell types. It has been suggested that ER plays important roles in the regulation of growth of epithelial cells and fibroblasts by binding to receptors of EGF-related ligands. ER is an autocrine growth factor in normal human keratinocytes, and organizes epidermal structure by regulating keratinocyte proliferation and differentiation, as well as the expression of \rightarrow transforming growth factor- α (TGF- α), heparin-binding EGF-like factor (HB-EGF), and amphiregulin (AR) [H. Toyoda et al., *J. Biol. Chem.* **1995**, 270, 7495; Y. Shirakata et al., *J. Biol. Chem.* **2000**, 275, 5748].

Epitope, a commonly (but not very precisely) termed antigenic determinant characterizing the portion of a protein → antigen that is recognized by → antibodies.

EPL, expressed protein ligation.

EPO, erythropoietin.

Equilibrium-controlled enzymatic synthesis, *thermodynamically controlled enzymatic synthesis*, an approach to → protease-catalyzed peptide synthesis according to the direct reversal of → proteolysis. Characteristic hallmarks are the use of acyl donors with free carboxylate function, and the possibility of applying all proteases independently of their individual mechanism as potential catalysts. General drawbacks are the low reaction rates, the high enzyme requirement, and the need of direct approaches to shift the unfavorable equilibrium position. The rationale behind this is based on the thermodynamic barrier to the reverse of hydrolysis that is determined predominantly by the energy required to transfer a proton from the reacting group of the nucleophile to that of the negatively charged carboxylate moiety of the acyl donor. The addition of organic solvents, which lowers the dielectric constant of the medium, and results in a reduced acidity of the acyl donor's carboxylate function, increases the equilibrium constant for this proton transfer, and thus promotes the reverse reaction. Furthermore, reaction conditions that lead to product precipitation or extraction increase the efficiency of the reverse reaction [H.-D. Jakubke et al., *Angew. Chem. Int. Ed.* **1985**, 24, 85].

Era, *E.coli Ras-like protein*, a multifunctional, essential GTPase occurring in all bacteria (with the exception of some obligate intracellular eubacteria), coupling cell growth with cytokinesis. Era binds to the 16S ribosomal RNA of the small (30S) ribo-

somal subunit [D. D. Leipe et al., *J. Mol. Biol.* **2002**, 317, 41; C. E. Calcon, P. E. March, *Curr. Opin. Microbiol.* **2003**, 6, 135; M. R. Sharma et al., *Mol. Cell* **2005**, 18, 319].

Erythropoietin (EPO), a monomeric glycoprotein that stimulates the production and release of erythrocytes. It is synthesized in the kidney and liver of adults, but only in the liver of fetuses and neonates. A lack of oxygen or a shortage of red blood cells stimulates the synthesis and secretion of EPO into the bloodstream. EPO completes the action of the classical → colony-stimulating factors. Human EPO consists of 165 aa ($M_r \sim 30$ kDa with carbohydrate), including four Cys and three potential glycosylation sites. The erythropoietin receptor (EPOR) is assumed to be activated by ligand-induced homodimerization. Crystal structure analysis of the extracellular domain of EPOR in its unligated form has revealed a dimer. The human gene is located on chromosome 7. EPO is quickly degraded and excreted by the kidneys. EPO is used in the treatment of anemia arising from kidney disease, and misused in doping. It is synthesized in large quantities by recombinant technology. The design and synthesis of a homogeneous polymer-modified erythropoiesis protein consisting of 166 aa and two covalently attached, branched polymer moieties was described in 2003 [K. Jacobs et al., *Nature* **1985**, 313, 806; H. Pagel, W. Jelkmann, *Deutsch. Med. Wochenschr.* **1989**, 114, 957; O. Livnah et al., *Science* **1999**, 283, 987; G. G. Kochendoerfer et al., *Science* **2003**, 299, 884].

Esculentins, two peptide families of → ranid frog peptides. *Esculentin-1 family*, consisting of *esculentin-1SEa*, GLFSKFNKKK¹⁰IKSGLIKI²⁰TAGKEAGLEA³⁰LRTGIDVIGC⁴⁰KIKGEC, a 46 peptide; and *esculentin-1SEb*, a 46-peptide with similar sequence, whereas the *esculentin-2*

family has only one member, named *esculentin-2SE*, GFFSLIKGVK¹⁰IATKGLAKNL²⁰GKMGLDLVGC³⁰KISKEC. All members of the esculentins exhibit histamine releasing activity on rat peritoneal mast cells and growth-inhibiting activity towards the bacteria *M. luteus* and *E. coli* [C. Graham et al., *Peptides* **2006**, *27*, 1313].

ESI-MS, electrospray ionization mass spectroscopy.

ESR, electron spin resonance.

ET, endothelin.

Et, ethyl.

Etamycin, *Viridogrisein*, Hypic-Thr-D-Leu-D-aHyp-Sar-Me₂Leu-Ala-PhSar-OH (lactone ring between Thr and PheSar), a heptapeptide lactone antibiotic (→ depsipeptides) produced by *Streptomyces griseoviridis*. The α -amino function of Thr is blocked by the hydroxyisopicolinic acid (Hypic), and further unusual building blocks are L- β -N-dimethylleucine (Me₂Leu), sarcosine (Sar), L- α -phenylsarcosine (PhSar), and D-*allo*-hydroxyproline (D-aHyp). Etamycin is active against Gram-positive bacteria and *Mycobacterium tuberculosis* [F. Kamal, E. Katz, *J. Antibiot. (Tokyo)* **1976**, *29*, 944].

ETH, ecdysis-triggering hormone.

Et_m, ethoxymethyl.

EtS, ethylsulfanyl.

Eumenitin, LNLKGIFKKV¹⁰ASLLT, an antimicrobial 15-peptide isolated from the venom of the solitary eumenine wasp *Eumenes rubronotatus*. It has characteristic features of cationic linear α -helical → antimicrobial peptides. Eumenitin shows inhibitory activity against both Gram-positive and Gram-negative bacteria. It may play a role in preventing potential infection by microorganisms during prey consumption by

their larvae [K. Konno et al., *Peptides* **2006**, *27*, 2624].

Eupeptide, a peptide in which amino acid residues are linked only through α -functions, i.e., a so-called normal or ordinary peptide. This term seems to be without importance in the real literature of peptide science [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, *12*, 79].

European Peptide Society (EPS), an association of scientists in peptide research in Europe. The EPS was founded in 1989, primarily in order to ensure that the valuable but informal European Peptide Symposia should be continued on a sound basis. The Statutes state that is a non-profit association established for the public benefit to promote in Europe and in certain neighboring countries the advancement of education, and in particular the scientific study of the chemistry, biochemistry, and biology of peptides. Its most important activity is the organization in Europe of the biennial international symposium (25th Symposium, Budapest 1998; 26th Symposium, Montpellier 2000; 27th Symposium, Sorrento 2002; 28th Symposium, Prague 2004; 29th Symposium, Gdansk 2004), which regularly attracts about 1000 participants from all over the world. The Proceedings are published biennially. Although the early symposia (from 1958 onwards) were necessarily devoted largely to the development of chemical methods for the synthesis of peptides, the programs now extend to the biology of peptides, and include, for example, structure-activity relationships, conformational studies, peptide vaccines, and the immunology of peptides. The Society also provides financial support to smaller local meetings and workshops. The Society, in association with John Wiley, publishes an official *Journal of Peptide Science*, with a reduced rate of

subscription for members. In addition, it circulates a Newsletter, which contains brief reports of meetings and other news, book reviews, and lists, and a calendar of relevant symposia. The Newsletter is available electronically, as is part of the *Journal of Peptide Science*. The Society administers the *Josef Rudinger Memorial Lecture* and the *Leonidas Zervas Award*, and a fund to assist younger members to attend symposia. EPS has close and cordial relations with other Peptide Societies (→ American Peptide Society, → Japanese Peptide Society, → Australian Peptide Association). The EPS has a membership of about 1300 (from some 30 countries), who pay no subscription at present. The principle was established at the outset that there would be no subscription in order to ensure that all peptide scientists in Europe would be able to enroll.

Exenatide, → exendins.

Exendins, peptides isolated from the venom of the lizard (*Heloderma suspectum* and *H. horridum*) that are members of the → secretin-glucagon-VIP family. *Exendin-4* (*H. suspectum*), HGEFTFTSDL¹⁰SKQMEEE AVR²⁰LFIEWLKN³⁰G³⁰PSSGAPPPSa, is a 39-peptide amide, and *exendin-3* (*H. horridum*) differs only in two positions (S² and D³) from exendin-4. Exendin-4 and → glucagon-like peptide (GLP)-1 (7–36) amide bind with similar affinity to the GLP-1 receptor. However, exendin-4 has a longer half-life than GLP-1, and could be important in the treatment of type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD). *Exenatide* is a synthetic 39-peptide with the same sequence as exendin-4, and shows similar glucoregulatory activities to GLP-1, including glucose-dependent enhancement of insulin secretion by β -cells. By using exenatide, the risk of hypoglycemia should

be reduced as the stimulation of insulin secretion occurs only in the presence of elevated blood-glucose concentrations. Exenatide is approved by the FDA as an adjunctive therapy to improve glycemic control in patients with → type 2 diabetes mellitus. N-terminal shortened sequences such as exendin-(3–39), exendin-(5–39) and exendin-(9–39) are potent GLP-1 receptor antagonists [J. Eng et al., *J. Biol. Chem.* **1992**, 267, 7402; J. Egan et al., *J. Clin. Endocrinol. Metab.* **2002**, 87, 1282; M. B. Davidson et al., *Nature Rev.* **2005**, 4, 713; X. Ding et al., *Hepatology* **2006**, 43, 173].

Exorphins, protein-derived opioid peptides of exogenous origin. They are mainly produced from food proteins during digestion. Especially, milk proteins, such as α -casein, β -casein, κ -casein, α -lactoglobulin, β -lactoglobulin and lactoferrin contain partial fragments that behave like opioid receptor ligands under *in vitro* and *in vivo* conditions (→ milk protein-derived opioid peptides). The most important members of this group are the → β -casomorphins. *Gluten-exorphins* are opioid peptides released from wheat gluten pepsin-elastase digest. The sequence of *gluten-exorphin* A5, H-Gly-Tyr-Tyr-Pro-Thr-OH, occurs 15 times in the primary structure of wheat gluten. The A5 peptide is selective for δ -receptors. After oral administration to rats, A5 stimulates postprandial insulin release, and this effect could be reversed by the opioid antagonist naloxone. Besides gluten exorphin A5, A4 (H-Gly-Tyr-Tyr-Pro-OH), B5 (H-Tyr-Gly-Gly-Trp-Leu-OH), and B4 (H-Tyr-Gly-Gly-Trp-OH) are further gluten-exorphins. *Hemorphins* are peptides with opioid-like activity found after proteolytic treatment of hemoglobin. During the early 1990s it became clear that hemoglobin also serves *in vivo* as a source of bioactive peptides that

might play a role in homeostasis. From this fact, a so-called tissue-specific peptide pool has been formulated which should be a novel system of peptidergic regulation besides hormonal and neuromodulatory systems [H. Teschemacher et al., *Inc. Biopoly.* **1997**, 43, 99; S. Fukudome et al., *FEBS Lett.* **1997**, 412, 475; V. T. Ivanov et al., *Inc. Biopoly.* **1997**, 43, 171].

Expressed enzymatic ligation (EEL), an approach of → biochemical protein ligation that combines the advantages of → expressed protein ligation and the → substrate mimetic approach of protease-catalyzed ligation. Especially for peptide – but in particular for protein synthesis – the approach works best when, in addition to substrate mimetics, engineered proteases with minimized proteolytic activity are used. The latter ensure successful ligations, even in the presence of cleavage-

sensitive amino acid moieties within the starting peptide fragments. In the original report describing expressed enzymatic ligation, the enzyme was non-covalently modified by thioglycolic acid, which inhibited the native proteolytic activity of the protease completely. Alternatively, the undesired cleavage activity of proteases could be suppressed by manipulating the enzyme directly both via site-directed and directed evolution approaches. Appropriate examples are reported for both cases. Finally, the enzyme can be manipulated in terms of its substrate specificity by covalent chemical modifications, mainly within the active site of the biocatalyst [Z. Machova et al., *Angew. Chem. Int. Ed.* **2003**, 42, 4916].

Expressed protein ligation, → biochemical protein ligation.

F

F₁F₀-ATPase, *proton-translocating ATPase*, *proton-pumping ATPase*, a multisubunit transmembrane protein of the inner mitochondrial membrane catalyzing the synthesis of ATP. The ATPase uses the energy stored in the electrochemical proton gradient in the ATP synthesis, coupling this process to the exergonic transport of H⁺ back into the mitochondrial matrix [P. C. Hinkle, R. E. McCarty, *Sci. Am.* **1978**, 238, 104; H. S. Penefsky, R. L. Cross, *Adv. Enzymol.* **1991**, 64, 173].

Fa, 3-(2-furyl)acryloyl.

Fab, antigen binding Ig fragment.

Fab fragment, a papain cleavage product of an IgG molecule yielding two Fab fragments and one F_c fragment.

FAB-MS, fast atom bombardment mass spectroscopy.

FACS, fluorescence-activated cell sorter.

Factor II, → prothrombin.

Factor IIa, → thrombin.

Farn, farnesyl.

Farnesylated peptides, *N*- or *S*-substituted peptides with the farnesyl (Farn) moiety. Based on the hydrophobicity of this C₁₅ unit, isoprenoid farnesylated peptides are characterized by increased bioavailability. Farnesylated peptides are useful building blocks for the synthesis of special biological/pharmaceutical model targets, since the farnesyl group in proteins may participate in specific protein–protein interactions. *In vivo*, farnesylation is performed by the

enzyme → farnesyltransferase. Farnesylation is obligatory for the function of the → Ras proteins, and other physiologically important proteins. This modification is the first and important step in an ordered series of post-translational modifications that mediate membrane localization and protein–protein interactions for various proteins involved in cellular regulatory events [G. Byk, D. Scherman, *Int. J. Pept. Protein Res.* **1996**, 47, 333; D. M. Leonard, *J. Med. Chem.* **1997**, 40, 2971; B. Bader et al., *Nature* **2000**, 403, 223; R. Roskoski, Jr., *Biochem. Biophys. Res. Commun.* **2003**, 303, 1].

Farnesyltransferase (FTase), an enzyme catalyzing the transfer of a farnesyl group from farnesyl diphosphate (FPP) to proteins (→ farnesylated proteins). This process occurs via a Cys residue located in a C-terminal CY₁Y₂X motif, where C is the modified Cys, Y₁ and Y₂ are often an aliphatic residue, and X is Ser, Met, Ala, or Gln. Farnesylation is obligatory for the function of the oncoprotein Ras (→ Ras proteins). Since mutated forms of Ras genes are among the most common genetic abnormalities in human cancer, the development of FTase inhibitors as antineoplastic agents has led to various inhibitors that currently undergoing Phase I, II, and III clinical trials [P. Dunten et al., *Biochemistry* **1998**, 37, 7907; X. Chen et al., *Chin. Med. Sci. J.* **1999**, 14, 138; J. M. Troutman et al., *Bioconjugate* **2005**, 16, 1209].

FaRP, FMRFamide-related peptide.

Fbg, fibrinogen.

Fc, ferrocenyl.

Fc fragment, a papain cleavage product of an IgG molecule beside to molecules of the → Fab fragment.

Fd, ferredoxin.

Ferredoxins (Fd), members of → iron-sulfur proteins involved in electron transfer processes. They are the most widely distributed metalloprotein electron carriers in nature. Highly homologous *2Fe-Fd* with 96 to 98 aa, including four to six Cys, occur in blue-green bacteria, higher plants, and green algae. *4Fe-Fd* contain a single 4Fe-4S cluster as an active center. The iron atoms are bound to the only four Cys residues in the protein. These Fd have been found primarily in bacteria such as *Desulfovibrio gigas*. *8Fe-Fd* contain two identical 4Fe-4S clusters, each of which forms a cube and is covalently linked to four Cys residues in the peptide chain, which consists of about 55 residues, including eight Cys. This type of Fd takes part in many electron transport processes in *Clostridia* and photosynthetic bacteria. A special type of Fd is the *high potential iron-sulfur protein (HiPIP)*, as isolated from some photosynthetic bacteria. This contains a single 4Fe-4S cluster, and is characterized by a positive standard potential of about +350 mV; this is in contrast to the other Fd, which have standard potentials of about -420 mV [A. J. Thompson, in: *Metalloproteins*, P. Harrison (Ed.), Verlag Chemie, Weinheim, 1985; Part I, p. 79; G. Backes et al., *J. Am. Chem. Soc.* 1991, 113, 2055; H. Matsubara, K. Saeki, *Adv. Inorg. Chem.* 1992, 38, 223].

Ferritins, a family of proteins produced in a variety of amounts and types, depending on the state of development of an animal, or of the differentiation state of a particular cell type, or of the environment. The main function of the ferritins is iron storage

when iron is needed for intracellular use for a variety of iron proteins, e.g., cytochromes, ribonucleotide reductase, oxidases, nitrogenases, or photosynthetic reaction centers. The ferritins are characterized by a very complex structure. The subunits consist of bundles of four α -helices, and show remarkable sequence conservation among plants and animals. This structure is probably related to the need to form a hollow sphere pierced by 14 channels for the passage of iron. Ferritin consists of a protein coat of 24 partly carbohydrate-containing subunits ($M_r \sim 450$ kDa). The shell-like ferritin, with a diameter of 80 Å, is capable of storing up to 4500 Fe(III) atoms as iron-hydroxide-oxide micelles. Ferritin is the major storage depot for iron, and contains (together with the related → hemosiderin) 25% of the body's iron [E. C. Theil, *Adv. Enzymol. Relat. Areas Mol. Biol.* 1990, 63, 421; P. M. Harrison, P. Arosio, *Biochim. Biophys. Acta* 1996, 1275, 161].

α -Fetoprotein (AFP), *alpha-fetoprotein*, a glycoprotein belonging to the α -globulins that is formed in the serum of mammalian embryos (0.1 mg mL⁻¹), but occurs in the serum of adults only in traces (< μ g mL⁻¹). Synthesis is performed first by the yolk sac and later by the fetal liver. At birth, AFP is replaced by serum albumin. *Human AFP* (hAFP) is a single-chain polypeptide consisting of 590 aa ($M_r \sim 70$ kDa) that contains 3–5% carbohydrate. It is characterized by a triplicate domain structure of nearly 200 aa, each forming intramolecular loops stabilized by disulfide bridging. The helical V- or U-shaped structure was first described in 1983. Beside its secretion during pregnancy, hAFP can be expressed in adult teratomas, hepatomas, and yolk sac tumors of the ovary. It has been employed in the clinical laboratory as a tumor and gestational age-dependent fetal defect marker,

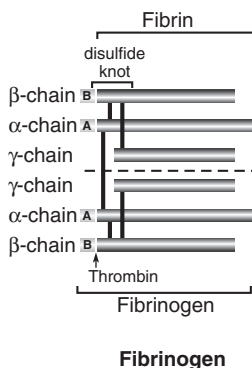
and is presently utilized as a screening agent for neural tube defects and aneuploidies. In addition, hAFP has importance as a serum tumor marker for liver, yolk sac, and germ cell cancers. Last, but not least, it has been determined as a growth factor for both fetal and tumor cells, and enhances growth in both cellular environments. In 1996 it was reported that the third domain of hAFP contained an encrypted 34-peptide segment with growth-suppressing properties (\rightarrow growth inhibitory peptide), in contradistinction to the growth-enhancing activities of the full-length hAFP molecule [I. G. Abelev, *Adv. Cancer Res.* **1971**, 14, 295; A. J. Luft, F. L. Lorscheider, *Biochemistry* **1983**, 22, 5978; G. J. Mizejewski, in: *Alpha-Fetoprotein and Congenital Disorders*, G. J. Mizejewski, I. H. Porter (Eds.), Academic Press, Orlando, **1985**, p. 5; G. J. Mizejewski et al., *Mol. Cell. Endocrinol.* **1996**, 118, 15; G. J. Mizejewski, *Exp. Biol. Med. (Marywood)* **2001**, 226, 377; G. J. Mizejewski, G. Butterstein, *Curr. Prot. Pept. Sci.* **2006**, 7, 73].

FGF, fibroblast growth factor.

Fibrin, a globular protein belonging to the plasma proteins involved as main component in blood coagulation. Fibrin is formed from the soluble plasma protein \rightarrow fibrinogen via a proteolytic reaction catalyzed by \rightarrow thrombin. It aggregates spontaneously to form fibers with a banded structure that repeats every 225 Å. The rather fragile "soft clot" is converted to a "hard clot" by crosslinking of fibrin molecules catalyzed by the transamidase termed *fibrin-stabilizing factor* (*FSF* or *XIII_a*). This process is triggered by the binding of Ca^{2+} , and activated by thrombin. The blood clots consist of crosslinked fibrin forming an insoluble fibrous network which provides a stable wound closure. *Fibrin sealant* is a hemostatic and wound support [R. F.

Doolittle, *Annu. Rev. Biochem.* **1984**, 53, 195; D. A. Gabriel et al., *J. Biol. Chem.* **1992**, 267, 24259; C. J. Dunn, K. L. Goa, *Drugs* **1999**, 58, 863].

Fibrinogen (Fbg), *factor I*, the only coagulable protein in the blood plasma consisting of three pairs of non-identical but homologous peptide chains $[(\text{A}\alpha)_2(\text{B}\beta)_2\gamma_2]$ crosslinked by disulfide bonds, and two pairs of *N*-linked oligosaccharides. A and B represent the \rightarrow fibrinopeptides in the subunits $\text{A}\alpha$ (610 aa) and $\text{B}\beta$ (461 aa), whereas the γ -polypeptide chain contains 411 aa. The six peptide chains of fibrinogen are linked by 17 disulfide bonds, seven within each half of the dimer and three joining these two protomers. The conversion of fibrinogen to \rightarrow fibrin starts by thrombin cleavage of the fibrinopeptide A from the $\text{A}\alpha$ -chains, yielding fibrin I monomers. The second cleavage in the $\text{B}\beta$ -chain is performed after the fibrin I monomers have polymerized end-to-end to form protofibrils. Fibrinogen occurs in the blood plasma of vertebrates and some arthropods. Human blood contains $2\text{--}3 \text{ g L}^{-1}$ of fibrinogen [R. F. Doolittle, *Sci. Am.* **1981**, 245, 126; R. F. A. Zwaal, H. C. Henker (Eds.), *Blood Coagulation*, Elsevier, Amsterdam, **1986**].



Fibrinolysin, \rightarrow plasmin.

Fibrinopeptides, peptides proteolytically released from \rightarrow fibrinogen during the conversion to \rightarrow fibrin in the blood-clotting process. With *fibrinopeptide A* (human), ADSGEGDFLA¹⁰ EGGGVA, and *fibrinopeptide B* (human), <EEGVNDNEEG¹⁰FFSAR, two pairs of peptides exist that are cleaved by thrombin from the N-termini of the α and β chains of fibrinogen. Fibrinopeptide A ranges in the size from 14 to 21 residues, depending on the species. The fibrinopeptides show vasoconstrictive activity. Fibrinopeptides gained importance when they were used to establish a detailed phylogenetic tree for mammals [B. Blomback et al., *Biochim. Biophys. Acta* **1966**, 115, 371; A. Vindigni, E. Di Cera, *Biochemistry* **1996**, 35, 4417].

Fibrin-stabilizing factor (FSF, Factor XIII), a blood coagulation factor. FSF is a transamidase occurring both in platelets and plasma.

Fibroblast growth factors (FGFs), *heparin binding growth factor*, *HBGFs*, a large family of important signaling molecules essential for mammalian development such as cell differentiation, embryogenesis, growth, survival, migration, angiogenesis, tissue repair, and wound healing. FGFs regulate physiological processes via complex combinatorial signaling pathways. Four specific cell-surface receptors (FGFRs 1–4) encoded by four distinct genes are expressed together with the 22 structurally related FGF ligands in specific spatial and temporal patterns. It has been shown that different FGFs demonstrate different expression patterns that range from nearly ubiquitous expression in the case of FGF2 to highly restricted expression in the case of FGF4. FGFRs are transmembrane proteins showing tyrosine kinase activity. Numerous receptor isoforms produced via alternative splicing have been described.

One receptor can be activated by several FGFs. The interaction between receptor and FGF ligands requires the participation of heparin or heparan sulfate proteoglycans (HSPGs). The latter bind both FGF and FGFR, stabilizing the formation of the receptor dimer. Mutations and inappropriate expression can provide FGFs that can cause various pathological processes resulting in morphogenetic disorders and cancer. The FGFs share the β -trefoil fold consisting of 12 β -strands that form six β -hairpins. The term β -trefoil fold has been originated from the threefold symmetry that produces three “trefoil” subdomains of four β -strands each. Besides other proteins, interleukin-1 α and interleukin-1 β (\rightarrow interleukins) share this structural fold. Recently, the structure of rat FGF1 (acidic FGF) at 1.4 Å resolution has been published and compared with structures of human, bovine, and newt FGF1, which have been reported previously. Interestingly, human and rat FGF1 were found to have similar structures [D. M. Ornitz et al., *J. Biol. Chem.* **1996**, 271, 15292; J. Schlesinger, *Cell* **2000**, 103, 211; D. M. Ornitz, N. Itoh, *Genome Biol.* **2001**, 2, 3005; N. Kulahin et al., *Acta Crystallogr.* **2007**, F63, 65].

Fibroin, a fibrous protein occurring very often in silk produced by insects and arachnids. Silk protein exists as a semicrystalline array of antiparallel β -sheets [D. Kaplan et al., *Silk Proteins*, American Chemical Society, New York, **1994**].

Fibronectin (FN), an extracellular adhesive glycoprotein mediating cell-matrix adhesion. FN is a dimer consisting of two similar (but not identical) subunits, each with almost 2500 residues. The subunits are joined together by a pair of disulfide bonds located near their C-termini. Each polypeptide chain is folded into a series of globular domains connected by flexible

sequence segments. Special groups of these domains are responsible for binding of heparin, cells, and collagen. Analysis of the cell-binding domain led to the discovery of a specific tripeptide sequence (Arg-Gly-Asp or RGD) that is responsible for the cell-binding activity. The RGD sequence is a common motif in a variety of extracellular adhesive proteins, and is recognized by cell-surface receptors that bind the specific protein. Besides the RGD sequence, receptor binding may also depend on other parts of the sequence of the adhesive molecule. The RGD sequence is the most important site for recognition by a cell-surface FN receptor, the $\alpha_5\beta_1$ integrin heterodimer. Further cell-surface receptors of FN are heparan sulfate and chondroitin sulfate heterodimers, and glycolipids. The \rightarrow integrins are the best-characterized FN receptors in terms of binding specificity and functional roles. FN occurs in three different forms. The soluble dimeric form, termed *plasma FN*, circulates in the blood and other body fluids enhancing wound healing, blood clotting, and phagocytosis. *Cell-surface-FN* formed from oligomers of FN occurs transiently attached to the surface of cells. *Matrix FN* formed from highly insoluble FN fibrils is found in the extracellular matrix. In the last two FN forms, additional disulfide bonds stabilize these structures by crosslinking. In addition to its function for cell adhesion, FN is also important for cell migration [R. O. Hynes, *Sci. Am.* **1986**, 254, 42; R. O. Hynes, K. M. Yamada, *J. Cell. Biol.* **1982**, 95, 369; L. M. Schnapp et al., *J. Biol. Chem.* **1995**, 270, 23196].

Fischer, Emil Hermann (1852–1919), German chemist and winner of the Nobel Prize in Chemistry 1902 for his work on the structure and synthesis of sugars and purines. Between 1899 and 1908, he made

great contributions to knowledge of proteins. In 1901, he published, in collaboration with Fourneau, the preparation of glycyl-glycine by partial hydrolysis of \rightarrow diketopiperazine. However, the publication of the first chemical peptide synthesis was performed by \rightarrow Curtius in 1902 using the \rightarrow acyl azide method. Later, Fischer synthesized oligopeptides which culminated in an octadecapeptide and had some characteristics of natural proteins. In 1881 he was appointed Professor of Chemistry at the University of Erlangen (Germany), and seven years later moved to the University of Würzburg. In 1892, Fischer was asked to succeed A. W. Hofmann in the chair of chemistry at the University of Berlin, where he remained until his death in 1919 [F. W. Lichtenthaler, *Emil Fischer, His Personality, His Achievements, and His Scientific Progeny*, *Eur. J. Org. Chem.* **2002**, 4095].

FITC, fluorescein isothiocyanate.

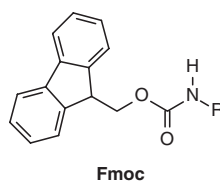
FIZZ, a family of cysteine-rich secreted proteins, also termed as resistin-like molecules, *RELM*. *FIZZ1* or *RELM α* (found in inflammatory zone 1) was detected in bronchoalveolar lavage fluid from animals with an allergic pulmonary inflammation in 2000. *FIZZ2* or *RELM β* was localized in proliferating epithelia at the base of the crypts in the intestinal tract. The third member of this family, *FIZZ3*, is also known as \rightarrow resistin. [I. N. Holcomb et al., *EMBO J.* **2000**, 19, 4046; C. M. Stephan et al., *Proc. Natl. Acad. Sci. USA* **2001**, 98, 502; M. W. Rajala et al., *Mol. Endocrinol.* **2002**, 16, 1920].

FK506-binding proteins (FKBP), a family of \rightarrow peptidyl prolyl *cis/trans* isomerases. FKBP are cellular targets of the macrocyclic lactam FK506. Beside the prototypic FKBP12, up to 15 additional FKBP with higher molecular masses constitute the

ensemble of these enzymes in humans. Phylogenetic conservation of the FKBP family up to organisms with a minimal set of genes suggests a basic function for cellular life. The three-dimensional structure of human FKBP12 is dominated by β -sheets complemented by little helical structure. Upon binding to FKBP12, FK506 inhibits its peptidyl prolyl *cis/trans* isomerases activity in a subnanomolar concentration range. Besides FK506, the related derivative rapamycin has also high affinity for FKBP12. *Trigger factor*, which was shown to interact with the nascent chain emerging from bacterial ribosomes, is a 48 kDa FKBP-like protein. It is composed of three domains, the middle one of which is the FKBP-like catalytic domain. Both FK506 and \rightarrow cyclosporin A block the protein phosphatase activity of \rightarrow calcineurin subsequent to binding of their respective binding proteins. In contrast, the FKBP12/rapamycin complex is inert toward calcineurin but highly inhibitory towards the kinase activity of mammalian TOR, a translational regulator via ribosomal protein S6 kinase and eukaryotic translation initiation factor 4E-binding proteins [M. Arevalo-Rodriguez et al., *Front. Biosci.* **2004**, 9, 2420].

9-Fluorenylmethoxycarbonyl group (Fmoc), an amino-protecting group of the urethane type of widespread practical importance, and cleavable under mildly basic conditions. Fmoc-Cl and, alternatively Fmoc-OSu (9-fluorenylmethyl-*N*-succinimidyl carbonate), have been recommended for the formation of Fmoc-protected amino acids. Usually, 20% piperidine in DMF is applied routinely, where cleavage of the Fmoc group occurs within seconds at room temperature. Piperidine also traps the dibenzofulvene initially formed in the reaction. Other reagents, such as 1,8-diazabicyclo[5.4.0] undec-7-ene

(DBU) or fluoride ion may be used as an alternative. Although introduced into peptide chemistry during the early 1970s, the Fmoc-protecting group scheme (\rightarrow Sheppard tactics) has only been widely applied in SPPS since 1978 [L. A. Carpino, G. A. Han, *J. Org. Chem.* **1972**, 37, 3404].



Fluorescent peptide probes, peptide-based fluorescence probes for *in-vivo* diagnostic imaging. These probes can be classified into targeting, crosslinking, and protease-activable probes, and have shown great potential in biomedical research [C.-H. Tung, *Biopolymers (Pept. Sci.)* **2004**, 76, 391].

Fluorinated peptides, peptides that contain fluorine substituents may display unusual chemical and biochemical properties. A fluorine substituent very much resembles a hydrogen substituent with respect to van der Waals radius. However, as fluorine is the most electronegative element, the polarity and dipole moment is drastically changed. Moreover, fluorine substituents are reputed to influence lipophilicity and metabolic stability. Therefore, fluorinated peptides have the potential to display increased resistance towards proteolytic degradation. In the case of 4-fluoroproline derivatives, the conformational preference of the pyrrolidine ring is changed compared to 4-hydroxyproline derivatives. Fluorinated peptides containing the radionuclide ^{18}F are radiopharmaceuticals or radiodiagnostics for PET (Positron Emission Tomography). Peptides containing fluoromethylketone moieties have found widespread application as enzyme

inhibitors [R. E. Weiner, M. L. Thakur, *Bio-Drugs* **2005**, 19, 145; R. Smits, E. Koks, *Curr. Top. Med. Chem.* **2006**, 6, 1483; M. Sani, *Curr. Top. Med. Chem.* **2006**, 6, 1545;].

Fm, 9-fluorenylmethyl.

FMDV, foot-and-mouth disease virus.

Fmoc, 9-fluorenylmethoxycarbonyl.

Fmoc amino acid fluorides, highly carboxy-activated amino acid derivatives suited both for solution syntheses and for \rightarrow SPPS. These species are especially recommended for SPPS of complicated longer peptides, and also mainly for the coupling of sterically hindered amino acid building blocks. Fmoc amino acid fluorides are usually stable crystalline derivatives and can be synthesized from the Fmoc amino acids with DAST, cyanur fluoride, or the \rightarrow TFFH reagent [L. A. Carpino et al., *J. Org. Chem.* **1986**, 51, 3732; L. A. Carpino et al., *J. Am. Chem. Soc.* **1990**, 112, 9651; L. A. Carpino et al., *J. Am. Chem. Soc.* **1995**, 117, 5401].

Fmoc/Bu^t chemistry, *Sheppard tactics*, a widely applied alternative approach to the Boc-based SPPS (\rightarrow Merrifield tactics) that makes use of the base lability of the \rightarrow 9-fluorenylmethoxycarbonyl group in SPPS. The semipermanent side-chain-protecting groups are mostly of the *tert*-butyl type, and can be cleaved under relatively mild reaction conditions with TFA. Linker moieties displaying comparable acid lability are mainly used.

FMRFamide, H-Phe-Met-Arg-Phe-NH₂, FMRFa, isolated from the ganglia of the venus clam *Macrocallista nimbosa*. This molluscan cardioexcitatory tetrapeptide amide was the first member of a large family of bioactive peptides possessing the motif -Arg-Phe-NH₂ at their C-terminus, called firstly \rightarrow FMRFamide-related pep-

tides [D. A. Price, M. J. Greenberg, *Science* **1977**, 197, 670].

FMRFamide-related peptides (FaRP), term for neuropeptides with C-terminal sequence similarities to \rightarrow FMRFamide. Nowadays, FaRP are very often included in the family \rightarrow RFamide peptides.

FN, fibronectin.

Foldamers, oligomers with a characteristic tendency to fold into a specific structure in solution stabilized by non-covalent interactions between non-adjacent subunits. Oligomers containing key structural elements in an artificial sequence show periodical folded conformations such as helices, reverse-turn secondary structures, and non-polar and polar strands that are prone to form pleated sheets. The formation of foldamers is promoted by conformationally restricted building blocks such as β -amino acids or γ -amino acids. Especially, \rightarrow β -peptide secondary structures appear to be very stable, e.g., those oligomers of just six residues adopt very stable helical conformations in aqueous solution. Based on their peculiar structural features, foldamers have found various applications in chemistry, biochemistry, and medicine. However, scientists have also focused their interest on the synthesis and study of oligopeptide *foldamers based on natural amino acids* that are capable of recognizing and transforming selected molecular targets [N. Voyer, *Top. Curr. Chem.* **1996**, 184, 1; S. H. Gelman, *Acc. Chem. Res.* **1998**, 31, 173; L. Baltzer et al., *Chem. Rev.* **2001**, 101, 3153; G. Licini et al., *Eur. J. Org. Chem.* **2005**, 969].

Follicle-stimulating hormone releasing hormone, \rightarrow gonadoliberin.

Folliliberin, → gonadoliberin.

Follistatin (FS), a 288 aa protein ($M_r \sim 35$ kDa) acting as an important mediator of cell secretion, development, and differentiation in a number of tissue and organ systems. In 1987, it was first isolated from ovarian follicular fluid as a protein factor that is capable of suppressing the secretion of → follitropin by pituitary cells in culture, as does inhibin. Later, it became clear that this effect of FS was only one of its many properties in reproductive and non-reproductive systems. FS regulates cellular differentiation and secretion through its potent capability to bind and bionutralize → activin, with which it is co-localized in many tissue systems [N. Ueno et al., *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 8282; W. Vale et al., *Recent Prog. Horm. Res.* **1988**, *44*, 1; D. J. Philipps, D. M. de Kretser, *Front. Neuroendocrinol.* **1998**, *19*, 287; C. Peng, S. T. Mukai, *Biochem. Cell Biol.* **2000**, *78*, 261].

Follitropin, *follicle-stimulating hormone*, (**FSH**), a member of the → gonadotropins. FSH is a glycoprotein ($M_r \sim 25$ kDa) consisting of a α subunit (hFSH: 96 aa), which is identical to those of → thyrotropin, → lutropin (LH), and → chorionic gonadotropin, and a β subunit (hFSH: 111 aa). FSH causes spermatogenesis in male testes, and controls maturation of the female follicle. Synthesis and release of FSH is regulated by → gonadoliberin. FSH and its receptor are essential for normal gamete development in males and females. It has been indicated that FSH binds to the central module of the extracellular domain of the follitropin receptor [N. B. Schwartz, *Can. J. Physiol. Pharmacol.* **1995**, *73*, 675; J. A. Dias, P. Van Roey, *Arch. Med. Res.* **2001**, *32*, 510].

For, formyl.

Forced peptide synthesis, formation of an amide bond by physically pushing the reactants together. A plasma-oxidized flat PDMS stamp inked with an *N*-Boc-L-amino acid was pressed into contact with an amine monolayer on gold to form an amide bond. Following this approach, an RGD peptide (-Arg-Gly-Asp-) was synthesized and shown to support cell adhesion, and a 20-mer peptide nucleic acid (→ PNA) strand was synthesized step-by-step on the surface and proven to hybridize with a 16-mer dsDNA [T. P. Sullivan et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 4190].

Formin-related protein (FRL), a 160-kDa protein encoded by *frl* cDNA. The *frl* (formin-related gene in leukocytes) cDNA was isolated as a novel mammalian member of the formin gene family. FRL binds to Rac and regulates cell motility and survival of macrophages [S. Yayoshi-Yamamoto et al., *Mol. Cell. Biol.* **2000**, *20*, 6872].

Formyl group, a N^α -amino protecting group of the carboxamide-type which can be cleaved by solvolysis, oxidation, or hydrazinolysis.

FP LC, fast protein liquid chromatography.

FPP, farnesylpyrophosphate.

Fractalkine, → chemokines.

Franguloline, → sanjoinine A.

FRET, fluorescence resonance energy transfer.

FRL, formin-related protein.

FS, follistatin.

FSF, fibrin-stabilizing factor.

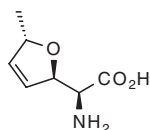
FSH, follicle-stimulating hormone.

FTase, farnesyltransferase.

Fulicin, H-Phe-D-Asn-Glu-Phe-Val-NH₂, a neuroactive 5-peptide amide containing a D-amino acid in position 2 such as, e.g., → dermorphin, → deltorphins and → achatin. Fulicin was isolated from the ganglia of the African giant snail *Achatina fulica*. Structure–activity studies concerning the possible role of the D-Asn residue have been performed in the *Achatina fulica* penis, resulting in increasing resistance to enzymatic digestion and stabilizing a conformation favorable for receptor interaction. In 1997, the sequences of nine *fulicin gene-related peptides* (FGRP-1 to -9) were predicted from the cDNA encoding the ganglia fulicin precursor, and the transcripts were detectable in the heart. Furthermore, it has been reported that fulicin regulates the female reproductive organs of the snail [N. Ohta et al., *Biochem. Biophys. Res. Commun.* **1991**, 178, 486; M. Kobayashi et al., in: *Peptide Chemistry* **1992**, N. Yanaihara (Ed.), p. 353, ESCOM, Leiden, **1993**; Y. Yasuda-Kamatani et al., *Peptides* **1997**, 18, 347; Y. Fujisawa et al., *Peptides* **2000**, 21, 1203].

Furanomycin, a naturally occurring L-α-amino acid isolated from *Streptomyces threomyticus*, showing antibiotic activity against several bacterial species. Further-

more, it was found to be a substrate of *E. coli* isoleucyl aminoacyl tRNA synthetase which catalyzes the incorporation of furanomycin *in vitro* into proteins instead of isoleucine [K. Katagiri et al., *J. Med. Chem.* **1967**, 10, 1149; T. Kohno et al., *J. Biol. Chem.* **1990**, 265, 6931; P. J. Zimmerman et al., *Eur. J. Org. Chem.* **2005**, 3450].



Furanomycin

Fusaricidins, cyclohexadepsipeptides (→ depsipeptides) isolated as minor components from the culture broth of *Bacillus polymyxa* (KT-8). The fusaricidins A–D contain an unusual fatty acid, 15-guanidino-3-hydroxypentadecanoic acid, as a side chain, beside four D-amino acids. They strongly inhibit the growth of various kinds of fungi, and surprisingly show strong inhibitory activity against Gram-positive bacteria such as *Staphylococcus aureus* or *Micrococcus luteus* [Y. Kajimura, M. Kaneda, *J. Antibiot.* **1997**, 50, 220; M. Kanada, Y. Kajimura, *Yakugaku Zasshi* **2002**, 122, 651].

Fuzeon, → T20.

G

G proteins, *guanine nucleotide-binding proteins*, *GTP-binding regulatory proteins*, regulating proteins involved in cell signaling. G proteins are heterotrimers; the α subunit ($M_r \sim 39\text{--}46$ kDa), which binds GTP and GDP and displays GTPase activity, is loosely bound to a tightly associated heterodimer between the β ($M_r \sim 37$ kDa) and γ ($M_r \sim 9$ kDa) subunits, except for Ras proteins and the structurally unknown G_p . G proteins form a superfamily with 20 distinct genes for the α subunit, five for the β subunit, and 12 for the γ subunit providing a large number of specialized protein complexes. G Proteins are classified into four families according to the sequence of the α subunit: *Stimulatory G proteins* (G_s) are addressed by hormone receptors or olfactory receptors, and activate adenylylate cyclase (AC). *Inhibitory G proteins* (G_i) inactivate AC upon GPCR occupancy. The *transducins* (G_t), responsible for the vertebrate phototransduction cascade of the eye, are also classified as G_i proteins because of their sequence homology to other members of the family. On the other hand, G_q forms a link in the phosphoinositide cascade and is connected to phospholipase C, while the G_{12} subfamily is much less characterized. Signal transduction involves ligand binding to a cell-surface receptor coupled to a G protein (G protein-coupled receptors, GPCR), where physiological responses are triggered upon binding of hormones, neurotransmitters and sensory stimuli to the GPCR. Hundreds of GPCRs have been identified that share a common architecture characterized by seven membrane-spanning segments. Receptor

activation stimulates nucleotide exchange and dissociation of the G protein, releasing the α subunit in its GTP-bound state from the $\beta\gamma$ dimer. The resulting subunits can stimulate various target enzymes and elicit biochemical responses. Inactivation requires hydrolysis of the GTP bound to the α subunit. Since deactivation of G protein signaling pathways *in vivo* can occur 10- to 100-fold faster than the rate of GTP hydrolysis by G^α subunits *in vitro*, it has been suggested that *GTPase-activating proteins* (GAPs) can accelerate the GTPase activity of α subunits [M. Rodbell, *Nature* **1980**, 284, 17; A. G. Gilman, *Cell* **1984**, 36, 577; Y. Kaziro et al., *Annu. Rev. Biochem.* **1991**, 60, 349; D. E. Coleman et al., *Science* **1994**, 265, 1405; N. Watson et al., *Nature* **1996**, 383, 172; H. G. Dohlman, J. Thorner, *J. Biol. Chem.* **1997**, 272, 3871; E. M. Ross, T. M. Wilkie, *Annu. Rev. Biochem.* **2000**, 69, 795].

GABA, γ -aminobutyric acid.

Galanin (Gal), GWTLNSAGYL¹⁰LGPLHA VGNHR²⁰SFSDKNGLTLS³⁰ (hGal), a non-amidated 30-peptide that differs from the C-terminally amidated 29-peptide amide found in other species. The 29-peptide amide version, differing from hGal in six amino acid residues and the C-terminal moiety, was first discovered in the porcine intestine in 1983, bearing a C-terminal Ala-NH₂ residue. This peptide is highly conserved among different species, with the exception of the tuna galanin. The name galanin is related to the N- and C-terminal amino acids (Gly and Ala) found in porcine and bovine GAL. Gal inhibits

gastrointestinal motility and delays gastric emptying. Furthermore, it inhibits the release of \rightarrow gastrin and \rightarrow somatostatin from isolated perfused rat stomachs. The neuropeptide galanin and its three receptors are distributed throughout the central nervous system and peripheral nervous system of many different species, including human. The three galanin receptors (GalR1, GalR2, and GalR3) belong to the G protein-coupled receptors. Gal is co-localized with neurotransmitters, including acetylcholine and serotonin as well as noradrenaline. The galaninergic system regulates various cognitive and affective behaviors that are essential for normal homeostasis. Interestingly, a large body of preclinical evidence suggests that Gal and its receptors represent putative targets for the development of novel anxiolytic and antidepressive drugs [K. Tatemoto et al., *FEBS Lett.* **1983**, 164, 124; W. E. Schmidt et al., *Proc. Natl. Acad. Sci. USA* **1991**, 88, 11435; X. Lu et al., *Drug Develop. Res.* **2005**, 65, 227; T. Hökfelt, *Neuropeptides* **2005**, 39, 125].

Galanin-like peptide (GALP), a 60-peptide produced in neurons in the hypothalamic arcuate nucleus. The sequence of porcine GALP-(9–21) is completely identical to the N-terminal portion 1–13 of \rightarrow galanin. The amino acid sequences 1–24 and 41–53 are highly conserved between humans, rats, and pigs. GALP shows a high affinity for the galanin receptor GALR 2 ($IC_{50} = 0.24$ nM). GALP is processed from a 120 aa GALP precursor protein and is implicated in the neural control of feeding behavior [T. Ohtaki et al., *J. Biol. Chem.* **1999**, 274, 37041; Y. Dong et al., *J. Neurophysiol.* **2006**, 95, 3228; H. Kageyama et al., *J. Neuroendocrinol.* **2006**, 18, 33].

Gallerimycin, an antifungal 76-peptide from the greater wax moth *Galleria*

mellonella isolated from a cDNA library of genes expressed during innate immune response in the caterpillars. The recombinant peptide was active against the enteropathogenic fungus *Metarhizium anisopliae*, but not against yeast or Gram-negative or Gram-positive bacteria. Recently, it has been shown that gallerimycin confers resistance to pathogenic fungi in tobacco. Gallerimycin contains six cysteines, of which five are conserved. The three-dimensional structure consists of an α -helix and a threefold anti-parallel β -sheet held together by three disulfide bridges with the pattern: $C^{47}-C^{67}/C^{52}-C^{72}/C^{56}-C^{74}$. The structure of gallerimycin shows similarity to the scorpion peptides cobatoxin-like knottins. It is a member of the \rightarrow defensins that are present in animals and plants [V. Seitz et al., *Dev. Comp. Immunol.* **2003**, 27, 207; B. Schuhmann et al., *Arch. Insect. Biochem. Physiol.* **2003**, 53, 125; G. Langen et al., *Biol. Chem.* **2006**, 387, 549].

Gallidermin, a naturally occurring analogue of \rightarrow epidermin.

Gallinacins, a group of mammalian antifungal peptides. They contain three intramolecular disulfide bonds, are relatively cationic, and are rich in Lys and Arg. It has been reported that gallinacin-1 and -1 α inhibit *C. albicans* in a radial diffusion assay, whereas gallinacin-2 was not active at up to 400 μ g mL⁻¹ in this assay [M. K. Harwig et al., *FEBS Lett.* **1994**, 342, 281].

GALP, galanin-like peptide.

Galparan, GWTLSAGYL¹⁰LGPINLKALA²⁰ ALAKKILa, a chimeric 27-peptide consisting of the N-terminal sequence 1–13 of \rightarrow galanin linked to \rightarrow mastoparan via a peptide bond. This synthetic peptide powerfully stimulates insulin secretion

from isolated rat pancreatic islets in a reversible and dose-dependent manner. Since galparan incarnates an "address" to B cells, analogous to the galanin receptor recognizing the *N*-terminal sequence part 1–13 of galanin, and a "message" such as the mastoparan portion of galparan, this chimeric peptide may be useful in examining the molecular mechanism of insulin exocytosis in both normal and diabetic states. Recently, it has been reported that galparan, besides other chimeric peptides, differentially modulates GTPase activity, displays altered binding affinities for appropriate G protein-coupled receptors, and possesses disparate secretory properties [U. Langel et al., *Regul. Pept.* **1996**, 62, 47; C.-G. Ostenson et al., *Endocrinology* **1997**, 138, 3308; S. Jones, J. Howl, *Curr. Prot. Pept. Sci.* **2006**, 7, 501].

Ganodermin, an antifungal protein ($M_r \sim 15$ kDa) from fruiting bodies of the medicinal mushroom *Ganoderma lucidum*. Ganodermin inhibited the mycelial growth of *Botrytis cinera*, *Fusarium oxysporum*, and *Physalospora piricola* [H. Wang, T. B. Ng, *Peptides* **2005**, 27, 27].

Gas-phase sequencer, an automated equipment for *N*-terminal sequence analysis of peptides and proteins (\rightarrow Edman degradation). A chemically inert disc of glass-fiber, sometimes coated with polybrene, is used for the application of the analysis sample. Exact quantities of basic and acidic reagents, respectively, are delivered as a vapor in a stream of argon or nitrogen, and then added to the reaction cell at programmed times. Under these conditions the peptide loss can be significantly minimized, and such an instrument is capable of processing up to one residue per hour. The thiazolinone derivative is automatically removed and converted to the PTH derivative. The *pulsed-liquid sequencer* is a variant

of the gas-phase sequencer. Here, the acid is delivered as a liquid for very rapid degradation, which requires an accurately measured quantity sufficient to moisten the protein sample and to prevent it from being washed out. Such a procedure shortens the cycle by up to 30 min [R. W. Hewick et al., *J. Biol. Chem.* **1981**, 256, 7990].

Gastric inhibitory polypeptide, \rightarrow glucose-dependent insulinotropic polypeptide.

Gastrin (GT), a gastrointestinal peptide hormone. GT is produced in the G cells of the antrum and duodenum as prepro-gastrin (101 aa) which yields, after co- and post-translational processing, mainly the bioactive peptides G-71, G-34, G-17, and G-6. The formation of prepro-gastrin is stimulated by partially digested protein, amino acids, and by the vagus nerve in response to stomach distension. Gastrin stimulates gastric acid and pepsinogen secretion, and it is the parent compound of the \rightarrow gastrin family. In humans, GT is encoded by a distinct gene on chromosome 17q21. The gene encodes only one prohormone with one active site that is processed to a number of bioactive molecular forms with the same C-terminal sequence. The cDNA-deduced amino acid sequence of human pro-gastrin comprises 80 residues. After co-translational cleavage of the 21-residue signal peptide from prepro-gastrin by signalase, pro-gastrin is transported to the Golgi apparatus, where O-sulfation of Tyr⁶⁶ by tyrosyl-protein sulfotransferase is performed. After trimming by the endoproteolytic enzyme proprotein convertase and carboxypeptidase E, peptidylglycine α -amidating monooxygenase forms the amidated bioactive peptide. Human *gastrin-71* has the following sequence: SWKP RSQQPD¹⁰APLGTGANRD²⁰LPLPWLEQ QG³⁰PASHHRR↓QLG⁴⁰PQGGPHLVAD⁵⁰PSKK↓QGPLe⁶⁰EEEEAY^SGWMD⁷⁰Fa;Y^S:

Tyr(SO₃⁻). The arrows ↓ indicate the dibasic processing sites providing *gastrin-17* and *gastrin-34*, respectively, with N-terminal pyroglutamic acid residues formed by subsequent glutaminy cyclizations. In humans, more than 90% of the gastrins are gastrin-17, 5% are gastrin-34, and the remainder is a mixture of gastrin-71, gastrin-52, gastrin-14, and short C-terminal 7- and 6-peptide amide fragments. Non-amidated precursors are present in small proportions, mainly glycine-extended gastrin, and approximately one-half of the amidated gastrins are sulfated at Tyr. The synthetic *pentagastrin* (Gastrodiagnost®), Boc-β-Ala-Trp-Met-Asp-Phe-NH₂, is used as a diagnostic tool for maximum stimulation of the secretion of gastric acid in the analysis of gastric juice. GT is structurally related to → cholecystokinin (CCK), another gut hormone characterized four years later. Both hormones share five C-terminal amino acids (Gly-Trp-Met-Asp-Phe-NH₂). Because of their sequence similarity in their bioactive region, GT and CCK share some biological and pharmacological effects, exerting their biological functions via membrane GPCRs termed CCK receptors located on multiple cellular targets and in the CNS and peripheral organs. Two types of CCK receptor (type A, “alimentary” and type B, “brain”) have been identified; these were later renamed CCK1 receptor (CCK1R) and CCK2 receptor (CCK2R) [J. S. Edkins, *J. Physiol. (Lond.)* **1906**, 34, 133; H. Gregory et al., *Nature* **1964**, 204, 931; J. F. Rehfeld, *Physiol. Rev.* **1998**, 78, 1087; M. Dufresne et al., *Physiol. Rev.* **2006**, 86, 805].

Gastrin family, a member of the gastroenteropancreatic peptide families. This family comprises the mammalian hormones → gastrin and → cholecystokinin, the protochordan neuropeptide → cionin, and

the frog skin peptide → cerulein. The homology of this family is decisively concentrated in and around the well-defined active site, and the common C-terminal 4-peptide sequence (-Trp-Met-Asp-Phe-NH₂). In the literature this family is also often termed the cholecystokinin-gastrin family [J. F. Rehfeld, *Physiol. Rev.* **1998**, 78, 1087].

Gastrin-releasing peptide (GRP), hGRP: VP LPAGGGTV¹⁰LTKMYPRGNH²⁰WAVGH LMa, the mammalian counterpart to → bombesin, with a widespread distribution and multiple effects on endocrine and exocrine secretions and metabolism. The prohormone Pro-GRP (125 aa) is processed to the amidated, biologically active GRP₁₋₂₇ and GRP₁₈₋₂₇. GRP-R and BRS-3 are two mammalian receptors for GRP which are members of the G protein seven transmembrane receptor superfamily. GRP-R has a high affinity for GRP, whereas BRS-3 has only a low affinity. The C-terminal sequence of GRP is identical with the C-terminus of bombesin, which has full agonist activity at the receptor GRP-R. GRP has been shown to stimulate insulin secretion under *in-vivo* conditions, as well as in isolated islets of Langerhans and insulin-producing RINm5F cells. GRP shows more potent effects than the other bombesin-like peptide → neuromedin B (NMB) in most of the assays mediated through the GRP receptors and the NMB receptor, respectively. The distribution of GRP and NMB is overlapped in many brain regions and digestive tissues. Immunodetection of GRP in malignant melanoma cells has been reported. Recently, conformational analysis of GRP in solution using NMR spectroscopy and molecular dynamics simulations has been described. In 1979, GRP was isolated from porcine gastric and intestinal tissues using bioassays for gastrin release. GRP belongs

to the → bombesin family [T. J. McDonald et al., *Biochem. Biophys. Res. Commun.* **1979**, 90, 227; S. Karlsson, B. Ahren, *Peptides* **1996**, 17, 909; H. Ohki-Hamazaki, *Prog. Neurobiol.* **2000**, 62, 297; K. N. Charitopoulos et al., *Melanoma Res.* **2000**, 10, 395; C. Shin et al., *Biochem. Biophys. Res. Commun.* **2006**, 350, 120].

Gastroenteropancreatic peptide families, → gastrointestinal hormones.

Gastrointestinal hormones, peptides hormones released to the circulation from endocrine cells, and also from neurons in the gastrointestinal tract. The gut seems to be the largest endocrine organ in the body, since today more than 30 hormone genes are known to be expressed in the stomach and intestines. From the point of structural homology, eight gastroenteropancreatic families can be classified, each of which is assumed to originate from a common ancestral gene, such as the → gastrin family, → secretin family, → insulin family, → EGF family, → somatostatin family, → tachykinin family, → PP-fold family, and → ghrelin family [J. R. Rehfeld, *Hormon. Metab. Res.* **2004**, 36, 735].

GC, gas chromatography.

gCSF, granulocyte colony-stimulating factor.

GE3, a cyclohexadepsipeptide (→ depsipeptides) isolated from *Streptomyces* sp. GE3 collected from a Japanese soil. Building blocks of the rather complex structure are, e.g., *N*-hydroxyalanine, *N*-methyl-D-leucine, and both enantiomers of piperazic acid. The structure of the open-chain form GE3B was also assigned. GE3 shows strong cytotoxic activity and weak antibacterial activity [T. Agatsuma et al., *J. Antibiot.* **1997**, 50, 704].

Geodiamolides, cyclodepsipeptides (→ depsipeptides) isolated from various

sponges. Geodiamolides A and B were first discovered in the sponge *Geodia* sp., collected off Trinidad. Geodiamolides C–F were found together with A and B, and → jaspamide in the sponge *Pseudaxinyssa* sp. (Papua New Guinea), whereas the origin of Geodiamolide TA was the sponge *Hemiassterella minor* (South Africa coast), and the source of the structurally similar *neosophoniamolide* A, the sponge *Neosiphonia superstes* (New Caledonian coast). All compounds are 18-membered macrocycles, bearing as key features the halogenated tyrosine moiety and a 12-carbon polypropionate unit. They exhibit cytotoxicity against various cell lines [W. R. Chan et al., *J. Org. Chem.* **1987**, 52, 3091; E. D. de Silva et al., *Tetrahedron Lett.* **1990**, 31, 489; M. V. D'Auria et al., *J. Nat. Prod.* **1995**, 58, 121].

GFP, green fluorescent protein.

GH, growth hormone.

Ghrelin, GSS^xYFLSPEHQ¹⁰RVQQRKES KK²⁰PPAKLQPR, (human ghrelin), a 28-peptide hormone with an essential *n*-octanoic moiety (X = CH₃-(CH₂)₆-CO-) esterified with the hydroxy group of Ser³ originally discovered as the endogenous ligand of the → growth hormone secretagogue receptor. The name “ghrelin” is related to “ghre”, a word root in Proto-Indo-European languages for “grow”. Ghrelin is secreted primarily from the stomach, especially in the oxyntic glands of the gastric epithelium (X/A-like cells), and secondarily from the small intestine and colon. Furthermore, it may also be expressed in hypothalamus, in the pancreatic islets, pituitary, and several tissues in the periphery. In addition to its predictable effect on growth hormone secretion, ghrelin has an important function in the short-term regulation of appetite and the

long-term regulation of energy balance and glucose homeostasis. Recent reports have implicated ghrelin in the regulation of gastrointestinal, cardiovascular, immune function, and bone physiology. Interestingly, \rightarrow obestatin, derived from the same gene as ghrelin, shows opposite actions on energy homeostasis and gastrointestinal function, making the physiology of ghrelin more complex. Ghrelin is highly conserved among mammals, and has even been discovered in fish, chickens, dog, goose, emu, turkey, and bullfrogs. The human gene of prepro-ghrelin is located on chromosome 3p25-26 consisting of five exons with four introns. The 117 aa prepro-ghrelin precursor is processed to yield ghrelin, and further esterified by octanoic acid at the third amino acid – usually a serine, but in some species a threonine. This post-translational modification is essential for ghrelin's biological activities, but the exact enzymatic mechanism leading to ghrelin esterification has not been established. The physiological function of des-acyl ghrelin present in plasma has not yet been elucidated. The amino acid sequence of human ghrelin differs from rat ghrelin at residues 11 and 12, with Arg substituted to Lys and Val substituted to Ala. Porcine ghrelin differs from human ghrelin at residue 12, with Val substituted to Ala, at residue 22 with Ala substituted to Pro and residue 26 with Lys substituted to Gln. Des-Gln¹⁴-ghrelin with *n*-octanoyl modification at the hydroxyl group of Ser³ like ghrelin stimulates the release of growth hormone after injection into rats. Ghrelin and \rightarrow motilin share significant sequence homology, but motilin is not modified at Ser³. In principle, motilin can activate GHS-R-expressing cells, but its activity is very weak. It has been suggested that ghrelin and motilin might have evolved from a common ancestral

peptide. In 1999, the discovery of ghrelin was a milestone in the understanding of the interplay between the stomach and the brain, and has brought new light into the neuroendocrine networks that regulate food intake, energy balance, gastrointestinal function, and growth [M. Kojima et al., *Nature* **1999**, 402, 656; M. Kojima et al., *Trends Endocrinol. Metab.* **2001**, 12, 118; M. Kojima, K. Kangawa, *Physiol. Rev.* **2005**, 85, 495; L. L. Anderson et al., *Dom. Anim. Endocrinol.* **2005**, 29, 111; J. P. Camina, *J. Neuroendocrinol.* **2005**, 18, 65; N. A. Tritos, E. G. Kokkotou, *Mayo Clin. Proc.* **2006**, 81, 653; H. Hosoda et al., *J. Pharm. Sci.* **2006**, 100, 398; A. F. Leite-Moreira, J. B. Soares, *Drug Discov. Today* **2007**, 12, 276].

Ghrelin family, a member of the gastroenteropancreatic peptide families comprising \rightarrow ghrelin, and \rightarrow motilin.

GHRH, growth hormone-releasing hormone.

GHS, growth hormone secretagogue.

GHS-R, growth hormone secretagogue receptor.

GIP, glucose-dependent insulinotropic polypeptide.

Gla, γ -carboxyglutamic acid.

Glaucacyclopeptides, \rightarrow cherimolacyclopeptides.

GLC, gas-liquid chromatography.

Glc, glucose, glucosyl.

GlcNAc, *N*-acetyl-D-glucosamine.

Gliadin, a glycoprotein occurring in wheat and some other cereals. It belongs to the \rightarrow prolamins. Gliadin is rich in glutamine and forms, together with glutelins, \rightarrow gluten. Gliadins can be extracted from wheat, and

individual groups such as α -, β -, γ -, ω -1 and ω -2 have been purified. α -Gliadins are characterized by a lower content of Pro and Phe, in contrast to γ -gliadins which have high values of Pro, Phe, and Glx. It has been reported that some people are sensitive to this protein due to disorders such as Crohn's disease or celiac disease. Nowadays, proteomics-based approaches have been used for characterizing wheat gliadins [G. Mamone et al., *Proteomics* **2005**, 5, 2859].

Glicentin, RSLQNTEEK¹⁰RSFPAPQTDP²⁰LDDPDQMTED³⁰KRHSQGTFTS⁴⁰DYSKYLDSRR⁵⁰AQDFVQWLMN⁶⁰TKRNKNNIA, a 69-peptide from the porcine small intestine. Glicentin corresponds to the N-terminal fragment 1–69 of proglucagon, and is secreted together with the two \rightarrow glucagon-like peptides in the L-cells of the gut. The biological activity of glicentin remains a controversial issue. Glicentin-(33–69) corresponds to the sequence of *oxyntomodulin* [C. Orskov et al., *Endocrinology* **1986**, 119, 1467; J. J. Holst, *Annu. Rev. Physiol.* **1997**, 59, 257].

Glicentin-related pancreatic peptide (GRPP), \rightarrow glucagon.

Gln, glutamine.

Globin, a somewhat archaic term for globular proteins that are globular in shape. Members of globin proteins include \rightarrow hemoglobin and \rightarrow myoglobin.

Globulins, a generic term for a family of simple proteins insoluble in pure water but soluble in dilute salt solutions. The globulins occur in all animal and plant cells and body fluids, including serum and milk. They are precipitated by ammonium sulfate at various concentrations, depending on the type of globulin. Many enzymes and glycoproteins belong to this group of pro-

teins. The serum globulins are the most familiar members (\rightarrow plasma proteins).

Glomosporin, a cyclodepsipeptide (\rightarrow depsipeptides) isolated from a barley solid culture of *Glomospira* sp. (BAUA 2825). Glomosporin contains 3,4-dihydroxy-4-methylhexadecanoic acid and seven amino acids. It exhibits antimicrobial activity against fungi, including clinically important *Aspergillus fumigatus* [T. Sato et al., *J. Antibiot.* **2000**, 53, 597].

Glp, pyroglutamic acid (also pGlu and <E); 5-oxoproline.

GLP, glucagon-like peptide.

Glu, glutamic acid.

Glucagon, HSQGTFTSDY¹⁰SKYLDSRRAQ²⁰DFVQWLMNT, a 29-peptide hormone formed in the α -cells of the islets of Langerhans located in the endocrine part of the pancreas. An increased secretion of glucagon occurs in response to a decrease in blood glucose concentration. Glucagon stimulates glucose release through both glycogenolysis and lipolysis. The most important target organ is the liver, where it stimulates the formation of glucose from glycogen and ketone bodies. Glucagon inhibits fatty acid synthesis in hepatocytes, and stimulates lipolysis in brown adipose tissue. Molecular biology studies have shown that glucagon and its receptor are expressed in numerous other tissues. The human and rat glucagon gene consists of six exons and five introns, and encodes *preproglucagon* (180 aa). Interestingly, each functional domain of the large precursor is encoded by a separate exon. Post-translational proteolytic cleavage of the precursor protein gives rise to the following main cleavage fragments: genuine pancreatic glucagon (sequence 33–61), \rightarrow glucagon-like peptide-1 (GLP-1) (sequence 78–108)

and GLP-2 (sequence 126–159). Prepro-glucagon cDNA from various tissues and organs shows identity in its sequence, but its post-translational processing can differ significantly. In the α -cells of the pancreatic islets the precursor protein is processed to release the pancreatic glucagon, whereas GLP processing remains incomplete. On the other hand, the L cells of the gut process the precursor in a different way to release GLPs, but glucagon remains as a part of glicentin. This prohormone fragment can be further processed to glucagon-related pancreatic peptide (GRPP) and oxyntomodulin. Glucagon and GLP-1 show an extensive sequence homology, but they exert their action through different specific receptors. In 1993, the rat glucagon receptor was cloned; this receptor causes an increase in the intracellular concentration of cAMP, and also transduces a signal that leads to an increasing concentration of Ca^{2+} . The receptor shows similarities to the calcitonin and parathyroid hormone receptors. Glucagon belongs to the \rightarrow secretin family. The total chemical synthesis of glucagon was performed by Wünsch et al. in 1968. Glucagon is used in the treatment of hypoglycemia; for this it can be applied parenterally, by using a portable pump, or in a depot form, nasally or as eye drops [E. Wünsch et al., *Chem. Ber.* **1968**, *101*, 3664; G. I. Bell et al., *Nature* **1983**, *304*, 368; L. J. Jelinek et al., *Science* **1993**, *259*, 1614; J. J. Holst et al., *J. Biol. Chem.* **1994**, *269*, 18827; G. G. Nussdorfer et al., *Peptides* **2000**, *21*, 309].

Glucagon-like peptides (GLP), peptide hormones belonging to the \rightarrow secretin family. In mammals, the glucagon gene is expressed not only in the pancreas but also in the intestinal L cells, where *proglucagon* (PG, 160 aa) provides the glucagon-containing peptide \rightarrow glicentin (PG 1–69), the two glucagon-

like peptides (GLP), and the so-called intervening peptide 2 (PG 111–123). The GLP are glucagon-like because of their $\sim 50\%$ sequence homology with glucagon. GLP-1, GLP-1-(7–36)-amide, (PG 78–107-NH₂), HAEGTFTSDV¹⁰SSYL EGQAAK²⁰EFIAWLVKGR³⁰a was originally predicted to consist of 37 residues (PG 72–108; N-terminally extended sequence: His-Asp-Glu-Phe-Glu-Arg-), and, therefore, the secreted hormone is frequently alluded to as GLP-1-(7–36)-amide. The insulinotropic peptide amide is secreted from endocrine cells in the gut mucosa in response to meal ingestion. In addition, small amounts (20%) of the Gly-extended GLP-1-(7–37), GLP-1-Gly, are also formed; this has the same affinity to the GLP-1 receptor but it is less resistant to enzymatic cleavage at the C-terminus compared to the amidated form. Each of the GLP interacts with a specific receptor, underlying the point that their actions diverge in spite of their close sequence homology. They exert multiple effects on the gastrointestinal tract and pancreas to regulate the digestion, absorption, and assimilation of ingested nutrients, as well as providing feedback signals to the brain to modulate food intake. GLP-1 belongs to the \rightarrow incretins. A prominent action of GLP-1 is to potentiate glucose-induced insulin secretion in β -cells, mediated by activation of its seven-transmembrane domain G protein-coupled receptor. In addition, it exerts islet-trophic effects by stimulating replication and differentiation and by decreasing the apoptosis of β -cells. The GLP-1 receptor is expressed in various other tissues important for carbohydrate metabolism, including pancreatic α -cells, hypothalamus and brainstem, and the proximal intestinal tract. GLP-1 also appears to exert important actions in muscle, fat, and liver. In summary,

GLP-1 suppresses glucagon secretion, promotes satiety, delays gastric emptying, and stimulates peripheral glucose uptake. The insulinotropic effect is preserved in patients with type 2 diabetes mellitus, in whom the secretion of glucagon is also inhibited. After GLP-1 infusion, blood glucose may be completely normalized. GLP-1 appears to regulate plasma glucose levels through various and independent mechanisms. It is an excellent candidate option for the treatment of patients with type 2 diabetes mellitus. Since GLP-1 is extremely rapidly metabolized *in vivo*, initially by the action of dipeptidyl peptidase-IV (DPP-IV), for practical diabetes therapy either stable analogues or inhibitors for the degrading enzyme are promising solutions. On the other hand, great interest has also resulted in the development of a variety of receptor agonists for this purpose. As a result of clinical trials, it can be assumed that first agonists of GLP-1 (→ exenatide, → liraglutide) will be available in near future. The structure of GLP-2 (PG 126–159), HADGRFSDEM¹⁰ NTILDNLAAR²⁰DFINWLIQTK³⁰ITDRa, was recently determined and confirmed by synthesis. GLP-2 is secreted from gut endocrine cells and promotes nutrient absorption. GLP-2 regulates gastric motility, gastric acid secretion, intestinal hexose transport, and increases the barrier function of the gut epithelium. It reduces mortality and decreases mucosal injury, cytokine expression, and bacterial septicemia in the setting of small and large bowel inflammations. It is assumed that GLP-2 is the intestinal growth factor of the intestinal L cell. Based on its intestinotrophic effects, GLP-2 is considered for the treatment of those gastrointestinal diseases that are connected with insufficient intestinal mucosal function. The finding that GLP-2 is less extensively degraded by DPP-IV than

GLP-1 may provide access to an interesting spectrum of clinical applications [H.-C. Fehmann et al., *Endocr. Rev.* **1995**, 16, 390; B. Hartmann et al., *Peptides* **2000**, 21, 73; R. Perfetti, P. Merkel, *Eur. J. Endocrinol.* **2000**, 143, 717; J. J. Holst, *Regul. Pept.* **2000**, 93, 45; A. Wettergren, *Dan. Med. Bull.* **2001**, 48, 19; D. J. Drucker, *Endocrinology* **2001**, 142, 521; D. J. Drucker, *Gastroenterology* **2002**, 122, 531; P. L. Brubaker, *Ann. N. Y. Acad. Sci.* **2006**, 1070, 10; D. D. De Leon et al., *Int. J. Biochem. Cell Biol.* **2006**, 38, 845].

Glucagon-secretin family, → secretin family.

Glucose-dependent insulinotropic polypeptide, also referred to as *gastric inhibitory polypeptide*, GIP, YAEGTFISNY¹⁰SIAMD KIHQQ²⁰DFVNWLLAQK³⁰GKKNDWKH NI⁴⁰TQ, a 42-peptide involved in the regulation of fat and glucose metabolism. GIP was initially discovered from porcine intestinal extracts in 1970. The early assumed inhibitory effect on gastric acid secretion could not be confirmed. More importantly, GIP acts as an incretin hormone (→ incretins). GIP is released from K cells in the gut after meal ingestion, acting in concert with glucagon-like peptide 1 (→ glucagon-like peptides) to augment glucose-stimulated insulin secretion. Furthermore, GIP cells are also found in the entire small intestinal mucosa. Besides its insulinotropic effect, other physiological GIP effects have been described. The human gene comprises 10 kb and is located on the long arm of chromosome 17. In humans, GIP derives from the 153-residue precursor prepro-GIP, the proteolytic cleavage of which gives rise to the main product GIP, in addition to other fragmentation products. However, specific functions for these other fragments have not been

identified. Interestingly, the GIP-(7–42) fragment shows antibacterial activity. The GIP receptor has been cloned, and belongs to the family of G protein-coupled receptors. It is expressed in the pancreatic islets, as well as in the gut, heart, adipose tissue, pituitary, adrenal cortex, and in several regions of the brain. The human GIP receptor shows 41% homology with the GLP-1 receptor, and is related to the receptors for the other members of the \rightarrow secretin family. Processing of the 144 aa rat prepro-GIP yields GIP and N- and C-terminal flanking peptides of 22 and 59 residues, respectively. The rat GIP receptor ($M_r \sim 52$ kDa) is a 455-mer glycoprotein [J. C. Brown et al., *J. Physiol.* **1970**, 209, 57; *Can. J. Biochem.* **1971**, 49, 255; K. Yasuda, Y. Seino, *Jap. J. Clin. Med.* **1996**, 54, 1078; J. J. Meier et al., *J. Physiol. (Endocrinol. Metab.)* **2004**, 286, E621; J. J. Meier, M. A. Nauck, *Horm. Metab. Res.* **2004**, 36, 859].

Glutamic acid, (Glu, E), α -aminoglutaric acid, $\text{HOOC-CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{-COOH}$, $\text{C}_5\text{H}_9\text{NO}_4$, M_r 147.13 Da, a proteinogenic amino acid.

Glutamine, (Gln, Q), glutamic acid γ -semiamide, $\text{H}_2\text{N-CO-CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{-COOH}$, $\text{C}_5\text{H}_{10}\text{N}_2\text{O}_3$, M_r 146.15 Da, a proteinogenic amino acid.

Glutaminyl cyclase (QC), EC 2.3.2.5, an acyltransferase responsible for N-terminal pyroglutamate formation from glutaminyl precursors in peptides and proteins. The first QC was isolated from the latex of *Carica papaya* in 1963. Later, it was established that glutaminyl cyclases occur in both animal and plant sources. They are abundant in mammalian neuroendocrine tissues, such as hypothalamus and pituitary, and are highly conserved from yeast to human. From the crystal structure of human glutaminyl cyclase it follows that a single zinc ion in the active site is coordinated

to three conserved residues and one water molecule, which is replaced by an imidazole nitrogen upon binding of inhibitors. Interestingly, in 2004 it was reported that human and papaya QC also catalyze N-terminal glutamate cyclization into pyroglutamate, a conversion favored at pH 6.0, while Gln conversion occurs with an optimum at pH 8.0. This glutamyl cyclase activity is probably related to the formation of several plaque-forming peptides, such as \rightarrow amyloid- β peptides, and collagen-like amyloid plaque components playing a important role in \rightarrow Alzheimer's disease [M. Messer, *Nature* **1963**, 197, 1299; W. H. Fischer, J. Spiess, *Proc. Natl. Acad. Sci. USA* **1987**, 84, 3628; S. Schilling et al., *FEBS Lett.* **2004**, 563, 191; K.-F. Huang et al., *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13117; S. Schilling et al., *Biochemistry* **2005**, 44, 13415].

Glutamyl cyclase, \rightarrow glutaminyl cyclase.

Glutaredoxins, a family of redox proteins found in prokaryotes and eukaryotes as well as viruses. Their catalytic activity is based on the alternate formation and reduction of a disulfide bond between a pair of cysteines in a characteristic CXXC sequence motif [A. P. Fernandes, A. Holmgren, *Antioxid. Redox. Signal.* **2004**, 6, 23].

Glutathione (GSH), H-Glu(Cys-Gly-OH)-OH (reduced), a naturally occurring tripeptide found in virtually all cells of animals, most plants and bacteria, involved in metabolism, transport, and cellular protection. It acts as a biological redox agent, as a coenzyme and cofactor, and as a substrate in certain reactions catalyzed by glutathione S-transferase. GSH scavenges free radicals and reduces peroxides, and is important in the lens and in certain parasites lacking catalase to remove H_2O_2 [A. Meister, *Science* **1983**, 220, 472; M.

E. Anderson, *Methods Enzymol.* **1985**, *113*, 548].

Glutelins, a group of globular proteins from grain containing up to 45% Glu. They are the major storage proteins in soybean and rice. Generally, theutelins are insoluble in water, salt solutions and dilute ethanol, but at extreme pH values they are soluble in water. Main members of theutelins are glutenin in wheat, hordenin in barley, and oryzenin in rice [J. A. Ewart, *J. Sci. Food Agric.* **1972**, *23*, 687; H. Wieser et al., *Z. Lebensm. Unters. Forsch.* **1988**, *187*, 27].

Gluten, a mixture of approximately equal parts of → gliadin and →utelins found in cereals such as wheat, rye, and barley. Gluten enables wheat and rye flours to form dough during bread making, whereas oat and rice grains are not suitable for baking due to the lack of gliadin. Gluten has been fractionated yielding gliadin, glutenin and high-molecular-weight and low-molecular-weight glutenin subunits. Coeliac (celiac) disease, an autoimmune disorder of the small intestine, is caused by reaction to gliadin, and is treated with a lifelong gluten-free diet. Several grains and starch sources such as maize, potatoes, rice, and tapioca are considered acceptable for a gluten-free diet [N. M. Edwards et al., *Cereal Chem.* **2003**, *80*, 755; F. Benkebil, A. Nydegger, *Rev. Med. Suisse* **2007**, *100*, 515].

Gluten-exorphins, → exorphins.

Glycine (Gly, G), α -aminoacetic acid $\text{H}_2\text{N}-\text{CH}_2-\text{COOH}$, $\text{C}_2\text{H}_5\text{NO}_2$, M_1 , 75.07 Da, a proteinogenic amino acid.

Glycomimetic peptides, peptides that functionally and/or structurally mimic oligosaccharide structures. Especially oligosaccharides that are exposed on the surface of, e.g., tumor cells or microbial pathogens can be regarded as potential therapeutic targets due to their spatial accessibility. Despite the

tremendous methodological advancements in carbohydrate synthesis, the development of carbohydrate-based therapeutics comprises multi-step syntheses and must always cope with unfavorable ADME (absorption – distribution – metabolism – excretion) parameters of oligosaccharides. Glycomimetic peptides are targeted as functional and/or structural mimics of the natural oligosaccharide parents. The peptide sequences can be retrieved, e.g., by phage display or combinatorial peptide synthesis [M. A. Johnson, B. M. Pinto, *Aust. J. Chem.* **2002**, *55*, 13; D. Bächle et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 6582].

Glycopeptide remodeling, modification of glycoproteins by the removal or addition of carbohydrate units.

Glycopeptides, peptides and glycoproteins (glycans) with one or more carbohydrate moieties being covalently attached to the side chain of an appropriate amino acid residue within a peptide sequence. Most naturally occurring glycoproteins contain oligosaccharide moieties either O-linked to serine, threonine, or tyrosine across an α -glycosidic bond, or N-linked to asparagine across a β -glycosidic bond. The carbohydrate proportion in glycoproteins ranges between <1 and >70 mass %. Glycoproteins can be found both in soluble and membrane-bound forms in all cells, as well as in the extracellular matrix and in extracellular liquids. They occur naturally as microheterogeneous mixtures – the so-called “glycoforms” – that share the same sequence but differ in both nature and site of glycosylation. It is difficult to isolate unique glycoforms from natural sources, and this complicates the determination of structure–activity relationships. The total synthesis of homogeneous glycopeptides and glycoproteins provides the best chance for a systematic understanding of glycan function. The high chemical lability of the

N- and O-glycosidic bonds greatly complicates glycopeptide synthesis. These bonds are rather acid-sensitive, so that strongly acidic deprotection methods are precluded from application in their synthesis. Furthermore, O-glycosides are degraded by relatively mild alkaline treatment, which causes β -elimination. The stereoselective formation of glycosides is not trivial, and anomerization is a permanent risk during subsequent manipulations. Numerous methods exist for the synthesis of glycopeptides. The most common approach uses amino acid "cassettes" with appropriately protected saccharides for the stepwise synthesis of the glycopeptide. The alternative approach of blocking glycosylation is characterized by the conjugation of complex saccharides to short synthetic peptides. Nowadays, \rightarrow chemical ligation, expressed protein ligation techniques (\rightarrow biochemical protein ligation) and enzymatic manipulations have also found application in glycopeptide synthesis [T. J. Tolbert, C. H. Wong, *J. Am. Chem. Soc.* **2000**, 122, 5421; H. Herzner et al., *Chem. Rev.* **2000**, 100, 4495; O. Seitz, *ChemBioChem* **2000**, 1, 214; N. Besay et al., *Angew. Chem. Int. Ed.* **2001**, 113, 2350; H. T. Liu et al., *J. Am. Chem. Soc.* **2003**, 125, 1702; J. D. Warren et al., *J. Am. Chem. Soc.* **2004**, 126, 6576; A. Brik et al., *J. Am. Chem. Soc.* **2006**, 128, 15026; L. C. Hsieh-Wilson, *Nature* **2007**, 445, 31].

Glycophorins (GP), erythrocyte transmembrane proteins with a high carbohydrate content, especially rich in sialic acids. They are complex heavily glycosylated antigens bearing peptidic and glycopeptidic epitopes, and serve as ligands for viruses, bacteria, and parasites. The glycophorins comprise GPA, GPB, GPC, GPG, and GPE, and have been fully characterized at both the protein and DNA levels. They are closely related proteins of highly homologous

genes located in tandem on the human chromosome. Based on the similarity between the genes, a number of genetic variants have been described as a result of unequal crossover events. GPA (131 aa; $M_r \sim 31$ kDa) is the major sialoglycoprotein of the erythrocyte membrane, and consists of 60% carbohydrate by weight. GPA is a transmembrane glycoprotein bearing 15 O-linked oligosaccharides, and one that is N-linked. It consists of three domains. The N-terminal domain (72 aa) bears 16 carbohydrate chains (about 100 sugar residues), the transmembrane domain consists of 19 sequential predominantly hydrophobic residues, and the C-terminal domain (40 aa) in the cytosol has a high proportion of charged and polar residues. GPB ($M_r \sim 23$ kDa) and GPC ($M_r \sim 19$ kDa) occur in the erythrocyte membrane, at low content. The term glycophorin was proposed initially for human red cell sialoglycoproteins, but later was also used for sialoglycoproteins in animal red cell membranes [H. Furthmayr, V. T. Marchesi, *Methods Enzymol.* **1983**, 96, 268; J. P. Cartron, C. Rahuel, *Transfus. Med. Rev.* **1992**, 6, 63; M. J. Tanner, *Baillieres Clin. Haematol.* **1994**, 6, 333].

Glycoproteins, \rightarrow glycopeptides.

Glycosylation, the introduction of carbohydrate moieties into peptides and proteins. Glycosylation is the most complex post-translational modification of proteins [H. Schachtner, *Curr. Opin. Struct. Biol.* **1991**, 1, 755; C. Abeijon, C. B. Hirschberg, *Trends Biochem. Sci.* **1992**, 17, 32].

Glycyl-L-histidyl-L-lysine (GHK), *liver cell growth factor*, a growth-modulating plasma tripeptide. It produces a disparate set of responses ranging from stimulation of growth and differentiation to outright toxicity after addition at nanomolar concentrations to a wide group of cultured

systems. It may act by facilitating copper uptake into cells. The Cu(II) complex of the tripeptide promotes wound healing. A new fluorescent chemosensor for Cu²⁺ has been described by modifying GHK with 9-carbonylanthracene [L. Pickart, S. Lovejoy, *Methods Enzymol.* **1987**, 147, 314; Y. Zheng et al., *Org. Lett.* **2001**, 3, 3277].

GLYX-13, H-Thr-Pro-Pro-Thr-NH₂, a synthetic monoclonal antibody-derived 4-peptide amide acting as a NMDA receptor modulator. Resulting from the transformation of the monoclonal antibody B6B21 that binds at the glycine site of the *N*-methyl-D-aspartate receptor (NMDA receptor) into a family of small synthetic peptides, GLYX-13 was found to be the most active member of the → glyxins. GLYX-13 readily crosses the blood-brain barrier and functions as a NMDA receptor modulator, similar to the partial agonist D-cycloserine. It should be a new drug candidate with potential for the treatment of cognitive disorders [J. R. Moskal et al., *Neuropharmacology* **2005**, 49, 1077].

Glyxins, a group of synthetic peptides acting as NMDA receptor modulators. A potent member of this group is → GLYX-13 [J. R. Moskal et al., *Neuropharmacology* **2005**, 49, 1077].

Glyoxylylpeptides, peptides with an *N*-terminal glyoxylyl residue, suitable electrophilic components for hydrazone- or semicarbazone-based peptide ligation. The glyoxylyl residue is obtained by periodate oxidation of *N*-terminal Ser or Thr under neutral aqueous conditions. This moiety can also be used for peptide immobilization or the attachment of reporter groups [C. Olivier et al., *Bioconj. Chem.* **2003**, 14, 430; J. Marik et al., *Methods Mol. Biol.* **2005**, 310, 217].

GnIH, gonadotropin-inhibitory hormone.

GnIH-related peptides, peptides present in the brains of vertebrates, such as mammals, amphibians, and fish, characterized by a C-terminal LPXRFa (X = L or Q) sequence motif. They belong to the → LPXRFa peptides, which are member of the → RF-amide peptide family [K. Ukena, K. Tsutsui, *Mass Spectrom. Rev.* **2005**, 24, 469].

GnRH, gonadoliberin-releasing hormone.

Gold nanoparticles, peptide-capped gold nanoparticles bearing both single and dual biological functionality. The gold nanoparticles exhibit the specific recognition properties of the biological functionalities. Their specific and selective binding to artificial, DNA-modified target particles and to DNA and protein microarrays has been demonstrated. This approach should be extended to peptide and peptide conjugate labels, including a large number of peptides that recognize, with high specificity and affinity, both biological and non-biological structures [A. P. Alivisatos, *Nature Biotechnol.* **2004**, 22, 47; R. Levy et al., *J. Am. Chem. Soc.* **2004**, 126, 10076; Z. Wang et al., *Bioconj. Chem.* **2005**, 16, 497].

Gonadoliberin, → gonadotropin-releasing hormone.

Gonadotropin-inhibitory hormone (GnIH), SIKPSAYLPL¹⁰RFa, a 12-peptide amide identified in the quail brain inhibiting → gonadotropin release from the cultured anterior pituitary. GnIH was the first hypothalamic peptide reported to inhibit → gonadotropin release in vertebrates, but it is still not clear how it exerts its effects in terms of receptor binding, and downstream processing, or competes with GnRH for binding sites. The peptide contains a C-terminal LPLRFa sequence (→ LPXRFamide peptide family), and is a member of the → RFamide peptide superfamily [K. Tsutsui et al., *Biochem. Biophys.*

Res. Commun. **2000**, 275, 661; K. Ukena, K. Tsutsui, *Mass Spectrom. Rev.* **2005**, 24, 469].

Gonadotropin-releasing hormone (GnRH), *gonadoliberin*, pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly¹⁰NH₂, a 10-peptide amide formed in the hypothalamus which stimulates collectively the synthesis and secretion of the gonadotropins, e.g., *luteinizing hormone* (LH), and *follicle-stimulating hormone* (FSH) in the adenohypophysis, that in turn regulates ovulation/spermatogenesis. GnRH is identical with *luteinizing hormone-releasing hormone* (LH-RH) and *follicle-stimulating hormone-releasing hormone* (FSH-RH). It is the key hormone that regulates reproduction. More than 20 forms have been identified in vertebrates and invertebrates. Among these, the N-terminal sequence pGlu-His-Trp-Ser- and the C-terminal sequence -Pro-Gly-NH₂ are strictly conserved, and mammalian GnRH is assumed to adopt a β II' turn conformation around residues 5–8 in the receptor-bound conformation. The sequence of GnRH is synthesized as part of the precursor prepro-GnRH consisting of 92 residues from which GnRH is proteolytically released followed by amidation in a Cu²⁺- and ascorbate-dependent reaction catalyzed by the peptidylglycine α -amidating monooxygenase. GnRH is found in the hypothalamus, and also, in the liver, heart, pancreas, kidneys, small intestine, adrenal glands, and gonads. Many analogues have been synthesized for structure–activity studies, and tested with the aim of developing GnRH analogues with potential use as non-steroidal contraceptives or as fertility agents. Several GnRH agonists are currently used in the treatment of prostate cancer, precocious puberty, endometriosis, and other indications dependent on estrogen or testosterone. Analogues that are 10-fold or more as potent than the

native hormone are designated “superagonists”. These cause a feedback inhibition, decreasing the number of GnRH receptors (down-regulation), e.g., by receptor internalization, which in turn suppresses ovulation or spermatogenesis. Among those analogues described, [D-Trp⁶]GnRH and [D-Leu⁶,desGly¹⁰NH₂]GnRH-ethylamide (leuprolide) show relative activities of 3600 and 5000%, respectively, compared to the native hormone. The latter is indicated for treating advanced prostate cancer due to its capability of decreasing testosterone levels. Similar application has been found for → goserelin. Leuprolide has also been used, under court order, to cause male chemical castration. Instead of a therapy by receptor down-regulation, which is accompanied by strong pain in the initial phase, antagonists can also be used as this application does not show such effect. Antagonists are also being tested as male and female contraceptive agents. Antagonists of the “third generation” are currently in clinical trials for induced hormone suppression, e.g., in sex steroid-dependent benign and malignant diseases, and for premature LH surges in assisted reproduction. Members include *cetrorelix*, Ac-[D-Nal¹, D-p-Cl-Phe², D-Pal³, D-Cit⁶, D-Ala¹⁰]GnRH (SB-75) and *detirelix*, Ac-[D-Nal¹, D-p-Cl-Phe², D-Trp³, D-Har(Et₂)⁶, D-Ala¹⁰]GnRH. GnRH was first isolated by Andrew Schally and co-workers in 1971 [A. Nagy, A. V. Schally, *Biol. Reprod.* **2005**, 73, 851; J. B. Engel et al., *Lett. Drug. Des. Discov.* **2005**, 2, 533; J. P. Moreau et al., *Clin. Ther.* **2006**, 28, 1485].

Gonadotropins, *gonadotropic hormones*, a family of protein hormones from the anterior pituitary gland and the placenta. Gonadotropins comprise → lutropin, → follitropin, → prolactin, → chorionic gonadotropin, and the human menopausal

gonadotropin (urogonadotropin, hMG). Gonadotropins mediate their action via specific receptors in the theca and follicle cells of the ovary and corpus luteum, and the Leydig interstitial cells in the testes. The released cAMP stimulates, as second messenger, the production of steroid sex hormones [N. R. Mondgal (Ed.), *Gonadotropins and Gonadal Function*, Academic Press, New York, 1974; S. D. Gharib et al., *Endocr. Rev.* **1990**, 11, 177].

Goodman, Murray, (1928–2004) an American chemist and one of the great pioneers of peptide chemistry. He received his Ph.D from the University of California, Berkeley, in 1953. In 1956, he joined the Polytechnic Institute in Brooklyn and rose through the ranks to become director of the Polytechnic's Polymer Research Institute. In 1970, he joined the UCSD faculty as Professor of Chemistry. Murray Goodman has remained at UCSD ever since, serving as chair of the Department of Chemistry for six years, and was recently honored with the establishment of an endowed professorship in his name, the Goodman Chair in Chemistry. His exceptional scientific work in peptide synthesis methodology, the stereochemistry of biopolymers, and the conformational analysis of bioactive peptides and peptidomimetics for drug design has been recognized worldwide by numerous awards and honors. As editor-in-chief of the five-volume Houben-Weyl *Synthesis of Peptides and Peptidomimetics* (2002–2003), he leaves as a legacy a treatise on the state of the art in the field to the peptide community.

Goralatide, Ac-Ser-Asp-Lys-Pro-OH, AcS-DKP, a 4-peptide derivative isolated from fetal calf bone marrow, acting as a physiological regulator of hematopoiesis. Goralatide inhibits the entry into the S-phase of murine and human hematopoi-

etic stem cells. It may be derived from thymosin β 4, which contains N-terminally the goralatide sequence. Goralatide is degraded *in vivo* and *in vitro* by \rightarrow angiotensin-converting enzyme. It has been reported that renal function is essential to maintain stable goralatide plasma levels, and at high levels it acts as a uremic toxin causing partial resistance to \rightarrow erythropoietin and inhibiting erythropoiesis [M. Lenfant et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 779; A. Masse et al., *Blood* **1998**, 91, 441; Y. Le Meur et al., *Am. J. Kidney Dis.* **2001**, 38, 510].

Goserelin, [D-Ser(Bu^t)⁶, AzaGly¹⁰]GnRH, a superagonist of \rightarrow gonadotropin-releasing hormone (GnRH), marketed by AstraZeneca with the brand name Zoladex[®]. It reduces the production of testosterone in the body by mimicking the action of LH-RH, a hormone stimulating the release of luteinizing hormone (LH). In men, LH is transported to the testis where it stimulates testosterone production. Goserelin is an effective hormonal treatment for prostate cancer as it reduces testosterone production, thereby removing the growth stimulus for cancer cells within the prostate [B. Waymont et al., *Br. J. Urol.* **1992**, 69, 614; M. Roach, A. Izaguirre, *Expert. Opin. Pharmacother.* **2007**, 8, 257].

GPCR, G protein-coupled receptor.

GPh, guanidinophenyl.

Gramicidins, a group of cyclic or linear peptide antibiotics produced by *Bacillus brevis* strains. *Gramicidin S*, cyclo-(Val-Orn-Leu-D-Phe-Pro)₂, primarily acts on Gram-positive bacteria. Together with \rightarrow tyrocidins, gramicidins are used as antibacterial drugs in a variety of formulations for the topical treatment of infections of the upper respiratory tract. Biosynthesis is performed by the gramicidin S-synthetase, an enzyme complex of two subunits.

Gramicidin S-synthetase 1 (GS1, EC 5.1.1.11, $M_r \sim 127$ kDa, phenylalanine racemase) encoded by the *grsA* gene is responsible for activation and epimerization of the first amino acid Phe to D-Phe. The D-Phe enantiomer is transferred to gramicidin S-synthetase 2 (GS2, $M_r \sim 510$ kDa), which is encoded by the *grsB* gene. GS2 is responsible for activating and coupling Pro, Val, Orn, and Leu to the appropriate pentapeptide according to the mechanism of the multiple carrier model at modular multienzymatic templates. Last, but not least, the cyclization is carried out by two head-to-tail condensations between two pentapeptide sequences. *Gramicidins* A–C are linear 15-peptides with alternating D- and L-amino acid residues, a formyl group at the N-terminus, and a characteristic C-terminal ethanolamine moiety. They are ionophores forming channels through membranes transporting monovalent cations. Depending on the N-terminal amino acid (Val or Ile), a differentiation may be made between [Val]*Gramicidin* A–C and [Ile]*Gramicidin* A–C. [Val]*Gramicidin* A, HCO-Val-Gly-Ala-D-Leu-Ala-D-Val-Val-D-Val-Trp-D-Leu¹⁰-Trp-D-Leu-Trp-D-Leu-Trp-NH-CH₂-CH₂-OH, is capable of transporting monovalent cations, e.g., alkali ions, NH₄⁺, and H⁺, through membranes. From electrophysiological studies, it can be concluded that the channel is formed by a dimer, and that the membrane conductivity fluctuates in such a way that the channel cycles between closed and open states. As shown by X-ray crystallography, the dimer forms a left-handed, antiparallel, double-stranded helix. Other models favor channel formation by left-handed, single-stranded helices, with the two monomers associated with a head-to-head dimer via their N-termini. *Gramicidin B* has a Phe residue in position 11, whereas *Gramicidin C* has Tyr in this

position. Gramicidins are broad-spectrum antibiotics effective against Gram-positive, Gram-negative bacteria and fungi. However, they are toxic to human red blood cells. Analogues with decreasing toxicity have been synthesized by modifying the ring size and amphipathicity [R. Sarges, B. Witkop, *J. Am. Chem. Soc.* **1964**, *86*, 1862; D. W. Urry et al., *Science* **1983**, *221*, 1064; A. Finkelstein, O. S. Andersen, *J. Membr. Biol.* **1981**, *59*, 155; D. A. Langs, *Science* **1988**, *241*, 188; T. Stein et al., *J. Biol. Chem.* **1996**, *271*, 15428; L. D. Lee, R. S. Hodges, *Biopolymers* **2003**, *71*, 28].

Grammistins (Gs), a family of peptides isolated from the skin secretion of soapfishes. They belong to the membrane-lytic antibacterial peptides bearing an amphiphilic α -helical structure, and seem to serve as defense substances against invasive bacteria as well as against predators. Two Grammistins, Gs1 (LFGFLIKLIP¹⁰SLFGALSNI²⁰RNRNQ) and Gs 2, and six grammistins (Pp 1, Pp 2a, Pp 2b, Pp 3, Pp 4a and Pp 4b), have already been isolated from *Grammistes sexlineatus* and *Pogonoperca punctata*, respectively. Furthermore, five grammistins (Gs A–E) together with Gs 1 and Gs 2, were isolated from *G. sexlineatus* by gel filtration and reverse-phase HPLC [K. Shiomi et al., *Toxicon* **2000**, *38*, 91; N. Sugiyama et al., *Toxicon* **2005**, *45*, 595].

Granuliberin R, FGFLPIYRRP¹⁰ASa, a mast cell-degranulating 12-peptide amide first isolated from the skin of the frog *Rana rugosa* [T. Nakajima, T. Yasuhara, *Chem. Pharm. Bull.* **1977**, *25*, 2464; M. Kozakiewicz et al., *Cell. Mol. Biol.* **2003**, *8*, 727].

Granulysin, a cationic protein expressed in human cytotoxic T cells and natural killer cells as both 15- and 9-kDa proteins. The 9-kDa form is released by proteolytic cleavage

at both the N- and C-termini of the higher molecular form. Granulysin is cytolytic against microbial and tumor targets. It belongs to the saposin-like protein family of lipid-binding proteins, and is co-localized in cytolytic granules with \rightarrow perforin and granzymes. It has been reported that granulysin is also a chemoattractant and pro-inflammatory activator [D. A. Hanson et al., *Mol. Immunol.* **1999**, 36, 413; A. Deng et al., *J. Immunol.* **2005**, 174, 5243].

Green fluorescent protein (GFP), a chromophore-containing protein found in the margin of the umbrella of the jellyfish *Aequorea victoria*. The precursor molecule is a 238 aa linear protein and is non-fluorescent. If the GFP precursor is expressed in *E. coli* cells, the tripeptide sequence -Ser⁶⁵-Tyr-Gly⁶⁷- of the linear polypeptide chain is converted autocatalytically to the chromophore, involving an autocyclodehydration followed by autooxidation. The resulting molecule is observed to be fluorescent when viewed under near-UV light. The chemical synthesis of the GFP precursor was the masterly performance of a highly sophisticated synthesis strategy developed by Sakakibara, and belongs to the state-of-the-art protein syntheses [D. C. Prasher et al., *Gene* **1992**, 111, 229; S. Inouye, F. I. Tsuji, *FEBS Lett.* **1994**, 341, 277; **1994**, 351, 211; S. Sakakibara, *Biopolymers (Pept. Sci.)* **1999**, 51, 279].

GRF, growth hormone-releasing factor.

GroEL, (*hsp60*, *cpn60*) \rightarrow molecular chaperones.

Growth hormone (GH), *somatotropin*, *somatotropic hormone*, *STH*, a single-chain proteohormone ($M_r \sim 21.5$ kDa) produced by somatotrophs of the adenohypophysis. GH is an anabolic hormone that regulates the metabolism of proteins, sugars, fats

and minerals in mammals. Human GH consists mainly of a four-helix bundle (191 aa; two disulfide bridges). Until recently, the consensus was that the biosynthesis is regulated by the hypothalamic growth hormone-releasing hormone, GHRH, (\rightarrow somatoliberin) and the appropriate release-inhibiting hormone \rightarrow somatostatin, and some being also produced peripherally. Additionally, secretion of GH is stimulated by \rightarrow ghrelin acting via the \rightarrow growth hormone secretagogue (GHS) receptor (GHS-R). Furthermore, in some species, GH secretion is influenced by other peptides/proteins synthesized in the hypothalamus and in the periphery, such as \rightarrow insulin-like growth factor 1 (IGF-1), \rightarrow leptin, \rightarrow pituitary adenylate cyclase-activating polypeptide (PACAP) and \rightarrow thyroliberin (TRH). Recently, details of the molecular and cellular mechanisms and *in-vivo* approaches of growth hormone secretion have been published. The special mechanism for affecting GH secretion from the somatotrope by releasing hormones requires specific signal transduction systems such as cAMP and/or Ca^{2+} influx and/or mobilization of intracellular Ca^{2+} , and/or tyrosine kinases and/or nitric oxide/cGMP. GH regulates overall body and cell growth, protein-carbohydrate-lipid metabolism, and water-electrolyte balance. GH controls mainly, but in association with other hormones (\rightarrow insulin, thyroxin, etc.), growth, differentiation and the permanent renewal of body substances. Human GH causes its receptor to dimerize. This ligand-induced dimerization has important implications for the mechanism of signal transduction. GH is highly species-specific, therefore hGH only – and no other mammalian GH – are active in humans. High levels of GH result in excessive growth (*gigantism*), whereas GH deficiency causes insufficient

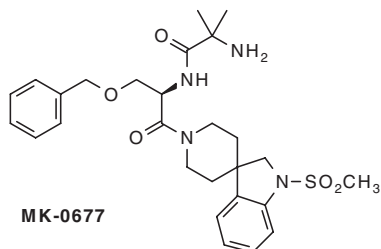
growth (*dwarfism*). Recombinant hGH is used in the therapy of hypophyseal dwarfism, in the treatment of Turner's syndrome, in the healing of wounds, and for increasing the mass and density of bones [C. H. Li, J. D. Yamashiro, *Am. Chem. Soc.* **1970**, 92, 7608; E. E. Muller et al., *Physiol. Rev.* **1999**, 79, 511; L. L. Anderson et al., *Exp. Biol. Med.* **2004**, 229, 291].

Growth hormone release-inhibiting hormone, → somatostatin.

Growth hormone secretagogue receptor, *GHS receptor*, **GHS-R**, a seven-transmembrane G protein-coupled receptor (7 TM GPCR) expressed in the pituitary, hypothalamus and hippocampus. It shows a high degree of homology in human, dog, pig, rat and mouse, ranging from 93 to 99% identity. GHS-R bind the endogenous ligands → ghrelin and → growth hormone secretagogues (GHS) that mediate the release of growth hormone by increasing the cellular Ca^{2+} concentration through inositol 1,4,5-trisphosphate signal transduction. GHS-R was identified by expression cloning in 1996. Two distinct receptor subtypes have been described. The GHS-R type 1a transduces information provided by ghrelin and GHS. In addition, GHS-R 1a has other binding sites that are different from the characterized GHS binding pocket, as revealed by investigations with → cortistatin and adenosine. GHS-R 1a is characterized by conserved cysteine residues in the first two extracellular loops, several N-linked glycosylation and phosphorylation sites, and a typical triplet sequence (E/DRY) located after TM3 in the second intracellular loop. The GHS-R type 1b receptor is a C-terminal truncated form of the type 1a receptor, and is pharmacologically inactive. Furthermore, an increasing number of so-called new receptors have been described as ghrelin receptors,

although these remain to be characterized [A. D. Howard et al., *Science* **1996**, 273, 974; K. K. McKee et al., *Mol. Endocrinol.* **1997**, 11, 415; R. G. Smith et al., *Trends Endocrinol. Metab.* **1999**, 10, 128; M. Kojima, K. Kangawa, *Physiol. Rev.* **2005**, 85, 495; J. P. Camina, *J. Endocrinol.* **2006**, 18, 65].

Growth hormone secretagogues (GHS), *growth hormone-releasing peptides*, **GHRP**, a group of synthetic peptides without structural similarities to → growth hormone-releasing hormone (GHRH) that stimulate the release of the → growth hormone when added to cultured pituitary cells or when injected intravenously. One of the first examples was **GHRP-6** (SK&F 110679), H-His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂, which showed about 10% of the GHRH activity. Another member of this group is **GHRP-1** (H-Ala-His-D-β-Nal-Ala-Trp-D-Phe-Lys-NH₂). **MK-0677**, formal a capped dipeptide, is a functional mimetic of GHRP-6. Besides MK-0677, non-peptidyl classes of benzolactam and spiroindolamine GHS, such as L-692,429, L-692,585, and L-163,255 with some improved oral bioavailability and pharmacokinetic properties have been developed. The actions of GHS are mediated through the → growth hormone secretagogue receptor (GHS-R). The endogenous ligand for the GHS-R is → ghrelin. GHS alone or in combination with → growth hormone-releasing hormone have been used for the diagnosis and treatment of various forms of growth hormone deficiency [C. Y. Bowers et al., *Endocrinology* **1984**, 114, 1537; K. Cheng et al., *Endocrinology* **1989**, 124, 2791; M. S. Akman et al., *Endocrinology* **1993**, 132, 1286; R. G. Smith et al., *Science* **1993**, 260, 1640; A. A. Patchett et al., *Proc. Natl. Acad. Sci. USA* **1995**, 92, 7001; C. Y. Bowers, *Cell. Mol. Life Sci.* **1998**, 54, 1316].



Growth hormone-releasing hormone (GHRH), *somatoliberin*, YDAIFTNSY¹⁰ RKVLGQLSAR²⁰KLLQDIMSQR³⁰GESNQ ERGAR⁴⁰R ARLa (hGHRH), a 44-peptide amide released from neurosecretory terminals in the median eminence that stimulates the synthesis and release of → growth hormone. The GHRH receptor belongs to the family of seven transmembrane receptors coupled to a heterotrimeric GTP binding protein. The GHRH receptor is coupled to a G_s protein, and its activation stimulates adenylate cyclase activity, resulting in increased intracellular cAMP and protein kinase A levels. GHRH is expressed in the arcuate nucleus of the hypothalamus and also in other tissues, such as gonads, intestine, immune tissues and the placenta. Human GHRH is synthesized as part of the precursor prepro-hGHRH. A cryptic 30-peptide, named *anorectin*, prepro-hGHRH-(78–107), <EV DSMWAEQK¹⁰QMELESILVA²⁰LLQKHSR NSQ³⁰a, results from post-translational processing of the precursor, in addition to the sequence of GHRH. It reduces food intake after injection into the third ventricle. The application of GHRH for the treatment of children with growth hormone deficiency is very important. Structure–activity studies led to the conclusion that GHRH can be shortened at the C-terminus. In children, hGHRH-(1–29)-amide still has 50% of the activity of the native hormone [A. Frohman, J.-O.

Jansson, *Endocrinol. Rev.* **1986**, 7, 223; L. A. Frohman, R. D. Kineman, in: *Handbook of Physiology*, J. L. Kostyo, H. M. Goddman (Eds.), Section 7, *The Endocrine System*, Volume V, *Hormonal Control of Growth*, American Physiological Society, New York, Oxford University Press, **1999**, 187].

Growth hormone-releasing peptides, → growth hormone secretagogues (GHS).

Growth inhibitory peptide (P149), [*The abbreviation P149 (batch production No. P149) has been used here instead of GIP, since the latter term is assigned to → glucose-dependent insulinotropic polypeptide in peptide nomenclature*], LSEDKLLACG¹⁰ EGAADIIIGH²⁰LCIRHEMTPV³⁰NGPV, a synthetic 34-peptide derived from the third domain of human → α-fetoprotein (hAFP) with growth suppression activity in a multitude of human tumors, both *in vitro* and *in vivo*. It has been reported that P149 is active at doses similar to taxol derivatives in use against breast and thymic carcinomas. The P149 segment corresponds to hAFP(445–479), a sequence stretch that normally lies buried in a molecular cleft in native hAFP. Generally, hAFP shows mainly growth-enhancing properties, regardless of whether the tissue is of fetal or cancer origin, whereas P149 has been shown to be growth-suppressive in various human tumor types and to suppress the spread of tumor infiltrates and metastases in human and mouse mammary cancers [G. J. Mizejewski, G. Butterstein, *Curr. Prot. Pept. Sci.* **2006**, 7, 73].

GRP, gastrin-releasing peptide.

GRPP, → glicentin-related pancreatic peptide.

GTP-binding regulatory proteins, → G proteins.

4-Guanidinophenyl ester (OGp), guanidine ($\text{H}_2\text{N}-\text{C}(\text{NH}_2)=\text{NH}$) substituted phenyl ester of N^α -protected amino acids and peptides that has been used as *substrate mimetics* in trypsin-catalyzed peptide synthesis [F. Bordusa et al., *Angew. Chem. Int. Ed.* **1997**, 36, 2473].

Guanidino protection, irreversible protecting groups for the guanidino function of arginine in peptide synthesis. Although the extremely strong basic guanidino group is usually protected by protonation under normal reaction conditions, the low solubility of the corresponding derivatives in organic solvents hampers peptide synthesis. Ideally, all three side-chain nitrogen atoms of the guanidine functionality should be protected, but most protection tactics rely on N^ω - or N^ω/N^δ -protection, respectively. The different protecting groups used can be divided into four classes: nitro, urethane (acyl), arenesulfonyl, and trityl types. However, the latter derivatives are poorly soluble in organic solvents and hence not widely used [M. Fujino et al., *J. Chem. Soc., Chem. Commun.* **1980**, 668; R. Ramage et al., *Tetrahedron* **1991**, 47, 6353; L. A. Carpino et al., *Tetrahedron Lett.* **1993**, 34, 7829].

Guanine nucleotide-binding proteins, \rightarrow G proteins.

Guanylin, PGTCEICAYA¹⁰ACTGC (hG; disulfide bonds: $\text{C}^4-\text{C}^{12}/\text{C}^7-\text{C}^{15}$), a 15-peptide activating intestinal guanylate cyclase. Guanylin was isolated from rat jejunum. Rat guanylin differs from

hG only in position 2 (Asn). Guanylin has a function in regulating fluid and electrolyte absorption in the intestine. Guanylin, \rightarrow uroguanylin, and the bacterial heat-stable enterotoxin (ST) peptides form a new family of cyclic guanosine 3',5'-monophosphate-regulating agonists [F. J. de Sauvage et al., *Proc. Natl. Acad. Sci. USA* **1992**, 89, 9089; M. G. Currie et al., *Proc. Natl. Acad. Sci. USA* **1992**, 89, 947; L. R. Forte, Jr., *Pharm. Ther.* **2004**, 104, 137].

Gurmarin, <EQCVKKDEL¹⁰IPYYLDCC EP²⁰LECKKVNWWD³⁰HKCIG (disulfide bonds: $\text{C}^3-\text{C}^{18}/\text{C}^{10}-\text{C}^{23}/\text{C}^{17}-\text{C}^{33}$), a sweetness-suppressing 35-peptide from the leaves of the Asclepiad vine *Gymnema sylvestre*. Gurmarin suppresses the sweet taste responses of sucrose, glucose, glycine, and saccharin, without affecting the responses to salty, sour, or bitter substances in laboratory animals (e.g., rats and mice). In humans, gurmarin has only a weak effect. Due to its ability to inhibit selectively the neural response to sweet tastants in rats, gurmarin has been used as a pharmaceutical tool in the investigation of sweet-taste transduction. It has been suggested that information from gurmarin-sensitive and -insensitive receptor processes converges onto neurons in the rat solitary nucleus. *Gurmarin sylvestre* has found application in Ayurvedic medicine in the treatment of diabetes mellitus [J. I. Fletcher et al., *Eur. J. Biochem.* **1999**, 264, 525; M. Ota et al., *Biopolymers* **1998**, 45, 231; C. H. Lemon et al., *J. Neurophysiol.* **2003**, 90, 911].

H

h, human.

HA, head activator.

Hageman factor (factor XII), a blood coagulation factor. Factor XII is a single-chain glycoprotein ($M_r \sim 75$ kDa) acting as the first factor in the intrinsic pathway; XII is activated by \rightarrow plasmin, \rightarrow kallikrein, and the high-molecular-weight kininogen. XII belongs to proteins of the contact system. Activated XII catalyzes the conversion of plasma prekallikrein into plasma kallikrein (\rightarrow kallikreins).

Halicylindramides, a family of \rightarrow depsipeptides isolated from the Japanese marine sponge *Halichondria cylindrata*. Halicylindramides A–C are 14-peptides containing a N-terminus blocked by a formyl group and a C-terminus lactonized with a threonine residue. Halicylindramides D and E were isolated some time later. Whereas halicylindramide D is a 13-peptide with an N-terminal formyl group and a C-terminus lactonized with a threonine residue, halicylindramide E is a truncated linear peptide with a C-terminal amide group. They exhibit antifungal activity against *Mortierella ramanniana* and cytotoxic activity against P388 murine leukemia cells [H. Li et al., *J. Nat. Prod.* **1996**, 59, 163].

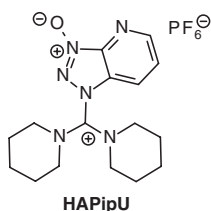
Halipeptins, 16-membered cyclodepsipeptides (\rightarrow depsipeptides) isolated from the marine sponge *Haliclona* sp. With halipeptin A (1), B (2), and C (3), three members of this family are known. These consist of (S)-alanine and three unique

components, the thiazoline-amino acid (ala)Thz, N-methyl hydroxyisoleucine (N-MeOH-Ile) (or N-MeVal for 3), and 3-hydroxy-2,2,4-trimethyl-7-methoxy (or hydroxy for 2 and 3) decanoic acid (HTMMD or HTMHD). Halipeptin A shows a strong anti-inflammatory activity *in vivo* [A. Randazzo et al., *J. Am. Chem. Soc.* **2001**, 123, 10870; K. C. Nicolaou et al., *Angew. Chem. Int. Ed.* **2005**, 44, 4925; S. Hara et al., *Tetrahedron Lett.* **2006**, 47, 1081].

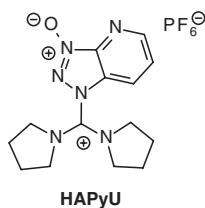
Hamburger pentapeptide, human IgE pentapeptide (HEPP), H-Asp-Ser-Asp-Pro-Arg-OH, a 5-peptide related to the human IgE sequence 330–334 inhibiting cutaneous and systemic IgE-mediated allergic reaction in humans [R. H. Hamburger, *Science* **1975**, 189, 389; G. S. Hahn, *Nature* **1986**, 324, 283; B. M. Prenner, *Ann. Allergy* **1987**, 58, 322].

Handle, linker, linker agent, spacer, in SPPS a bifunctional compound between the resin and the first amino acid of the peptide which allows the first amino acid to be attached to the resin in two discrete steps. Generally, the handle is joined chemically to the resin and the first amino acid linked to it either by esterification or amidation. Alternatively, the handle can be attached to the first amino acid in solution, and this so-called preformed handle is incorporated into the resin [G. Barany, R. B. Merrifield, in: *The Peptides. Analysis, Synthesis, Biology*, A. Gross, J. Meienhofer (Eds.) Volume 2, Academic Press, New York, **1979**, 1; G. Barany, F. Albericio, *J. Am. Chem. Soc.* **1985**, 107, 4939].

HAPipU reagent, a HOAt-derived “uronium-type” coupling reagent (\rightarrow uronium reagents) structurally similar to \rightarrow HATU and HAPyU, named *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate. The correct IUPAC name corresponding to the solid-state structure is 1-[bis-(piperidino)methylumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide hexafluorophosphate.



HAPyU reagent, a HOAt-derived “uronium-type” coupling reagent (\rightarrow uronium reagents) structurally similar to \rightarrow HATU and \rightarrow HAPipU, named *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate. The correct IUPAC name corresponding to the solid-state structure is 1-[bis-(pyrrolidino)methylumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide hexafluorophosphate.

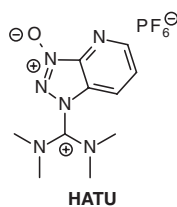


Harg, homoarginine.

Harzinins, a group of peptide antibiotics from *Trichoderma harzianum* belonging to the short-chain \rightarrow peptaibols. They consist of 14 residues including three Aib-Pro motifs in the positions 4/5, 8/9, and

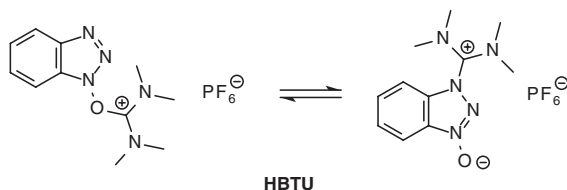
12/13. Harzinins show antagonistic activity against phytopathogenic fungi, increase the permeability of liposomes, and form as the long-chain peptaibols voltage-dependent transmembrane channels [S. Rebuffat et al., *J. Chem. Soc., Perkin Trans.* **1995**, 1849].

HATU reagent, a coupling reagent containing HOBT, similar to \rightarrow HBTU; incorrectly assigned as a “uronium-type” reagent with the name *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. X-ray analysis of similar derivatives has shown that it is in fact a “guanidinium” reagent with the correct IUPAC name 1-[bis-(dimethylamino)methylumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide hexafluorophosphate. It is reputed to efficiently form peptide bonds with very little epimerization.



Hb, hemoglobin.

GBTU reagent, a coupling reagent containing HOBT; incorrectly assigned as a “uronium-type” reagent with the name 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, from which the acronym GBTU is derived. While it is present in the solid state as a “guanidinium” reagent, the correct IUPAC name is: 3-[bis(dimethylamino)methylumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate. It is likely that a uronium–guanidinium equilibrium exists in solution.



HCRT, hypocretin.

Hcys, homocysteine.

HDL, high-density lipoprotein.

Head activator (HA), <EPPGGSKVIL¹⁰F, an 11-neuropeptide conserved from hydra to humans. HA is involved in the development of neuronal cells, and acts in hydra as an important factor in head regeneration. This morphogenic peptide was first isolated and sequenced from the coelenterates *Anthopleura elegantissima* and *Hydra vulgaris* in 1981. Later, HA was also isolated from tissues of higher organisms, e.g., bovine or human hypothalamus and rat intestine. In *Hydra*, HA initiates head-specific growth and differentiation processes, while in mammals it acts as a growth factor in neuronal development. The hydra low-affinity head activator receptor ($K_d \approx 1$ nM) from the multiheaded mutant of *Chlorohydra viridissima* has been characterized as a 200-kDa protein glycosylated mainly as the N-linked type [H. C. Schaller, H. Bodenmüller, *Proc. Natl. Acad. Sci. USA* **1981**, 78, 7000; I. Franke et al., *Eur. J. Biochem.* **1997**, 244, 940].

Heat shock proteins (Hsp), *stress-response proteins*, a group of highly conserved proteins in both prokaryotes and eukaryotes, formed in response to hyperthermia or other noxious conditions. Almost all Hsp function as \rightarrow molecular chaperones. According to their molecular weight (in kDa), the Hsp are divided into six main families. (1) *Hsp100* belongs to the AAA + protein super family (adenosine triphosphatases with diverse activities) sharing a common

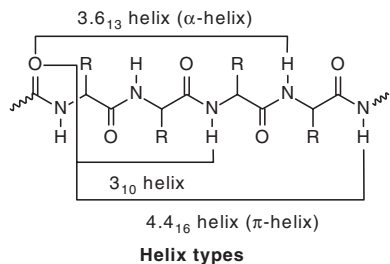
ATPase domain and forms large ring-shaped structures. The best-characterized member of the *Hsp100* family is yeast *Hsp104*, which regulates protein aggregation, disaggregation, and thermotolerance. However, no mammalian homologue has yet been discovered. (2) *Hsp90* is an essential chaperone of the eukaryotic cytosol involved in stabilizing misfolded proteins and regulating the activity of various signaling proteins, such as tyrosine kinases, steroid hormone receptors, calcineurin, and nitric oxide synthase. The *Hsp90* family of proteins in mammalian cells consists of *Hsp90 α* and β , *Grp94*, and *Trap-1* (*Hsp75*). (3) *Hsp60* chaperones consist of heptameric complexes of identical subunits stacked back-to-back in a double-ring structure. The resulting large central cavity is thought to be the place of protein folding. *Hsp60* family members that occur in mitochondria and cooperate with a cofactor of the *Hsp10* family are termed *Group I chaperonins*, whereas *Group II chaperonins* lacking a *Hsp10* cofactor form a second class of chaperonins that occur in the eukaryotic cytosol. *TriC* consisting of eight subunits per ring is the best-studied member of the *Group II chaperonins*. It is encoded by different genes and is thought to be crucial for the folding of \rightarrow actin and tubulin in the eukaryotic cytosol. (4) The *Hsp70* family acting with *Hsp40* as co-chaperones is involved in the stabilization and folding of many proteins occurring in most cellular compartments. In humans, 11 genes encode the members of the *Hsp70*

family comprising the stress-induced cytosolic Hsp70, the constitutive cytosolic member heat shock cognate 70 (HSC70), the ER-localized glucose-regulated protein 78 (GRP78), and the mitochondrial GRP75. All family members are characterized by a conserved N-terminal ATPase domain, and a C-terminal substrate-binding domain. (5) *Hsp40* bind protein substrates and target these proteins to Hsp70, thus enhancing the efficiency of the Hsp70/Hsp40 refolding cycle. The co-chaperone Hsp40 is bound to Hsp70 via a conserved J-domain, and stimulates ATP hydrolysis. Many Hsp40 family members are found in higher eukaryotes. (6) *Small heat shock proteins* (sHsp) are characterized by $M_r < 40$ kDa containing a conserved, C-terminal α -crystalline domain of about 100 aa that mediates oligomeric assembly into large structures resembling a hollow ball. Similar to Hsp90, sHsp stabilizes misfolded proteins; conceivably, the Hsp70/Hsp40 system can refold them. Generally, Hsp show a dual function depending on their intracellular or extracellular location. Intracellular Hsp have a protective function as they allow the cells to survive lethal conditions. Several Hsp can act as endogenous modulators of apoptotic cell death. Extracellularly located or membrane-bound Hsp mediate immunological functions [O. Bensaude et al., *Nature* **1983**, 305, 331; E. A. Craig et al., *Microbiol. Mol. Biol. Rev.* **1993**, 57, 402; R. I. Morimoto, A. Tissieres, C. Georgopoulos, *The Biology of Heat Shock Proteins and Molecular Chaperones*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, **1994**; C. Didelot et al., *Handbook Exp. Pharmacol.* **2006**, 172, 171; E. Schmitt et al., *J. Leukocyte Biol.* **2007**, 81, 15].

Hedgehog (HH), a secreted protein termed for the bristle phenotype observed in

Drosophila embryos lacking the corresponding gene. Three homologues of HH have been characterized that have critical functions in the development of multiple organ systems. These proteins are involved in the regulation of stem cell production, and in the activation of tissue repair after injury. Furthermore, they appear to drive proliferation in a variety of tumors. One of these mammalian homologues, the sonic hedgehog (SHH), has been reported to be an important regulator of neural patterning and neural cell proliferation. The cAMP/protein kinase A (PKA) pathway has been established as a major pathway that opposes HH signaling performed by phosphorylating intracellular signaling mediators and targeting them for degradation [J. A. Waschek et al., *Ann. N. Y. Acad. Sci.* **2006**, 1070, 120].

Helices, widely occurring secondary structure elements comprising a screw-like arrangement of the peptide backbone stabilized by intramolecular hydrogen bonds aligned in parallel to the helix axis. A helix is characterized by a well-defined number of amino acid residues per turn (n), the helix pitch (p , repeat distance), and the number of skeleton atoms incorporated into the "ring" formed by intramolecular hydrogen bonds. Helices are chiral objects, the direction of the helical turn being given by the letters "P" (plus) for clockwise and "M" (minus) for anticlockwise helices. The most common form is the α -helix ($n = 3.6$, $p = 540$ pm, torsion angles $\varphi = 57^\circ$, $\psi = 47^\circ$, 'ring-size' = 13) with the full nomenclature of a 3.6_{13} -P-helix, which was originally proposed by \rightarrow Pauling and Corey based on theoretical investigations regarding the X-ray diffraction patterns of α -keratins. Other helix types are 3_{10} -helix (3_{10} -P-helix, $\varphi = -60^\circ$, $\psi = -30^\circ$), π -helix (4.4_{16} -P-helix, $\varphi = -57^\circ$, $\psi = -70^\circ$), and γ -helix (5.1_{17} -helix).

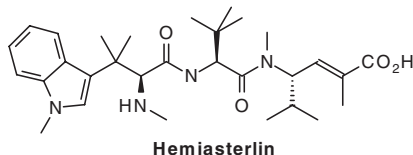


Helioferins, antifungal peptides produced from *Mycogone rosea*. Helioferins A and B inhibited the growth of *C. albicans*, but were toxic to chicken embryos at levels >0.5 mg kg^{-1} , and caused hemolysis at concentrations >100 $\mu\text{g mL}^{-1}$. They are members of the leucinostatin-trichopolyn group [U. Gräfe et al., *J. Antibiot.* **1995**, 48, 126].

Hemerythrin, one of the three major metalloproteins capable of the reversible binding of dioxygen, and found in animals of several marine invertebrate phyla. It differs significantly from \rightarrow hemoglobin and \rightarrow hemocyanins by possessing an active site comprising two iron atoms linked by a μ -oxo bridging atom. Hemerythrin, an octamer ($M_r \sim 108$ kDa), from the coelomic cavity of the sipunculid worm *Phascolopsis gouldii*, was the subject most of these investigations. Every polypeptide chain ($M_r \sim 13.5$ kDa; 2 Fe^{2+}) contains 113 residues and can bind one molecule of O_2 [R. E. Stenkamp, *Chem. Rev.* **1994**, 94, 715].

Hemiasterlin, a tripeptide isolated from several marine sponges (*Hemiasterella minor*, *Auletta* sp., *Cymbastela* sp., *Siphonochalina* sp.) exhibiting potent cytotoxicity against a variety of cancer cell lines *in vitro* via a tubulin antimetabolic mechanism. Its relatively simple structure allows structural modifications to obtain analogues with high potency such as *taltobulin* (HTI-286 also known as SPA110), which show more potent *in-vitro* cytotoxicity and antimetabolic ac-

tivity than the natural peptide [J. A. Nieman et al., *J. Nat. Prod.* **2003**, 66, 183; A. Zask et al., *J. Med. Chem.* **2004**, 47, 4774; *J. Am. Chem. Soc.* **2005**, 127, 17667].



Hemocyanins, large multi-subunit oxygen-transporting porphyrin-free copper proteins in the hemolymph of many chelicerate, crustacean, myriapod, and also possibly some insect species. The arthropod hemocyanins are members of a large protein superfamily including also the arthropod phenoloxidases, certain crustacean and insect storage proteins (pseudo-hemocyanins and hexamerins), and the insect hexamerin receptor. Oxygen-loaded hemocyanins are blue, whereas the oxygen-free form is colorless. The hemocyanin of arthropods are hexamers (subunit: $M_r \sim 75$ kDa) which are capable of aggregating to multi-hexamers. Molluscan hemocyanins are also oligomers from which each subunit ($M_r \sim 400$ kDa) contains eight O_2 -binding sites. The evolution of hemocyanin subunits, and also the formation of multi-hexamers, occurred independently within the arthropod subphyla. The arthropod hemocyanins originated more than 550 million years ago from oxygen-consuming phenoloxidases. The insect hexamerins and the crustacean pseudo-hemocyanins (cryptocyanins) are copper-less storage proteins [W. P. J. Gaykema et al., *Nature* **1984**, 309, 23; K. E. van Holde, K. I. Miller, *Adv. Protein. Chem.* **1995**, 47, 1; T. Burmester, *Micron* **2004**, 35, 121].

Hemoglobin (Hb), a vertebrate oxygen-transporting protein in the red blood

cells (erythrocytes). The tetrameric Hb ($M_r \sim 64.5$ kDa) contains two pairs of polypeptide chains and four heme groups, and carries oxygen from the lungs to other tissues. The heme-free protein of Hb is termed *globin*. Human adult Hb consists of approximately 97.5% of HbA₁ ($\alpha_2\beta_2$) and 2.5% HbA₂ ($\alpha_2\delta_2$). The α -chains of humans contain 141 aa, and the β -chains 146 aa. Different forms of Hb occur during embryonic development. The tertiary structure of a Hb chain is folded in a manner that is very similar to that of \rightarrow myoglobin (Mb). According to Mb, each of the four subunits of Hb non-covalently binds a single heme group. The latter effect is responsible for the red color of blood, and is the site at which each monomer of Hb binds one molecule of O₂. In Hb, the iron atom normally remains in the Fe(II) oxidation state, whether or not the heme is oxygenated (binds O₂). In desoxyHb, the central Fe(II) is 5-coordinated by the four pyrrole N atoms of protoporphyrin IX and by the globin's proximal His. The sixth ligand of Fe(II) is ligated by O₂ upon oxygenation. Hb of all human races, and even of chimpanzees, is identical. Anomalies of Hb arise through point mutations; the most frequent and best known is *sickle cell Hb*, in which Glu⁶ of the normal β -chain is replaced by Val ($\alpha_2\beta_2^{6\text{Glu}\rightarrow\text{Val}}$). The medical symptoms are anemia and acute ischemia, tissue infarction and chronic failure of organ function. Besides the basic function of oxygen transport, multiple functions of Hb were described in 1995 [M. F. Perutz, *Sci. Am.* **1978**, 239, 92; R. E. Dickerson, I. Geis, *Hemoglobin: Structure, Function, Evolution, and Pathology*, Benjamin/Cummings Publ. Co., **1983**; M. F. Perutz, *Q. Rev. Biophys.* **1989**, 22, 139; W. A. Eaton, J. Hofrichter, *Adv. Prot. Chem.* **1990**, 40, 63; B. Giardina et al., *Crit. Rev. Biochem. Mol. Biol.* **1995**, 30, 165].

Hemokinin-1 (HK-1), RSRTQFYGL¹⁰Ma, a novel \rightarrow mammalian tachykinin discovered in lymphoid B hematopoietic cells of mouse bone marrow. HK-1 shares the common C-terminal sequence typical of the tachykinin peptide family, and displays a high sequence homology with \rightarrow substance P. HK-1 is uniquely expressed outside the neural tissue in immune tissues. It is a full agonist at the NK₁, NK₂ and NK₃ receptors, with highest selectivity for NK₁ [Y. Zhang et al., *Nat. Immunol.* **2000**, 1, 392; N. N. Page et al., *Proc. Natl. Acad. Sci. USA* **2003**, 100, 6245].

Hemopexin, a plasma glycoprotein binding specifically one heme with high affinity to transport it to hepatocytes for salvage of the iron. Human hemopexin ($M_r \sim 63$ kDa) consists of a single peptide chain of 439 aa containing six intrachain disulfide bridges. The N-terminal Thr is substituted by an O-linked galactosamine oligosaccharide. Furthermore, the protein contains five glucosamine oligosaccharides N-linked to the acceptor core sequence Asn-Xaa-Ser/Thr. The protein consists of two similar halves connected by a histidine-rich, hinge-like region containing two glucosamine oligosaccharides. The crystal structure reveals a novel high-affinity heme site formed between two β -propeller domains [N. Takahashi et al., *Proc. Natl. Acad. Sci. USA* **1985**, 82, 73; U. Muller-Eberhard, *Methods Enzymol.* **1988**, 163, 536; M. Paoli et al., *Nature Struct. Biol.* **1999**, 6, 926].

Hemopressin (HP), rHP: H-Pro-Val-Asn-Phe-Lys-Phe-Leu-Ser-His-OH, a bioactive 9-peptide derived from the α_1 -chain of \rightarrow hemoglobin and initially isolated from rat brain extract. HP has been used as a natural peptide substrate for endopeptidase 24.15, neurolysin, and \rightarrow angiotensin-converting enzyme. The sequence of HP is well

conserved across mammalian species. Rat HP has been shown to possess systemic vasodepressor activity in the rat, to decrease systemic arterial pressure in rabbit and mouse, and to inhibit peripheral hyperalgesia via a naloxone-independent mechanism. Recently it was reported that rHP dilates the rat systemic vascular bed via the endogenous release of nitric oxide, independent of cyclooxygenase products including prostacyclin [V. Rioli et al., *J. Biol. Chem.* **2003**, 278, 8547; C. S. Dale et al., *Peptides* **2005**, 26, 431; P. A. Blais et al., *Peptides* **2005**, 26, 1317; H. Lippton et al., *Peptides* **2006**, 27, 2284].

Hemorphins, → exorphins.

Hemosiderin, a mammalian non-heme iron storage protein with a similar function to → ferritin. It contains iron oxyhydroxide cores similar to those of ferritin, and it has been reported that these cores are present as large, dense, membrane-bound aggregates *in vivo*. It is assumed that hemosiderin is produced by lysosomal degradation of ferritin or possibly of ferritin polymers. Hemosiderin is deposited in the liver and spleen, especially in diseases such as pernicious anemia or hemochromatosis. The deposits are yellow to brown-red pigments. The iron content of hemosiderin is about 37%. Non-heme iron is also abundantly present in the brain in different forms. In the so-called high-molecular-weight complexes, iron is bound to hemosiderin and ferritin. The total amount of iron may differ in health and disease [F. A. Fischbach et al., *J. Ultrastruct. Res.* **1971**, 37, 495; M. P. Weir, T. J. Peters, *Biochem. J.* **1984**, 223, 31].

Hep, heptyl.

Heparin binding growth factor, → fibroblast growth factor.

Hepcidin (hHEP), DTHFPICIFC¹⁰CGC CHRSKCG²⁰MCCKT (disulfide bonds: C⁷–C²² / C¹⁰–C²²; C¹¹–C¹⁹ / C¹³–C¹⁴), a 25-peptide synthesized in the liver via a 72 aa prepro-hepcidin. It was first detected in human urine and plasma. In addition to the 25-mer, urine contains also 20-mer and 22-mer forms truncated at the *N*-terminus. Hepcidin forms a simple hairpin stabilized by three disulfide bonds, and a vicinal disulfide bond in the turn. Hepcidin controls extracellular iron by regulating its intestinal absorption, placental transport, recycling by macrophages, and release from stores [T. Ganz, E. Nemeth, *Am. J. Physiol. Gastrointest. Liver Physiol.* **2006**, 290, G199; V. Atanasiu et al., *Eur. J. Haematol.* **2007**, 78, 1].

Hepes, *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid.

Hepsin, a membrane-anchored, trypsin-like serine protease expressed prominently in human liver. Due to its liver origin, the name hepsin was given to the enzyme. Hepsin is synthesized as a single-chain, 417 aa protein. Upon activation, hepsin is thought to be transformed into a two-chain form consisting of a light chain (1–163) and a heavy chain (164–417) linked by a disulfide bond. Hepsin has multiple functions, such as organogenesis, tissue rearrangement, maintenance of structural integrity of some mammalian cells, and possibly initiation of hemostasis at the cell surface. It has been reported that hepsin is implicated in prostate and ovarian cancers [S. P. Leylus et al., *Biochemistry* **1988**, 27, 1067; K. Kurachi et al., *Methods Enzymol.* **1994**, 244, 100; S. Herter et al., *Biochem. J.* **2005**, 390, 125].

Heterodetic peptides, peptides that beside peptide bonds can also contain other bonds, such as ester, disulfide, or thioester bonds.

Heteromeric peptides, peptides that also contain non-proteinogenic building blocks.

Hevein, a cysteine-rich, chitin-binding peptide ($M_r \sim 4.7$ kDa) found in the luteoid bodies of the rubber tree (*Hevea brasiliensis*) latex. It is heat-resistant (90 °C for 10 min), and occurs in the bottom fraction of the latex. Hevein resembles the chitin-binding lectin from the stinging nettle, *Urtica dioica*. Hevein inhibits the hyphal growth of fungi by binding to chitin. *Hevein-like peptides* are 43 aa chitin-binding peptides showing stronger antifungal activity than hevein [B. L. Archer, *Biochem. J.* **1960**, 75, 236; J. van Parijs et al., *Planta (Berl.)* **1991**, 183, 258].

Hevein-like peptides, \rightarrow hevein.

HG, human little gastrin.

hGH, human growth hormone.

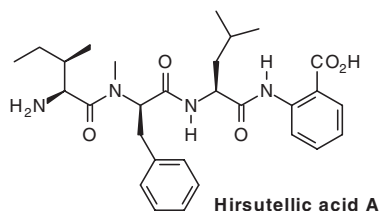
High-throughput screening (HTS), an approach to accelerate the pre-clinical drug discovery process. Millions of biochemical, genetic or pharmacological tests are performed automatically in a short period of time. In HTS usually 10 000 to 100 000 compounds are tested per day with respect to a specific biological activity, while *ultra-high-throughput screening* (uHTS) processes more than 100 000 samples per day. HTS and uHTS operate on a miniaturized scale and employ automation, robotics, miniaturized high-precision liquid handling, and highly sensitive detection, together with automated data processing and process control. The arrays are performed using microtiter plates with 384 wells (sample volume per well $\approx 20\text{--}30 \mu\text{L}$), 1536 wells (sample volume $\approx 2\text{--}8 \mu\text{L}$), or 3456 wells (sample volume $\approx 1 \mu\text{L}$). Even plates of 9600 wells have been described for screening at the $\leq 1 \mu\text{L}$

scale. Usually, compound libraries of 10^4 to 10^6 compounds (small molecules, peptides) are screened for biological activity towards a specific target in order to qualify as a potential drug candidate. Among 10^6 compounds tested, several thousand hits are to be expected, and eventually one to four potential lead compounds will be considered for further development. In HTS, the inhibition of binding events, the activation of a specific protein function, and the control of enzymatic reactions may be examined. Binding assays can be performed (e.g., with purified proteins), while functional assays make use of cell lines and may differentiate between agonist and antagonist activity. High reliability is required in the classification of biological activities of the compounds to be screened in order to eliminate false positives (non-active compounds assayed as active) and false negatives (active drug candidates assayed as inactive). Active compounds (hits) identified in the screening process are subsequently further evaluated eventually to provide a development candidate (lead). Detection relies on radioactivity, fluorescence, or luminescence. Fluorescence assays such as laser-induced fluorescence, fluorescence resonance energy transfer (FRET), fluorescence polarization, homogeneous time-resolved fluorescence, and fluorescence correlation spectroscopy, dominate because of their ease of application and inherent sensitivity. Confocal fluorescence techniques are required for uHTS, as they operate with a measurement volume of 1 fL and an assay volume of $1 \mu\text{L}$. Single-molecule techniques such as fluorescence correlation spectroscopy (FCS) or fluorescence intensity distribution analysis (FIDA) are also appropriate [J. Wölcke, D. Ullmann, *Drug Discov. Today* **2001**, 6, 637; C. Eggeling et al., *Drug Discov. Today* **2003**, 8, 632].

Himastatin, a dimeric cyclodepsipeptide (\rightarrow depsipeptides) consisting of two "monomers" linked by a biphenyl linkage. Each "monomer" of the molecule contains six residues with a pyrroloindoline moiety and 5-hydroxypiperazic acid as notable features. Himastatin exhibits activity against Gram-positive bacteria, but is inactive against Gram-negative bacteria. The structure was confirmed by total synthesis in 1998 [J. E. Leet et al., *J. Antibiot.* **1996**, 49, 299; T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1998**, 37, 2993].

Hip, hippuric acid.

Hirsutellin acid A, an antimalarial peptide from the entomopathogenic fungus *Hirsutella* sp. BCC 1528. The peptide showed activity against the malarial parasite *Plasmodium falciparum* K1, with an IC_{50} of 8 μ M, but was non-cytotoxic to Vero cells (African green monkey kidney fibroblasts) at a concentration of 95 μ M [J. Thongtan et al., *J. Nat. Prod.* **2006**, 69, 713].

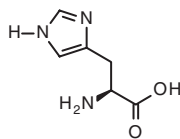


Hirudin, VVYTDCTESG¹⁰QNLCLCEGSN²⁰VCGQGKNKCIL³⁰GSDGEKNQCV⁴⁰TGEGT PKPQS⁵⁰HNDGDFEIP⁶⁰-EEY^SLQ [Y^{S/63}: Tyr(SO₃H); disulfide bridges: C⁶–C¹⁴ / C¹⁶–C²⁸ / C²²–C³⁹], a single-stranded, 65-peptide isolated from the salivary glands of the leech *Hirudo medicinalis*. Hirudin is the most potent natural inhibitor of the protease \rightarrow thrombin. It is the most efficient member of the thrombin inhibitors (K_i = 20 fM). Hirudin is a very effective anti-coagulant, as thrombin acts mainly on

\rightarrow fibrinogen and stimulates the coagulation of blood. The binding of hirudin to thrombin involves a non-covalent, ionic interaction, and is a two-step process. The rate-limiting step is the anchoring at the site distinct from the active site by the acidic domain of hirudin-(56–65). In the next step, the initial complex is rearranged to form a tighter complex in which the sequence around Lys⁴⁷ covers the active center of thrombin. Today, hirudin is produced by large-scale recombinant (rec) technology in high purity, as for \rightarrow lepirudin. Although rec-hirudin lacks the sulfate moiety at Tyr⁶³, CGP 39393 (Ciba-Geigy), for example, is a highly potent inhibitor (K_i = 230 fM). C-terminal fragments of 10–12 residues also act as antithrombotic agents. Recently, a convergent solid-phase synthesis of hirudin variant 1 (HV1) was described [F. Markwardt, *Naturwissenschaften* **1955**, 42, 537; F. Markwardt, *Methods Enzymol.* **1970**, 19, 924; J. H. Sohn et al., *Appl. Microbiol. Biotechnol.* **2001**, 57, 606; F. Markwardt, in: *Seminars in Thrombosis and Hemostasis* (E. F. Mammen, Ed.), **2002**, 28, 405; A. Greinacher, *Expert. Rev. Cardiovasc. Ther.* **2004**, 2, 339; S. Goulas et al., *J. Peptide. Sci.* **2006**, 12, 116].

Hirullin, hirudin-related peptides showing potent antithrombin activity. *Hirullin P 18*, a 62-peptide contains, similar to \rightarrow hirudin, a highly acidic C-terminus, but is significantly different in sequence compared to other known hirudin variants. *Bufrudin* from the Asian jawed leech *Hirudinaria manillensis* shows sequence identity of only about 60% compared with P18. *Hirullin PA* contains a sulfated tyrosine in its C-terminal functional domain, but its location differs by one position relative to hirudin. A 13-peptide, SDFEEFSLDD¹⁰IEQ, originally isolated from the leech *H. manillensis*, acts

as a hirudin-based fibrinogen recognition peptide inhibitor, and binds efficiently to thrombin [J. Dodt et al., *Biol. Chem. Hoppe-Seyler* **1986**, 367, 803; A. Electricwala et al., *J. Prot. Chem.* **1993**, 12, 365; X. Qiu et al., *J. Biol. Chem.* **1993**, 268, 20318].



Histidine (His) H

His, histidine.

His tag, an oligohistidine sequence bound to the C-terminus of a protein followed by complexation with a transition metal (Ni) and nitrilotriacetic acid (NTA) enables purification and detection of proteins, as well as immobilization on surfaces or tethering to lipid membranes. Adding competitors such as imidazole leads to a fast dissociation of the interactions under mild conditions. Furthermore, dissociation of the Me:NTA-histidine complexes can be performed by removing the metal ion. For example, the protein under investigation can be easily adsorbed onto a Ni-NTA agarose column, followed by thorough washing and elution of the His-tagged protein, as indicated above. While individual Me:NTA-oligohistidine complexes are typically formed by two coordination bonds with $K_d \approx 10 \mu\text{M}$, stronger interactions can be reached by multipoint attachment, since hexahistidine tags provide binding sites for three NTA moieties, and even more for larger oligohistidines (\rightarrow double-His₆) [E. Hochuli et al., *J. Chromatogr.* **1987**, 411, 177; E. Ueda et al., *J. Chromatogr. A* **2003**, 988, 1; S. Lata, J. Piehler, *Anal. Chem.* **2005**, 77, 1096; S. Lata et al., *J. Am. Chem. Soc.* **2005**, 127, 10205].

Histamine-releasing peptides, \rightarrow ranid frog peptides.

Histidine (His, H), imidazolylalanine, $\text{C}_6\text{H}_9\text{N}_3\text{O}_2$, M_r 155.16 Da, a proteinogenic amino acid.

Histones, relatively small basic globular proteins with a high content of Arg and Lys; these form preferentially the structure proteins of eukaryotic chromosomes. Histones are divided into five types based on the content of positively charged amino acids and the molecular weight. Additionally, these five types fall into two main groups, termed *H1 histones* and *nucleosomal histones*. *H1 histones* (215–220 aa; M_r 21.5–22 kDa) have been less conserved during evolution compared with the second main group. The *nucleosomal histones* are divided into *H2A* (129 aa; $M_r \sim 14$ kDa), *H2B* (125 aa; $M_r \sim 13.8$ kDa), *H3* (135 aa; $M_r \sim 15.3$ kDa) and *H4* (102 aa; $M_r \sim 11.3$ kDa). They are responsible for coiling the DNA into nucleosomes. H3 and H4 are the most highly conserved of all known proteins, and form the inner core of the nucleosome [I. Isenberg, *Annu. Rev. Biochem.* **1979**, 48, 159; R. S. Wu et al., *CRC Crit. Rev. Biochem.* **1986**, 20, 201; J. Zlatnanova, K. van Holde, *Prog. Nucleic Acids Res. Mol. Biol.* **1996**, 52, 217; C. Peterson, M. Laniel, *Curr. Biol.* **2004**, 14, R546].

Histone deacetylase inhibitors, peptides that inhibit histone deacetylases (HDAC). Inhibition of HDAC effects cell-cycle arrest and induces differentiation. Therefore, HDAC is considered a target for new types of pharmaceuticals for treatment of cancers, and several naturally occurring or synthetic peptides have been reported as lead structures. The most prominent family is a series of cyclic tetrapeptides containing the non-proteinogenic amino acid Aeoe [(2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic

acid] such as \rightarrow Chlamydocine [cyclo-(-Aib-Phe-D-Pro-Aoe-)], WF 3161 [cyclo-(-D-Phe-Leu-Pip-Aoe-)], trapoxin A [cyclo-(-Phe-Phe-D-Pro-Aoe-)], trapoxin B [cyclo-(-Phe-Phe-D-Pip-Aoe-)], HC Toxin [cyclo-(D-Pro-Ala-D-Ala-Aoe-)], Cyl-1 [cyclo-(-D-Tyr(Me)-Ile-Pro-Aoe-)], and Cyl-2 [cyclo-(-D-Tyr(Me)-Ile-Pip-Aoe-)]. Aoe is replaced by its des-epoxy analogue in apicidin [cyclo-(-(N^{im} -MeO-Trp))-Ile-D-Pip-L-(2-amino-8-oxodecanoyl-)]. In the synthetic analogues CHAP31 and CHAP50, Aoe is replaced by the hydroxamate (*S*)-2-amino-8-(hydroxyamino)-8-oxooctanoic acid. Depsipeptide FK228 is a naturally occurring bicyclic peptide HDAC inhibitor with a disulfide linkage, obtained as a fermentation product of *Chromobacterium violaceum* [Y. Komatsu et al., *Cancer Res.* **2001**, 61, 4459; N. Nishino et al., *Org. Lett.* **2003**, 5, 5079].

HIV, human immunodeficiency virus.

Hiv, α -hydroxyisovaleric acid.

HIV protease, monomer: PQITLWOR PL¹⁰VTIRIGGQLK²⁰EALLDTGADD³⁰TVL EEMNLPG⁴⁰KWKPKMIGGI⁵⁰GGFIKYRQ YD⁶⁰QIPVETCGHK⁷⁰AIGTVLVGPT⁸⁰PV NIIGRNLL⁹⁰TQIGCTLNF, an aspartyl protease consisting of two identical monomers with 99 residues, each of which is essential for the maturation of \rightarrow human immunodeficiency virus (HIV). HIV protease is responsible for the proteolytic maturation of the HIV structural proteins, reverse transcriptase, integrase, and RNase H, which are encoded by the viral *gag* and *pol* genes. The design of inhibitors with high potency for the HIV protease offers a logical approach to the formation of non-infectious viral particles. The crystal structure in complex with a low-molecular-weight inhibitor (VX-478) was described in 1995. The HIV protease and an analogue

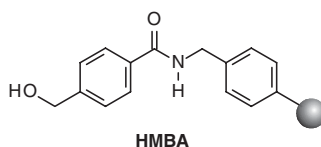
of this enzyme, containing D-amino acids only, have been synthesized chemically [T. D. Meek et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 1841; R. L. C. Milton et al., *Science* **1992**, 256, 1445; C. Debouck, *AIDS Res. Hum. Retroviruses* **1992**, 8, 153; E. E. Kim et al., *J. Am. Chem. Soc.* **1995**, 117, 1181; G. Moyle, B. Gazzard, *Drugs* **1996**, 51, 701].

HK-1, hemokinin-1.

Hmb, 2-hydroxy-4-methoxybenzyl.

HMBA, hydroxymethylbenzoic acid.

HMBA resin, an aminomethyl polystyrene resin acylated with 4-(hydroxymethyl)benzoic acid. It is completely resistant towards treatment with acids (even liquid HF), and enables on-resin side-chain deprotection. The highly versatile linker is cleaved by a variety of nucleophiles such as hydroxide ions (to give peptide acids), alcohols (to give esters), ammonia or amines (to give amides), hydrazine (to give peptide hydrazides), or LiBH₄ (to give peptide alcohols) [R. C. Sheppard, B. J. Williams, *Int. J. Pept. Protein Res.* **1982**, 20, 451].



HMG proteins, *high mobility group proteins*, a family of chromatin proteins first described during the 1970s. The name is related to their high mobility in polyacrylamide gel electrophoresis. According to this behavior and other properties, they resemble \rightarrow histones. The highly conserved HMG proteins contain ~25% basic and 30% acidic amino acids. The major members of this family constitute two pairs of

homologous proteins: *HMG1* and *HMG2* ($M_r \sim 25$ kDa), which bind both to single- and double-stranded DNAs; and *HMG14* and *HMG17* ($M_r \sim 10$ kDa), which show a higher affinity to nucleosomes than to DNA. Nowadays, the name refers to two classes of proteins: the *canonical HMGs*, and *HMG-motif proteins*. The first class is ubiquitous to eukaryotes but are absent in eubacteria and archaea. Furthermore, they can be divided into three families: HMG1/2, HMG-14/17, and HMG-I/Y. Each family is characterized by a functional sequence motif: the HMG box, the nucleosome binding domain, or the AT-hook. The HMG-motif proteins contain only one of these functional motifs, whereas the remainder of the sequences are different. HMG proteins are involved in the regulation of genes in normal or pathological conditions [M. Bustin, *Mol. Cell. Biol.* **1999**, 19, 5237; M. Wegner, *Nucleic Acids. Res.* **1999**, 27, 1409; M. E. Bianchi, M. Beltrame, *EMBO Rep.* **2000**, 1, 109].

HMPA, 4-hydroxymethyl-3-methoxyphenoxyacetic acid.

HMPAA, 4-(hydroxymethyl)phenoxyacetic acid.

HMPB resin, an aminomethyl polystyrene resin acylated with 4-hydroxymethyl-3-methoxyphenoxybutyric acid cleavable by extremely mild acidolysis similar to → SASRIN (super acid-sensitive resin). Detachment of the final product, even in form of the fully protected peptides, is achieved with dilute acid (1% TFA/dichloromethane) to yield peptide

acids [B. Riniker et al., *Tetrahedron* **1993**, 49, 9307].

HMPT, hexamethylphosphorous triamide (also HMP or HMPA).

HN, humanin.

Hnb, 2-hydroxy-6-nitrobenzyl.

HOAt, 1-hydroxy-7-azabenzotriazole.

HOBt, 1-hydroxybenzotriazole.

Hoc, cyclohexyloxycarbonyl.

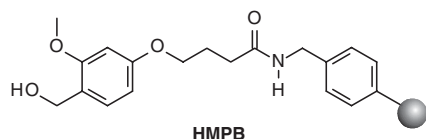
HODhbt, 3,4-dihydroxy-3-hydroxy-4-oxo-1,2,3-benzotriazine.

Hofmannolin, → cyanopeptolins.

Hofmeister, Franz (1850–1922), physiological chemist and pioneer of protein structure. He succeeded Hoppe-Seyler at Strasbourg, where he led a productive research school. Franz Hofmeister and → Emil Fischer exerted both, each in his own way, a significant influence on the development of the biochemical sciences. Already in 1902, at a historical meeting at Karlsbad, Franz Hofmeister first formulated scientifically the assumption of an amide-like linkage of the individual amino acids in proteins, four years before Fischer coined the term peptide [F. Hofmeister, *Naturw. Rdsch.* **1902**, 17, 529].

Holotricin 3, a glycine- and histidine-rich insect-derived → antimicrobial peptide from the larval hemolymph of *Holotrichia diomphalia*, which inhibits *C. albicans* growth [S. Y. Lee et al., *Biol. Pharm. Bull.* **1995**, 18, 1049].

Homocarnosine, γ -aminobutyryl-histidine, GABA-His, a naturally occurring dipeptide related to → carnosine with a wide spectrum of biological activities. Besides biological effects similar to those of carnosine and → anserine, homocarnosine was



suggested to be a precursor for the neurotransmitter γ -aminobutyric acid, termed GABA. Its action as a GABA reservoir is based on the modulation of one or several carnosinases that cleaves homocarnosine into GABA and histidine [O. A. C. Petroff et al., *Neurology* **2001**, 56, 709; A. Guiotto et al., *Curr. Med. Chem.* **2005**, 12, 2293].

Homocereulide, \rightarrow cereulide.

Homodetic peptide, a peptide containing exclusively peptide bonds.

Homomeric peptide, a peptide composed exclusively of proteinogenic amino acids.

HONdc, *N*-hydroxy-5-norbornene-2,3-dicarboximide.

HOPIp, *N*-hydroxypiperidine.

α -Hordothionin (α -HT), a 45-peptide from barley grains (*Hordeum vulgare*) that belongs to a family of membrane active plant toxins-thionins. The structure has been determined at 1.9 Å resolution by X-ray crystallography [K. H. Han et al., *Biochem. J.* **1996**, 313, 885; K. A. Johnson et al., *FEBS Lett.* **2005**, 579, 2301].

Host defense peptides (HDP), an alternative term for \rightarrow antimicrobial peptides.

HOSu, *N*-hydroxysuccinimide.

HPLC, high-performance liquid chromatography.

HSA, human serum albumin.

Hse, homoserine.

Hsp, heat shock protein.

HTRF, homogeneous time-resolved fluorescence.

HTS, high-throughput screening.

Human chorionic gonadotropin, \rightarrow chorionic gonadotropin.

Human chorionic somatomammotropin, \rightarrow chorionic mammotropin.

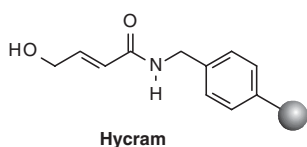
Human immunodeficiency virus 1 (HIV-1), the etiological agent of AIDS (acquired immunodeficiency syndrome) that establishes lytic, latent and non-cytopathic productive infection in cells in culture. HIV is a retrovirus bearing a reverse transcriptase, which enables the encoding of viral RNA into DNA of the host's cells. HIV is the causative agent of AIDS. The spread of HIV has reached worldwide epidemic proportions, and has become of major concern in the search for effective drugs. The viral genome shows a complex organization. Besides the genes encoding the virion capsid, envelope proteins and the enzymes required for proviral synthesis and integration, HIV-1 encodes four additional proteins (*tat*, *art*, *sor* and 3' *orf* proteins) that regulate virus replication. The gene product of the *vpu* open reading frame is the 16 kDa protein \rightarrow Vpu.

Humanin (HN), MAPRGFSCLL¹⁰LLTSEIDL²⁰PKRRRA, a 24-peptide encoded in mammalian genomes. HN was originally identified as an endogenous peptide that protects neural cells from apoptosis induced by mutant \rightarrow Alzheimer's disease genes. It has also been reported that HN prevents serum-deprivation-induced apoptosis of rat PC12 cells, and inhibits apoptosis by interfering with Bcl-2-associated X protein (Bax) activation. Recently, it has been shown that HN can increase ATP levels of human lymphocytes; it has also been proposed that HN expression might be induced in response to the energy crisis within affected fibers and vessels in MELAS muscles. HN may also be a therapeutic candidate for MELAS [B. Guo et al., *Nature* **2003**, 423, 465; S. Kariya et al., *Mol. Cell. Biochem.* **2003**, 254,

83; S. Kariya et al., *Acta Neuropathol.* **2005**, 109, 367].

Hybrid approach, → phase-change synthesis.

Hycram resin, *hydroxycrotonoylamidomethyl resin*, an allyl-based handle resin connection for SPPS of peptides and, especially, for glycopeptides, which is stable to base and mild acid. The cleavage of the final product from the resin occurs under neutral conditions by treatment with $(\text{Ph}_3\text{P})_4\text{Pd}/\text{THF}/\text{morpholine}$, and does not affect Boc, Fmoc, or glycosidic bonds [H. Kunz, B. Dombo, *Angew. Chem. Int. Ed.* **1988**, 27, 711].



Hydralysins, non-nematocystic paralytic toxins from the green hydra *Chlorohydra viridissima*, comprising a highly diverse group of β -pore-forming proteins [D. Sher et al., *J. Biol. Chem.* **2005**, 280, 22847].

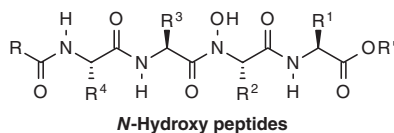
Hydrazino peptides, peptides composed of α -hydrazino acids, $\text{H}_2\text{N}-\text{NR}-\text{CH}_2-\text{COOH}$ and $\text{H}_2\text{N}-\text{NH}-\text{CHR}-\text{COOH}$, respectively. They are structurally related to → β -peptides because they also contain an additional skeleton atom between the amino and carboxy groups [A. Aubry et al., *Int. J. Pept. Protein Res.* **1994**, 43, 305; R. Günther, H.-J. Hofmann, *J. Am. Chem. Soc.* **2001**, 123, 247].

Hydrins, peptides isolated from the pituitary glands of *Xenopus laevis* and *Rana esculenta*, respectively. *Hydrin 1*: CY-IQNCPRGG¹⁰KR (disulfide bond: C¹–C⁶), *hydrin 1'*, [desArg¹²]*hydrin 1* and *hydrin*

2, [desArg¹²,desLys¹¹]*hydrin 1* show structural similarities to vasotocin, but lack any oxytocic and pressor activities. It is suggested that hydrins may be involved in the water-electrolyte regulation of amphibians [Y. Rouille et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 5272; S. Iwamuro et al., *Biochim. Biophys. Acta* **1993**, 1176, 143; R. Acher et al., *Biol. Cell* **1998**, 89, 283].

Hydrogen fluoride, anhydrous hydrogen fluoride is the preferred agent for the final deprotection of benzyl-type protecting groups [S. Sakakibara, Y. Shimonishi, *Bull. Chem. Soc. Japan* **1965**, 38, 1412].

N-Hydroxy peptides, peptides with N $^{\alpha}$ -hydroxy moieties. The hydroxamate groups in such pseudopeptides may act as metal coordination sites in order to preorganize peptide structures. The N $^{\alpha}$ -hydroxy group confers different hydrogen bonding capabilities compared to native peptides, thus modifying the conformation and potentially also molecular recognition [J. Lawrence et al., *Org. Biomol. Chem.* **2006**, 4, 3125].



Hydroxy protection, the temporary protection of the primary and secondary hydroxy functions of Ser and Thr, respectively, and the aromatic hydroxy group of Tyr in peptide synthesis. The blocking of these functionalities is necessary as they can react with acylating reagents. In SPPS, these amino acids are usually protected as benzyl ethers applying Boc/Bzl tactics or as *tert*-butyl ethers in Fmoc/Bu^t chemistry.

Hyl, δ -hydroxylysine.

Hylambatins, peptides isolated from the skin of the African frog *Hylambates maculatus*. *Hylambatin*, DPPDPDRFYG¹⁰MMa, increases plasma glucose and plasma insulin level. *Entero-hylambatin* differs from hylambatin 1 only in position 4 (Asn⁴ instead of Asp⁴) [H.-G. Guellner et al., *IRCS Med. Sci.* **1983**, 11, 1072; L. Negri et al., *Regul. Pept.* **1988**, 22, 13].

Hymenistatin 1 (HS-1), cyclo-(γ -Pro-Pro-Tyr-Val-Pro-Leu-Ile-Ile-), a cyclic 8-peptide isolated from the *Hymeniacidon* sponge, and totally synthesized in 1993. It causes an immunosuppressive effect in the humoral and cellular immune responses comparable to the action of \rightarrow cyclosporin A (CsA). Based on studies of the comparative influence of HS-1 and CsA on cytokine production, it could be concluded that the mechanisms of interaction with the immune system are different for the two compounds [R. K. Konat et al., *Helv. Chim. Acta* **1993**, 76, 1649; M. Cebrat et al., *Peptides* **1996**, 17, 191].

Hyp, 4-hydroxyproline.

Hypertensin, \rightarrow angiotensin.

Hypocretins (Hcrts), also known as *orexins*, two neuropeptides produced in the lateral hypothalamic area and stimulating appetite and stereotypic behavior associated with feeding. The Hcrts were discovered by three groups during the late 1990s. The name hypocretin reflects their hypothalamic origin and the similarity to secretin, but additionally they have also been termed orexins because of the stimulated acute food intake when administered to rats during daytime. In principle, the two terms are interchangeable and are both used extensively in the literature. The Hcrts have been initially identified as endogenous ligands for an orphan G protein-coupled

receptor. The initial orphan G protein-coupled receptor, Hcrtr1 (also referred to as OX1R) bound Hcrt-1 with high affinity, but Hcrt-2 with 100- to 200-fold lower affinity. A related receptor Hcrtr2 (OX2R), sharing 64% identity with Hcrtr1, identified by searching database entries with Hcrt-1, showed a high affinity for the two hypocretins. Both receptors are highly conserved (95%) across species. Human (bovine, rat, mouse) *hypocretin-1 (orexin-A)*, <EPLPDCCRQK¹⁰TCSCRLYELL²⁰HGAGNHAAGI³⁰LTLa (disulfide bonds: Cys⁶–Cys¹²/Cys⁷–Cys¹⁴), and human *hypercretin-2 (orexin-B)*, RPPGPGGLQGR¹⁰LQRLQLA NGN²⁰HAAGILTMa, are derived from the 131-residue *prepro-orexin*, which shows sequence similarities with members of the secretin family. The Hcrts are distributed in the lateral hypothalamus region, which has been implicated in feeding behavior. Intracerebroventricular administration of Hcrt-1 stimulates food consumption. The Hcrts also play roles in regulating drinking behavior, neuroendocrine function, and the sleep–wake cycle. The Hcrtc1 (OX1R) receptor shows structural similarities to certain neuropeptide receptors, especially to the Y₂ neuropeptide Y receptor [T. Sakura et al., *Cell* **1998**, 92, 573; L. de Lecea et al., *Proc. Natl. Acad. Sci. USA* **1998**, 95, 322; T. Sakura, *Regul. Pept.* **1999**, 85, 25; J. H. Lee et al., *Eur. J. Biochem.* **1999**, 266, 831; W. K. Samson, Z. R. Resch, *Trends Endocrinol. Metab.* **2000**, 11, 257; S. Taheri, S. Bloom, *Clin. Endocrinol.* **2001**, 54, 421; L. de Lecea, J. G. Sutcliffe (Eds.), *Hypocretins*, Springer, **2005**].

Hypomurocins (HM), a \rightarrow peptaibol family constituted by two groups of peptides. Six 11-peptides belong to the HM A group (A1–A5, A5a), and six 18-peptides to the HM B group (B1, B2, B3a, B3b, B4, B5). The HM have been

isolated from the ascomycetous fungus *Hypocrea muuroiana*. Recently, the first total synthesis of HM A1, Ac-Aib-Gln-Val-Val-Aib-Pro-Leu-Leu-Aib-Pro¹⁰-Leu-ol, using the \rightarrow azirine/oxazolone method has been described [D. Becker et al., *Liebigs. Ann./Recueil*. **1997**, 767; H. Heimgartner, *Angew. Chem. Int. Ed.* **1991**, 30, 238; N. Pradeille et al., *Chem. Biodivers.* **2005**, 2, 1127].

IAD, isoaspartyl dipeptidase.

IB-01212, a novel cytotoxic cyclodepsipeptide isolated from the mycelium extract of the marine fungus *Clonostachys* sp. ESNA-A009. IB-01212 is a cyclic dimer formed by two chains of Me₂Leu-Ser-MeLeu-MePhe bound by the two esters formed between the carboxyl function of MePhe and the hydroxyl group of Ser. The depsipeptide is highly cytotoxic to different tumor cell lines [L. J. Cruz et al., *J. Org. Chem.* **2006**, *71*, 3335, 3339].

Iberiotoxin, EFTDVDCSVS¹⁰KECWSVC KDL²⁰FGVDRGKCMG³⁰KKCRCYQ (disulfide bonds: C⁷-C²⁸ / C¹³-C³³ / C¹⁷-C³⁵), a 37-peptide isolated from the venom of the scorpion *Buthus tamulus*. Iberiotoxin shows 68% sequence homology with charybdotoxin. Both toxins inhibit the high conductance of a Ca²⁺-activated K⁺ channel, but they may bind at different sites and modulate the channel activity via different mechanisms. The three-dimensional structure has been elucidated by 2D ¹H-NMR [A. Galvez et al., *J. Biol. Chem.* **1990**, *265*, 11083; B. A. Johnson, E. E. Sugg, *Biochemistry* **1992**, *31*, 8151; T. R. Jones et al., *J. Appl. Physiol.* **1993**, *74*, 1879].

IC, inhibitory concentration.

ICAM, intracellular adhesion molecule.

IDSP sequence, a recognition sequence (-Ile-Asp-Ser-Pro-) of the vascular cell adhesion molecule-1 (VCAM-1).

IEC, ion-exchange chromatography.

IFN, interferon.

Ig, immunoglobulin.

IgE pentapeptide (human), → Hamburger pentapeptide.

IGF, insulin-like growth factor.

IGF receptor, → insulin-like growth factors.

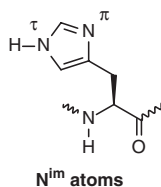
IHB, inhibin.

IL, interleukin.

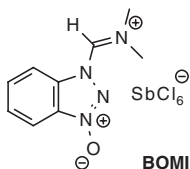
Ile, isoleucine.

im, imidazole.

Imidazole protection, temporary protection of the basic and nucleophilic imidazole group of histidine during peptide synthesis. The imidazole moiety has two non-equivalent, but similarly reactive nitrogen atoms, designated π and τ , which cause difficulties in both protection and His racemization in peptide synthesis. By application of Boc/Bzl tactics, the π -benzyloxymethyl (Bom) group is suitable as it prevents racemization and can be cleaved by HF. For Fmoc/Bu^t chemistry, the best acid-labile blocking group seems to be τ -trityl, as it is stable to bases and cleavable by aqueous TFA at room temperature [T. Brown et al., *J. Chem. Soc., Perkin Trans I* **1982**, 1553; P. Sieber, B. Riniker, *Tetrahedron Lett.* **1987**, *28*, 6031].



Immonium reagents, coupling reagents similar to \rightarrow uronium reagents. They are based on HOBT, HOAt, NHS, or pentafluorophenol as the active ester forming component, and differ from the \rightarrow uronium/guanidinium reagents in the replacement of an amino group by hydrogen, alkyl, or aryl moieties. X-ray analysis indicated that the reagent BOMI is present as the *N*-substituted form rather than as the isomeric *O*-substituted form, a situation that is known from uronium reagents [P. Li, J. Xu, *Tetrahedron* **2000**, 56, 4437].



Immunoglobulin gene superfamily (IgSF), an extensively diverse multigene protein family, the members of which share as a common structural feature the Ig fold. This superfamily includes, e.g., Ig molecules, T-cell receptors, MHC proteins, the CD2, CD4 and CD8 cell-cell adhesion proteins, some polypeptides of the CD3 complex associated with T-cell receptors, and the various Fc receptors containing one or more Ig-like domains. The Ig-like domain or Ig homology unit contains about 100 residues, and is folded into the characteristic sandwich-like structure consisting of two antiparallel β -sheets which are usually stabilized by a conserved disulfide bond [A. F. Williams, A. N. Barclay, *Annu. Rev. Immunol.* **1988**, 6, 381; T. Hunkapiller, L. Hood, *Adv. Immunol.* **1989**, 44, 1; S. M. Zhang et al., *Science* **2004**, 305, 251].

Immunoglobulins (Ig), *antibodies*, the most abundant defense proteins occurring in

blood plasma, lymph, and many body fluids of all vertebrates. An Ig molecule is composed of two identical *light* (L) chains (each contains ~ 220 aa) and two identical *heavy* (H) chains (each contains ~ 440 aa). These polypeptide chains are held together by disulfide bonds and non-covalent interactions, such that they form a Y-shaped symmetric dimer. Ig molecules are glycoproteins. Each H chain has an *N*-linked carbohydrate. Papain and pepsin split Ig molecules into different fragments. Papain forms two separate and identical *Fab* (fragment antigen binding) fragments, each bearing one antigen-binding site, and one *Fc* fragment (so termed because it readily crystallizes). Pepsin produces one *F(ab')₂* fragment consisting of two covalently linked *F(ab')* fragments, each of which is slightly larger than a *Fab* fragment. Humans have five classes of secreted Ig molecules, termed IgA, IgD, IgE, IgG, and IgM, each with its own class of H chain, designated α , δ , ϵ , γ , and μ . There are only two types of L chain, κ and λ , of which Ig can have either κ or λ , but not both. IgA [$(\alpha_2\kappa_2)_n$]; [$\alpha_2\lambda_2$]_n]; $n = 1, 2$, or 3 ; $M_r \sim 360$ – 720 kDa] occurs as monomers, dimers or trimers of its corresponding dimers. J is the *joining chain* ($M_r \sim 20$ kDa) that participates in joining IgA chains to form dimers, and J is also involved in joining two of the pentamer's heavy chains in IgM. IgD ($\delta_2\kappa_2$; $\delta_2\lambda_2$; $M_r \sim 160$ kDa), IgE ($\epsilon_2\kappa_2$; $\epsilon_2\lambda_2$; $M_r \sim 190$ kDa), and IgG ($\gamma_2\kappa_2$; $\gamma_2\lambda_2$; $M_r \sim 150$ kDa) exist only as (L–H)₂ dimers. IgG forms four subclasses (IgG1, IgG2, IgG3, and IgG4), differing in their γ chains. IgM [$(\mu_2\kappa_2)_5$ J]; [$(\mu_2\lambda_2)_5$]; $M_r \sim 950$ kDa] consists of pentamers of the corresponding dimers. IgM is the first Ig to be secreted in response to an antigen, and is most effective against invading microorganisms. IgG is the most common Ig of all; it is distributed equally between

the blood and the interstitial fluid, and its production starts 2–3 days after IgM first appears. IgG is the only Ig capable of crossing the placenta and providing the fetus with immunity. IgA is found in the intestinal tract, milk, colostrum, and in secretions such as sweat, saliva, and tears. IgE normally occurs in the blood in minute concentrations; it protects against parasites and is involved in allergic reactions. The function of IgD, which also occurs in the blood in minute concentrations, is not well established [D. A. Davies, H. Metzger, *Annu. Rev. Immunol.* **1983**, *1*, 87; F. W. Alt et al., *Science* **1987**, *238*, 1079; D. R. Davies, S. Chacko, *Acc. Chem. Res.* **1993**, *26*, 421; A. Cattaneo, S. Biocca, *Trends Biotechnol.* **1999**, *17*, 115; C. Janeway, P. Travers, M. Walport, M. Shlomchik, *Immunobiology*, 6th edn., Garland Science, **2004**].

In, indole.

Incretins, *incretin hormones*, insulinotropic hormones of the gut released by nutrients. They stimulate insulin secretion in physiological concentrations in the presence of elevated blood glucose levels. The incretin effect has been defined as the ratio between the integrated insulin response to an oral glucose load and an isoglycemic intravenous glucose infusion. In other words, when glucose is taken orally, insulin secretion is stimulated much more compared with when glucose is infused intravenously, so as to result in a similar glucose concentration. This effect is estimated as being responsible for 50–70% of the insulin response to glucose, and is mainly caused by the two intestinal insulin-stimulating hormones → glucagon-like peptide 1 (GLP-1) and → glucose-dependent insulinotropic polypeptide (GIP) that only fulfill the incretin definition of the known gut hormones. After

the ingestion of a meal, GLP-1 and GIP are released from L cells and K cells, respectively, and act via their receptors. GLP-1 stimulates insulin secretion, inhibits glucagon secretion, and delays gastric emptying. All effects are beneficial in controlling blood glucose. GIP shows a similar insulinotropic effect, but without inhibiting glucagon secretion and influencing gastric emptying in humans. The incretin effect seems to be important in the regulation of glucose metabolism in healthy subjects. In patients with type 2 diabetes mellitus, the incretin effect is markedly diminished, while the plasma levels of GIP and GLP-1 and their responses to nutrients are in the normal range. It has been postulated that a reduced responsiveness of the islet B cells to incretins might be the reason for this. The insensitivity of the diabetic B cells can be overcome by using pharmacological concentrations of GLP-1, but not by using GIP. The preserved effect of GLP-1 has initiated attempts to treat type 2 diabetes with this hormone. However, due to its short half-life, natural GLP-1 is not suitable for intravenous administration, and therefore procedures have been developed to improve the pharmacokinetics of GLP-1 by inhibiting the cleaving enzyme → dipeptidyl peptidase IV (DP IV), or by the application of synthetic DP IV-stable GLP-1 analogues [J. Dupre et al., *J. Clin. Endocrinol. Metab.* **1973**, *37*, 826; E. G. Siegel, W. Creutzfeldt, *Diabetologia* **1985**, *28*, 857; W. Creutzfeldt, *Exp. Clin. Endocrinol. Diabetes* **2001**, *109*, S288; T. Vilsboll, J. J. Holst, *Diabetologia* **2004**, *47*, 357].

Indole protection, temporary blocking of the side-chain group of tryptophan in peptide synthesis. When applying Boc/Bzl tactics, a popular choice for protecting the Trp indole group is the formyl (For) group, as this is removable by treatment with a

solution of piperidine in water, or using hydrazine or hydroxylamine. Indole Boc protection is useful for Fmoc/Bu^t chemistry [D. Yamashiro, C. H. Li, *J. Org. Chem.* **1973**, 38, 2594; H. Franzen et al., *J. Chem. Soc., Chem. Commun.* **1984**, 1699].

Indolicidin, ILPWKWPWWP¹⁰WRRa, a linear cationic, tryptophan-rich antimicrobial 13-peptide amide (→ antimicrobial peptides) first isolated from neutrophils of ox (*Bos taurus*). Its antimicrobial action involves the bacterial catoplasmic membrane. Indolicidin acts equally against Gram-negative and Gram-positive bacteria. It is also cytotoxic to T-cell lines [M. E. Selsted et al., *J. Biol. Chem.* **1992**, 267, 4292; D. Hultmark, *Trends Genet.* **1993**, 9, 178; T. J. Falla et al., *J. Biol. Chem.* **1996**, 271, 19298].

Inhibin (IHB), a glycoprotein which is secreted by the gonads and inhibits FSH production and release. Other sites of synthesis are the brain and placenta (in humans). *IHB-A* and *IHB-B* are heterodimers which are linked together by disulfide bonds. The α -chains are identical, and structural similarities exist between the α - and β -chains [N. Ling et al., *Endocr. Rev.* **1988**, 9, 267; J. K. Findlay et al., *Mol. Cell. Endocrinol.* **2001**, 180, 139].

Inhibiting factors, → statins.

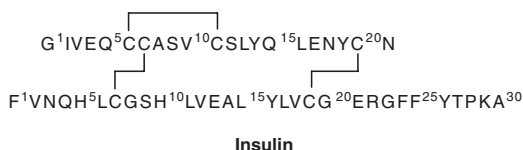
Insect diuretic peptides, two structurally distinct families of diuretic peptides (DP) that stimulate primary urine production by insect Malpighian tubules and regulate water loss from the excretory system. CRH-related diuretic peptides and insect kinins have been found in a number of species, and they may be ubiquitous in insects. *CRH-related diuretic peptides* belong to the vertebrate CRH/sauvagine/urotensin I/urocortin

superfamily. *Pea-DP*, TGSGPSLSIV¹⁰NPLDVLQRQL²⁰LLEIARRRMR³⁰QSQDQIQANR⁴⁰EILQTla, from *Periplaneta americana*, *Lom-DH*, MGMGPSLSIV¹⁰NPMDVLQRQL²⁰LLEIARRRLR³⁰AEEQIKANK⁴⁰DFLQQIa, *Acid-DP* (*Acheta domesticus*), *Mud-DP* (*Musca domestica*), *Mas-DH* (*Manduca sexta*), *Mas-DPII* (*Manduca sexta*) and *Tem-DH* (*Tenebrio molitor*) are members (not all sequences are shown) of this family. With the exception of *Tem-DH*, all peptides are amidated. These peptides increase urine production via a cAMP-dependent mechanism. *Lom-DH* has a hormonal function in the control of post-feeding diuresis in locusts. *Insect kinins*, which act via a Ca²⁺-dependent mechanism to stimulate urine production, are characterized by the C-terminal sequence -Phe-Xaa-Yaa-Trp-Gly-NH₂ (where Xaa can be His, Asn, Tyr, Phe or Ser, and Yaa is Pro, Ser or Ala) [G. M. Coast, *Am. Zool.* **1998**, 38, 442].

Insulin, a 51-polypeptide hormone consisting of the A chain (acidic chain; 21 aa) and the B chain (basic chain; 30 aa) linked by two disulfide bridges (Cys⁷_A-Cys⁷_B/Cys²⁰_A-Cys¹⁹_B). One more intrachain disulfide bond is located between Cys⁶-Cys¹¹ within the A chain. Although most species have only one type of insulin, three rodents (laboratory rat, mouse, spiny mouse) and two fish (toadfish, tuna) have two distinct insulin types. Insulin is biosynthetically derived from the single-chain, 84-residue precursor, named *proinsulin*. After three disulfide bridges have been formed within proinsulin, it is converted by proteolytic excision of the internal 33-residue C-chain, or *C-peptide*, to the two-chained active hormone. The pancreatic hormone insulin is secreted from the β cells of the islets of Langerhans in response to high blood glucose

levels. It stimulates glucose uptake by gluconeogenesis, protein synthesis, and lipogenesis mediated by the \rightarrow insulin receptor. Insulin acts together with its counterpart \rightarrow glucagon to maintain the correct concentration of blood glucose. As a rule, the biosynthesis of insulin is stimulated at glucose concentrations $>2\text{--}4\text{ mM}$, whereas glucose concentrations of $4\text{--}6\text{ mM}$ are required for the stimulation of insulin secretion. The normal concentration of circulating insulin in human blood is 1 ng mL^{-1} . Insulin increases cell permeability for glucose and other monosaccharides, as well as fatty acids and amino acids. Furthermore, it stimulates liver, muscle, and adipose cells to store these metabolites for further use in the form of glycogen, protein, and fat. In \rightarrow diabetes mellitus, insulin is either not secreted in sufficient concentration or does not efficiently stimulate its target cells. An abnormally high concentration of ketone bodies (ketosis) is one of the most dangerous effects. Two major forms of diabetes mellitus are known: \rightarrow insulin-dependent (type I) diabetes mellitus (IDDM), and \rightarrow non-insulin-dependent (type II) diabetes mellitus (NIDDM). Insulin secretion as a response to elevated blood glucose levels is triggered by an increase in the concentration of free cytosolic Ca^{2+} . Inositol triphosphate as the messenger releases Ca^{2+} from internal stores. An increased blood glucose level (hyperglycemia) is the physiological signal for the synthesis and secretion of this hormone. The liver is the major site of insulin degradation,

but most peripheral tissues also contain insulin-degrading enzymes. Insulin was discovered in 1921 by Banting (Nobel Prize 1923) and Best, and was purified and crystallized by Abel five years later. The elucidation of the primary structure was described by Sanger in 1955, who was awarded the Nobel Prize in 1958 for his pioneering work. \rightarrow Dorothy Crowfoot-Hodgkin determined the spatial conformation of insulin in 1969. Two alternative procedures are described for the production of recombinant insulin. Eli Lilly produced human insulin by separate overexpression of the A and B chains in the form of fusion proteins in *E. coli*. Following their isolation, both chains were connected by reductive thiolysis and subsequent oxidation (in air) to produce the active hormone. In a second variant, proinsulin was synthesized analogously to biosynthesis as a fusion protein in *E. coli* and transformed enzymatically into active insulin. Currently, insulin analogues designed to improve the therapeutic properties of insulin have been produced by recombinant DNA technology. The first clinically available insulin analogue, lispro (\rightarrow Liprolog[®]/Humalog[®]), was marketed in the U.S. in 1996. This dissociates more rapidly than regular human insulin after subcutaneous injection, resulting in higher insulin levels at an earlier point in time, and a shorter duration of action. A long-acting human insulin analogue is \rightarrow insulin glargine. The name insulin is derived from Latin *insula*, "island", as it is formed in the islets of Langerhans in the pancreas



[F. Sanger et al., *Biochem. J.* **1955**, 59, 509; J. Meienhofer et al., *Z. Naturforsch.* **1963**, 18b, 1120; P. Sieber et al., *Helv. Chim. Acta* **1974**, 57, 2617; G. I. Bell et al., *Nature* **1980**, 284, 26; M. P. Czech (Ed.), *Molecular Basis of Insulin Action*, Plenum Press, New York, **1985**; J. M. Conlon, *Peptides* **2001**, 22, 1183; I. B. Hirsch, *N. Engl. J. Med.* **2005**, 352, 174].

Insulin-dependent diabetes mellitus (IDDM), *type 1 diabetes, juvenile diabetes*, characterized by an absolute insulin insufficiency caused by immunological destruction of pancreatic β cells that synthesize and secrete \rightarrow insulin. The proportion of type I insulin-dependent \rightarrow diabetes mellitus among the 16 million diabetics in the United States has been estimated at $<10\%$ [R. Tisch, H. McDevitt, *Cell* **1996**, 85, 291].

Insulin family, a member of the gastroenteropancreatic peptide superfamilies. This family comprises \rightarrow insulin, \rightarrow the insulin-like growth factors, and \rightarrow relaxin.

Insulin glargine, HOE901, Lantus[®], a long-lasting insulin analogue produced using a non-pathogenic genetically engineered strain of *E. coli*. Suitable for the treatment of type 1 and type 2 \rightarrow diabetes mellitus [L. Heinemann et al., *Diabetes Care* **2000**, 23, 644; G. Bolli, D. Owens, *Lancet* **2000**, 356, 443; I. B. Hirsch, *N. Engl. J. Med.* **2005**, 352, 174].

Insulin-like growth factors (IGF), *somatomedins*, a group of polypeptides with structural and functional resemblance to \rightarrow insulin and \rightarrow relaxin belonging to the \rightarrow insulin family. The IGF occurring in the blood of vertebrates play an important role in the regulation of growth and differentiation of an ever-increasing number of tissues. They bind to high-affinity receptors (protein tyrosine kinases) which are

present on many cells and in many tissues. In the circulation, the IGF are bound to transport or binding proteins (IGF-BP). IGF-1, GPETLCGAEL¹⁰VDALQFVCGD²⁰RGFYFNKPTG³⁰ YGSSRRAPQ⁴⁰ TGIVDECCFR⁵⁰SCDLRRLEMY⁶⁰CAPLKPAKSA⁷⁰ (disulfide bonds: C⁶–C¹⁸/C¹⁸–C⁶¹/C⁴⁷–C⁵²), is a single-chain 70-polypeptide ($M_r \sim 7.6$ kDa) containing three intrachain disulfide bridges. IGF-1 mediates, in interaction with other hormones, the effects of \rightarrow growth hormone on bone growth. Similar to IGF-2, IGF-1 possesses growth-promoting activity on chick embryo fibroblasts at a concentration of 10^{-9} M. IGF-2, AYRPSETLCG¹⁰GELVDT LQFV²⁰CGDRGFYFSR³⁰ PASRVSRRSR⁴⁰GIVEECCFRS⁵⁰CDLALLE TYC⁶⁰ATPAKSE (disulfide bonds: C⁹–C⁴⁷/C²¹–C⁶⁰/C⁴⁶–C⁵⁰) is a single-chain 67-polypeptide ($M_r \sim 7.5$ kDa) containing three intrachain disulfide bridges. It participates in the fetal and embryonal development of the nervous system and the bones. Interest in IGF and their effects on carcinogenesis have increased because high serum concentrations of IGF-1 are associated with an increased risk of breast, prostate, colorectal, and lung cancers [E. M. Spencer (Ed.), *Insulin-like Growth Factors, Somatomedins*, de Gruyter, Berlin, **1983**; P. de Meyts, J. Whittaker, *Nat. Rev. Drug Discovery* **2002**, 1, 769; G. Furstenberger, H. J. Senn, *Lancet Oncol.* **2002**, 3, 298].

Insulin-like peptides (INSLP), members of the \rightarrow relaxin peptide family. The four insulin-like peptides 3 to insulin-like peptide 6, encoded in human by the genes *INSL3–INSL6*, are structurally related to \rightarrow insulin. They each contain individual A and B chains that are connected by two disulfide bonds and formed from a prohormone after proteolytic cleavage of

the intervening C chain. INSLP-3, also known as *relaxin-like factor* (RLF) and *Leydig cell insulin-like peptide*, is an A (26 aa)–B (31 aa) heteromer covalently linked by two interchain disulfide bonds (Cys_A¹¹–Cys_B¹⁰/Cys_A²⁴–Cys_B²²). It is predominantly expressed in the Leydig cells of the testes and ovarian thecal cells, and acts as an important mediator of testicular descent. INSLP-3 acts on the G protein-coupled receptor LGR8, which is closely related to the leucine-rich repeat-containing relaxin receptor LGR7 (→ relaxin). The solution structure and characterization of the LGR8 receptor binding surface of INSLP-3 has been described recently. Until now, the functions of the insulin-like peptide 4 (INSLP-4, placentin, early placenta insulin-like peptide, EPIL), insulin-like peptide 5 (INSLP-5, relaxin/insulin like factor-2, RIF2), and insulin-like peptide 6 (INSLP-6, relaxin/insulin like factor-1, RIF1) have not been elucidated; neither have their appropriate receptors been identified [R. Ivell, R. A. D. Bathgate, *Biol. Reprod.* **2002**, 67, 699; D. J. Scott et al., *Lett. Peptide Sci.* **2004**, 10, 393; T. N. Wilkinson et al., *BMC Evol. Biol.* **2005**, 5, 14; K. J. Rosengren et al., *J. Biol. Chem.* **2006**, 281, 28287].

Insulin receptor, a transmembrane glycoprotein ($M_r \sim 300$ kDa) with tyrosine-specific protein kinase activity converting the extracellular → insulin signal into the cell. The receptor is a tetramer ($\alpha_2\beta_2$), and consists of two identical subunits (a: 719 aa; b: 620 aa) joined together by disulfide bonds. The catalytic domain of the tyrosine-specific protein kinase is exposed on the cytoplasmic side of the plasma membrane. When activated by insulin binding, it phosphorylates itself, thereby enhancing the activity of the kinase, and transfers the terminal phosphate group from ATP to the hydroxy group on a tyrosine residue of

selected proteins in the target cell. Both polypeptide chains of the insulin receptor are encoded by a single gene, producing a precursor protein that is cleaved into the two disulfide-joined chains. The crystal structure of the activated insulin receptor tyrosine kinase in complex with a peptide substrate, and that of an ATP analogue was determined at 1.9 Å resolution in 1997 [A. Ullrich et al., *Nature* **1985**, 313, 756; S. R. Hubbard, *EMBO J.* **1997**, 16, 5572].

Insulin-releasing peptide (RK-13), RRKPLF-PFIP¹⁰RPK, an insulinotropic 13-peptide isolated from the skin secretion of *Agalychnis calcarifer* frogs. It shows sequence identity in seven of the 13 amino acid residues to the N-terminal sequence of → PR-39. Synthetic RK-13 stimulated insulin release in a dose-dependent, glucose-sensitive manner, exerting its effects via a cAMP-protein kinase A pathway, independent of pertussis toxin-sensitive G proteins [Y. H. A. Abdel-Wahab et al., *Biol. Chem.* **2005**, 386, 581].

Integrins, type I heterodimeric proteins composed of non-covalently associated α and β subunits mediating cell–cell and cell–extracellular matrix (ECM) interactions. This superfamily of cell-surface glycoproteins promotes cellular adhesion and belongs to the cell → adhesion molecules. Generally, cells interact with the ECM and other cells through cell adhesion receptors, including those of the integrin family. Typical members of ECM ligands are → collagen, → laminin, → fibronectin, → fibrinogen, VCAM-1, vitronectin, ICAMs, lipopolysaccharides, and von Willebrand factor. The interaction of many integrins with the ECM is mediated via an Arg-Gly-Asp (RGD) sequence present in adhesive proteins. In 1984, Pierschbacher and Ruoslahti demonstrated that cell adhesion mediated by fibronectin could be inhibited

by the tripeptide Arg-Gly-Asp (RGD). The latter sequence, identified as the minimal binding site in fibronectin, is capable of mediating cell adhesion. In protein and DNA databases, several hundred RGD or homologous sequences could be identified. Most ECM proteins characterized to date contain RGD sequences. In 1987, the term "integrin" was first suggested by Hynes to characterize a family of integral membrane receptors thought to link or "integrate" the intracellular cytoskeleton with ECM proteins. In mammals, 18 α chains and eight β chains can form over 24 distinct heterodimers. The α and β subunits are transmembrane, N-glycoproteins characterized by large extracellular domains, a single hydrophobic transmembrane region, and a short cytoplasmic domain. The specificity of ligand binding is determined by the particular $\alpha\beta$ combinations. The RGD sequence can be recognized by $\alpha_5\beta_1$, $\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_{IIb}\beta_3$, $\alpha_2\beta_1$, $\alpha_3\beta_1$ and $\alpha_4\beta_1$. Interestingly, some integrins are capable of binding a number of ligands. For example, $\alpha_V\beta_3$ recognizes fibrinogen, fibronectin, vitronectin, osteopontin, thrombospondin, von Willebrand factor, collagen, tenascin, and others. Strategies have been developed for the therapeutic modification of integrin function. Although integrins are vitally important for their biological function, they are also involved in several diseases. For example, integrins of the family $\alpha_V\beta_3$, expressed by endothelial cells, play a function in angiogenesis, thrombosis, osteoporosis, diabetic retinopathy, and restenosis, whereas $\alpha_{IIb}\beta_3$ integrins, expressed on platelets, are involved in thrombosis and restenosis. Integrins of the type $\alpha_4\beta_1$, present on leukocytes and neutrophils, are involved in asthma, reperfusion damages, arthritis, etc. Small-molecule ligands of the integrins $\alpha_V\beta_3$ have attracted much interest because

of their therapeutic potential. The highly selective cyclic peptide cyclo-(-Arg-Gly-Asp-D-Phe- N^{Me} Val-) (*cilengitide*), a ligand of integrin $\alpha_V\beta_3$, reached clinical Phase II trials for the treatment of glioblastoma (brain tumors). Furthermore, a large number of second-generation peptidomimetics and also non-peptidomimetics have been developed. Integrin-specific peptidomimetic antagonists, e.g.: *Integrilin*[®], which is marketed as a therapeutic for coronary thrombosis; *tirofiban*, which is used as an adjunct to angioplasty; *BIO-1211*, which is in pre-clinical studies for asthma and inflammatory bowel disease; and last – but not least – *WO9736858 A1*, which is potentially useful for the treatment of tumor metastasis, solid tumor growth, osteoporosis, angiogenesis, humoral hypercalcemia of malignancy, restenosis, and smooth muscle cell migration [M. D. Pierschbacher, E. Ruoslahti, *Nature* 1984, 309, 30; R. O. Hynes, *Cell* 1992, 69, 11; E. Ruoslahti, *Annu. Rev. Cell. Dev. Biol.* 1996, 12, 697; K.-E. Gottschalk, H. Kessler, *Angew. Chem. Int. Ed.* 2002, 41, 3767; C. Henry et al., *Mini Rev. Med. Chem.* 2002, 2, 531; J. P. Xiong et al., *Science* 2002, 296, 151; T. D. Penning et al., *Bioorg. Med. Chem. Lett.* 2004, 14, 1471].

Intein-mediated protein ligation, → biochemical protein ligation.

Interferons (IFN), cytokines that display antiproliferative, antitumor, antiviral, and immunomodulatory properties. They regulate somatic cell growth, division, and apoptosis. The biological effects of IFNs are primarily mediated via activation of the JAK/STAT pathway. IFN are glycoproteins secreted by virus-infected vertebrate cells preventing viral proliferation, largely by inhibition of protein synthesis in other infected cells. Three families of IFN have been characterized: (a) *IFN- α* or *leukocyte*

IFN, named according to the preferential formation by white blood cells, consist of a family of closely related proteins with sequence homology between 80 and 95%. In humans, all *IFN-α* genes are located on chromosome 9. Human *IFN-α* consists of 166–172 residues ($M_r \sim 16\text{--}27$ kDa). This family is divided into two subfamilies (*IFN-αI* and *IFN-αII* or *IFN-ω*). (b) *IFN-β* or *fibroblast IFN* are preferentially produced by fibroblasts (connective tissue cells), but there are many other cell sources. Human *IFN-β* (166 aa; $M_r \sim 20$ kDa) is encoded by a single gene on chromosome 9. (c) *IFN-γ* or *lymphocyte IFN* or *immune IFN* is a glycoprotein (143 aa; $M_r \sim 22$ kDa) occurring *in vivo* as a dimer. The gene is located on chromosome 12 and has three introns. *IFN-γ* is produced by T lymphocytes, and enhances the cytotoxic activity of T lymphocytes, macrophages, and natural killer cells. The action of *IFN* *via* inhibition of protein synthesis in infected cells is mediated by two independent pathways: (i) by inducing the production of a protein kinase (double-stranded RNA-activated inhibitor, DAI) which leads finally to the inhibition of ribosomal initiation; or (ii) by inducing the synthesis of (2',5')-oligoadenylate synthetase producing 2,5-A which activates the mRNA-degrading RNase L. Generally, *IFN* belong to the most potent biological compounds, and represent a major defense against viral infection. They are antiviral agents that are active in concentrations as low as 3×10^{-14} M. Currently, *IFN* are being used clinically in the treatment of hepatitis B and hepatitis C. As some cancers are virally induced, *IFN* have also attracted interest as potential anticancer drugs for the primary treatment of melanoma, leukemia, non-Hodgkin's lymphoma, and additionally of autoimmune diseases such as multiple sclerosis. The clinical use of *IFN* against viral infections and certain malignant tu-

mors has become possible by the development of large-scale molecular cloning techniques. The *IFN* were discovered by Isaacs and Lindenmann in 1957 [S. Pestka et al., *Immunol Rev.* **2004**, 202, 8; S. G. Maher, *Curr. Med. Chem.* **2007**, 14, 1279].

Interleukins (IL), regulatory proteins with main functions in the immune system. Interleukins belong to the \rightarrow cytokines. IL secreted by lymphocytes are also termed *lymphokines* (*T-cell cytokines*). According to recommendations of the *WHO-IUIS Nomenclature Subcommittee*, it is only appropriate to designate a cytokine as an IL when: (a) it has been purified and sequenced, and the gene is cloned; (b) it is a natural cell product; and (c) it plays a main function in the immune system. *Interleukin-1 (IL-1)*, *leukocyte activating factor (LAF)*, is a small protein ($M_r \sim 17$ kDa) that occurs in two forms (*IL-1α* and *IL-1β*) which differ significantly in their amino acid sequence (sequence homology: 22–26%). *IL-1* acts *via* *IL-1* receptors on a wide spectrum of target cells that are involved in immune and inflammation reactions. *Interleukin-2 (IL-2)*, *T-cell growth factor* (133 aa; $M_r \sim 15.5$ kDa), is involved in T-cell activation, improving *IFN-γ* production, modulation of T-cell receptor expression, where it contributes to the response to microbial infection as well as to non-self/self discrimination. Recombinant *IL-2* (Proleukin®) has been approved for the treatment of malignant melanoma and renal cell cancer. *Interleukin-3 (IL-3)* belongs as *multi-CSF* to the \rightarrow colony-stimulating factors; it assists the growth of, e.g., bone marrow stem cells. *Interleukin-4 (IL-4)*, *B-cell stimulating factor-1 (BSF-1)*, is a highly glycosylated protein (130 aa; $M_r \sim 25$ kDa); it increases class II MHC molecules expression, and stimulates *IgG*₁- and *IgE* production by B cells. *Interleukin-5*

(IL-5), is a homodimer (monomer: 115 aa; $M_r \sim 25$ kDa); it promotes the proliferation and growth of B cells and eosinophils. *Interleukin-6* (IL-6), *B-cell-stimulating factor-2* (BSF-2), *hybridoma/plasmacytoma growth factor* (HPGF), *hepatocyte-stimulating factor* (HSF), *monocyte granulocyte inducer type 2* (MGI-2), *interferon- β_2* (IFN- β_2), is a glycoprotein ($M_r \sim 23$ –30 kDa) which is one of the most important mediators of fever and of the acute phase response, and also plays an important role in immune defense. The designation IFN- β_2 is erroneous because of a lack of antiviral activity. The IL-10 family of cytokines includes IL-10, IL-20, IL-22, IL-24, IL-26, and several virus-encoded cytokines. Further representatives of interleukins include IL-7, IL-9, IL-10 (human cytokine synthesis inhibitory factor, CSIF), IL-11, IL-12 (plays an important role in the activities of natural killer (NK) cells and T lymphocytes), IL-13, IL-15, IL-16 (recruits and activates cells expressing CD4), IL-17 (induces and mediates pro-inflammatory responses, including the production of many other cytokines; commonly associated with allergic responses), and IL-18. IL-8 was renamed to CXCL8 (Chemokine C-X-C motif ligand 8). Today, the interleukins comprise 33 members (IL-1 to IL-33). The most recent additions to this ever-growing family of cytokinins include IL-27, IL-28A, IL-28B, IL-29, IL-31, IL-32, and IL-33. Many of the newly described interleukins (IL-27 to IL-33) have been identified by bioinformatics, which has shed new light on the intricacies of immune system regulation. They demonstrate pleiotropic actions in the range from antiviral immunity to the regulation of Th2 immune responses. *Interleukin-27* (IL-27) (IL-27p28/EBV-induced gene 3), a heterodimeric cytokine, can directly regulate T-cell functions and may play an important role in promoting Th1-type responses. It is produced early after

activation by antigen-presenting cells, and is capable of inducing the proliferation of naïve, but not memory, CD4⁺ T cells. It synergizes with IL-12 in IFN- γ production (\rightarrow interferons) of naïve CD4⁺ T cells. Potent antitumor activity of IL-27 has been described. *Interleukin-28* (IL-28A and IL-28B) and *Interleukin-29* (IL-29) are a family of class II cytokines stimulating antiviral responses via a heterodimeric receptor that is distinct from the type I interferon receptor. *Interleukin-31* (IL-31), which is primarily expressed in activated lymphocytes, mediates its actions through a heterodimeric receptor complex consisting of the IL-31 receptor alpha (IL-31R α) and the oncostatin M receptor. IL-31 mediates MAP kinase and STAT1/3 activation in intestinal epithelial cells, and its expression is up-regulated in inflammatory bowel disease. *Interleukin-32* (IL-32) and *Interleukin-33* (IL-33), both of which are yet to be fully characterized, are important components of the inflammatory response in allergy and autoimmunity. IL-32 was originally identified as a transcript the expression of which was increased in activated natural killer cells. It induces the production of tumor necrosis factor, macrophage inflammatory protein-2, and IL-8 in monocytic cell lines, indicating that it would be involved in the inflammatory responses. IL-33 is expressed in immunocompetent cells and is up-regulated when these cells are exposed to pro-inflammatory stimuli; therefore, it seems to be important in the pathogenesis of chronic inflammatory disorders, e.g., periodontal disease [WHO-IUIS Nomenclature Subcommittee on Interleukin Designation, Nomenclature for Secreted Regulatory Proteins of the Immune System (Interleukins), *Immunology Today* **1992**, 13, 118; H. Blumberg et al., *Cell* **2001**, 104, 9; J. Parrish-Novak et al., *J. Biol. Chem.* **2002**, 277, 47517; M. Gadina et al., *Curr. Opin.*

Infect. Dis. **2003**, 16, 211; Q. Chen et al., *Vitamins & Hormones* **2006**, 74, 207; G. Litwack (Ed.), *Interleukins, Vitamins and Hormones Advances in Research and Applications*, Vol. 74, Elsevier, **2006**].

Intermediary protecting groups, *temporary protecting groups, transient protecting groups*, protecting groups used for temporary blocking of the α -amino or α -carboxy function involved in subsequent bond formations. These protecting groups must be cleaved selectively under conditions that do not interfere with the stability of the peptide bonds already present, or that of \rightarrow semipermanent protecting groups at amino acid side chains.

Intermediate filaments, \rightarrow keratins.

Intermedin/adrenomedullin-2 (IMD), hIMD: TQAQLLRVGC¹⁰VLGTCQVQNL²⁰SHRLWQLMGP³⁰AGRQDSAPVD⁴⁰PSSP HSYa, (disulfide bond: C¹⁰–C¹⁵) a novel member of the \rightarrow calcitonin/calcitonin gene-related peptide family. IMD was initially isolated from the puffer fish, *Fugu rubripes*. The sequence is conserved across species including human, rat and mouse. Within the members of the calcitonin/calcitonin gene-related peptide family, IMD shows a greater structural homology to \rightarrow adrenomedullin. The human gene is localized on chromosome 22q13.33. Unlike mammals that contain only one gene, the puffer fish genome encodes two IMD peptides sharing >80% sequence identity in the mature region. IMD is expressed in the gastrointestinal tract, pituitary, kidney, lung, thymus, submaxillary glands, and brain. It has been reported that IMD functions as a pituitary paracrine factor regulating \rightarrow prolactin release. From *in-vivo* studies it has been concluded that IMD treatment led to blood pressure reduction in both normal and

spontaneously hypertensive rats, mediated via CRLR/RAMP receptor complexes (\rightarrow receptor activity-modifying proteins). An inhibitory effect on food intake and gastric emptying caused by IMD has also been described [J. Roh et al., *J. Biol. Chem.* **2004**, 279, 7264; Y. Takai et al., *FEBS Lett.* **2004**, 556, 53; C. L. Chang et al., *Peptides* **2004**, 25, 1633; *Mol. Endocrinol.* **2005**, 19, 2824; M. M. Taylor, W. K. Samson, *Brain Res.* **2005**, 1045, 199; H. B. Kandilci et al., *Peptides* **2006**, 27, 1390].

Intracrine hypothesis, an approach to provide a conceptual framework through which intracellular peptide hormone/factor action can be understood and which can serve as the basis for the formulation of testable and, in some cases, therapeutically relevant predictions [R. N. Re, J. L. Cook, *Regul. Pept.* **2006**, 133, 1].

Ion-exchange chromatography (IEC), a separation principle based on interaction of the protein's net charge with the charged groups on the surface of the packing materials. Polystyrene and cellulose, as well as acrylamide and dextran polymers, serve as the preferred support materials for the ion exchanger. They are functionalized by quaternary amines, diethylaminoethyl (DEAE) or polyethylenimine for anion exchange, and sulfonate or carboxylate groups for cation exchange. IEC is one of the most commonly practiced methods for protein purification [E. Kalsson et al., in: *Protein Purification*, J.-C. Janson, L. Rydén (Eds.), Wiley, New York, **1998**; P. R. Levison et al., *J. Chromatogr. A* **1997**, 760, 151].

Ionic liquid-mediated peptide synthesis (ILMPS), peptide synthesis using ionic liquids as non-conventional media or soluble support. The application of ionic liquids as non-aqueous reaction media in

biocatalysis has been described, including an enzyme-catalyzed synthesis of \rightarrow aspartame in 2000. Some years later, chemical peptide synthesis in room temperature ionic liquids using coupling agents such as \rightarrow HATU and \rightarrow BOP has been demonstrated. The new approach presents some advantages, especially in the coupling of sterically hindered amino acid derivatives. Furthermore, *ionic liquid-supported synthesis* has been developed. As in \rightarrow liquid-phase peptide synthesis, the first amino acid is anchored to a suitable ionic liquid, e.g., 3-hydroxyethyl-(1-methylimidazolium)-tetrafluoroborate using common coupling agents. After solvent washing, the next Boc-amino acids has been coupled step-by-step followed by detachment from the ionic liquid and phase-separation [P. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, Germany, 2003; M. Erbdinger et al., *Biotechnol. Progr.* 2000, 16, 1129; H. Vallete et al., *Tetrahedron Lett.* 2004, 45, 1617; W. Miao, T.-H. Chan, *J. Org. Chem.* 2005, 70, 3251].

IP, isoelectric point.

IPL, intein-mediated protein ligation.

iPr, isopropyl.

IR, infrared.

Iron-sulfur proteins, *Fe-S-proteins*, a family of proteins occurring in all organisms. They contain iron-sulfur centers (iron sulfur clusters), and can be subdivided into *simple Fe-S-proteins*, such as \rightarrow ferredoxin, \rightarrow rubredoxin, and *conjugated Fe-S-proteins*, e.g., Fe-S-molybdenum proteins. They are included in non-heme iron proteins as the iron is not bound in a porphyrin ring system. Fe-S clusters are cofactors of numerous proteins with important

functions in metabolism, electron transport, and regulation of gene expression. Fe-S proteins have occurred early in evolution and are present in cells of virtually all species. Their biosynthesis is a very complex process involving numerous components. For example, in mitochondria the iron-sulfur cluster (ISC) machinery is responsible for the biosynthesis of Fe-S proteins both within and outside the organelle. Fe-S proteins are involved, for example, in nitrogen and carbon dioxide fixation, oxidative and photosynthetic phosphorylation. Complex iron-sulfur metallocluster are found, e.g., in the active sites of enzymes that catalyze redox transformations of N_2 , CO, and H_2 . Interestingly, frataxin, an iron chaperone, protects the aconitase $[4Fe-4S]^{2+}$ cluster from disassembly and promotes the reactivation of the enzyme [R. Cammack, *Iron-sulfur proteins*, Academic Press, San Diego, 1992; U. Muhlenhoff, R. Lill, *Biochim. Biophys. Acta* 2000, 1459, 370; D. C. Rees, J. B. Howard, *Science* 2003, 300, 929; A.-L. Bulteau et al., *Science* 2004, 305, 242].

Islet amyloid polypeptide, \rightarrow amylin.

IS-MS, ion spray mass spectrometry.

Isoaspartyl dipeptidase (IAD), an enzyme catalyzing the hydrolytic cleavage of β -aspartyl peptides (\rightarrow isoaspartyl peptide bond). IAD is a member of the amidohydrolase superfamily. It has been assumed that the physiological function of IAD in *E. coli* is to prevent the accumulation of β -aspartyl dipeptides after proteolysis of these proteins. The catalysis mechanism has been elucidated [E. E. Haley, *J. Biol. Chem.* 1968, 243, 5748; J. D. Gary et al., *J. Biol. Chem.* 1995, 270, 4076; R. Marti-Arbona et al., *Biochemistry* 2005, 44, 7115].

Isoaspartyl peptide bond, a peptide bond formed via an intramolecular rearrangement of the peptide backbone of peptides and proteins at amide bonds of asparagine (\rightarrow aspartimide, \rightarrow β -aspartylpeptides). Sensitive peptide bonds such as Asp-Gly sequences are often prone to succinimide formation and concomitant isoaspartyl peptide ($\alpha \rightarrow \beta$ shift) formation, especially when treated with strong acids such as HF or TFMSA during peptide synthesis operations.

Isoleucine (Ile, I), L- α -amino- β -methylvaleric acid, $\text{H}_3\text{C}-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}(\text{NH}_2)-\text{COOH}$, $\text{C}_6\text{H}_{13}\text{NO}_2$, M_r , 131.18 Da, a proteinogenic amino acid.

Isopeptide bond, inter-residue amide bonds between side chain functionalities such as covalent crosslinking amide bonds between the ω -amino group of diamino carboxylic acids such as lysine or ornithine and the ω -carboxyl function of amino dicarboxylic acids such as glutamate or aspartate. Isopeptide bonds occur, for example, in polymerized \rightarrow fibrin and in native wool.

Isoxazolium method, peptide bond formation using *N*-ethyl-5-phenylisoxazolium-3'-sulfonate (Woodward reagent K) forming an enol ester with *N*-protected amino acids and peptides which reacts *in situ* with the amino component providing the desired product beside a water-soluble aryl sulfonate as a byproduct that is easy to separate [R. B. Woodward, R. A. Olofson. *J. Am. Chem. Soc.* **1961**, 83, 1010].

Iturins, a family of antifungal peptides produced by various strains of *Bacillus subtilis*. The iturins comprise small cyclic peptidolipids characterized by a lipid-soluble β -amino acid linked to a peptide containing D- and L-amino acids [F. Peypoux et al., *Tetrahedron* **1973**, 29, 3455; M. Klich et al., *Mycopathology* **1991**, 116, 77].

Iva, isovaline (α -ethylalanine).

Inverse peptide synthesis, a stepwise chain elongation starting at the *N*-terminal residue and carried out in the $C \rightarrow N$ direction, which is in agreement with Nature's way of synthesizing proteins (\rightarrow ribosomal peptide synthesis). This strategy has the advantage that only the *N*-terminal amino acid residue requires a N^α -protecting group, and this is removed on the completion of chain assembly. Furthermore, the reverse strategy allows the direct generation of C-terminal-modified peptides, which is advantageous for the synthesis of peptides with therapeutic importance, and also in fragment condensations for the assembly of large peptides and proteins (\rightarrow chemical protein synthesis). However, the activated carboxylic acid is a serious drawback due to the permanent danger of 5(4*H*)-oxazolone formation leading to epimerization of the α residue, and diketopiperazine formation with the risk of capping the growing chain. An inverse solid-phase variant was described as early as 1963. Stepwise synthesis in the $C \rightarrow N$ direction has been reported both in solution and on solid support, including mild enzymatic coupling procedures that circumvent the disadvantages mentioned above [R. L. Letsinger, M. J. Kornet, *J. Am. Chem. Soc.* **1963**, 85, 3045; F. Bordusa et al., *Angew. Chem. Int. Ed.* **1997**, 36, 1099; N. Thieriet et al., *Org. Lett.* **2000**, 2, 1815].

Ixodidin, an antimicrobial 65-peptide from the hemocytes of the cattle tick *Boophilus microplus*, with inhibitory activity against serine proteases. The name is derived from the family Ixodidae. The 65-mer ixodidin contains five intrachain disulfide bonds and an *N*-terminal pyroglutamic acid residue. In addition to growth inhibition of *E. coli* and *Micrococcus luteus*, it exerts inhibitory activity against elastase

and chymotrypsin [A. C. Fogaca et al., *Peptides* **2006**, 27, 667].

Ixosin, GLHKVMREVL¹⁰GYERNSYKKF²⁰FLR, a 23-peptide from salivary glands of

the hard tick *Ixodes sinensis* with antimicrobial activity against bacteria and fungi. Ixosin is the first antimicrobial peptide from ticks to lack cysteine in its sequence [D. Yu et al., *Peptides* **2006**, 27, 31].

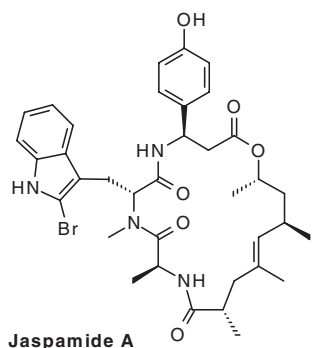
Jak proteins (JAKs), proteins of the Janus kinase (JAK) family comprising as members Tyk2, JAK1, JAK2, and JAK3. They are ~130 kDa non-receptor tyrosine kinases which are distinguished by the presence of two C-terminal kinase-related domains and the absence of a src homology 2 (SH2) domain. A signal transduction pathway which involves JAKs, and signal transducer and activator of transcription (STAT) proteins have been found to be regulated by various hematopoietic cytokine receptors, as described in the mid-1990s. The tyrosine kinases have been characterized in the signaling pathways activated by type I and II \rightarrow interferons. $\text{INF}\gamma$ activates JAK1 and JAK2, whereas $\text{INF}\alpha/\beta$ activates Jak1 and Tyk2. The STAT proteins are one key group of downstream effectors of the Jak proteins. The STATs form SH2 domain-mediated homo- and heterodimeric complexes upon tyrosine phosphorylation, which then migrate to the nucleus to effect gene expression. From biochemical studies to knockout mice it follows that JAKs play non-redundant roles in development, differentiation, and host defense mechanisms [J. J. Krolewski et al., *Oncogene* **1990**, 5, 277; S. Pellegrini, C. Schindler, *Trends Biochem. Sci.* **1993**, 18, 338; T. C. Yeh, S. Pellegrini, *Cell. Mol. Life Sci.* **1999**, 55, 1523].

Japanese Peptide Society (JPS), an association of scientists in peptide research of Japan founded in 1990. About 400 members of the JPS are actively pursuing research in various related areas, including physical science, pharmaceutical science,

agriculture, engineering, and medical sciences in universities, institutes, and private companies. This work is contributing to the development of the life science, bioscience and clinical medical science communities in Japan. The important roles played by the Japanese Peptide Society are to conduct domestic or international symposia concerning peptide science, to support young peptide scientists, to encourage collaboration between various research areas, and to accelerate the international exchange of peptide scientists. In 1962, a forum on peptide chemistry was held in Osaka, organized by Professor Shiro \rightarrow Akabori (Osaka University) as an exchange among chemists with mutual interests in peptide synthesis. The Proceedings, "Peptide Chemistry 1962", were published that detailed the events of the symposium. Since that auspicious beginning, the Peptide Chemistry Symposium has been held annually. Due to the growing awareness in peptide chemistry during this time, international peptide conferences were held in Japan: the 1st Japan Symposium on Peptide Chemistry (JASPEC) was held in 1987 (Kobe), and the 2nd in 1992 (Shizuoka), respectively, followed by the 1st International Peptide Symposium in Kyoto in 1997. At the 35th symposium in 1998, the name was formally changed to *Japanese Peptide Symposium* and the Proceedings "Peptide Science 1998" were published. In 2004, the 41st Japanese Peptide Symposium was held in Fukuoka as a joint international symposium with *The First Asia-Pacific International Peptide Symposium (APIPS)*. In 2000, the *Akabori*

Memorial Award was established by the Japanese Peptide Society as a commemoration of Professor Shiro Akabori.

Jaspamides, *Jaspakinolides*, three cyclodepsipeptide (\rightarrow depsipeptides) from marine sponges of the *Jaspis* genus collected off Fiji and Papua New Guinea. Jaspamides A–C contain (*R*)- β -tyrosine and D- δ -bromotryptophan—two rare amino acids—in conjugation with a polyketide moiety that varies slightly among members. The ring size varies between 16 and 18 members. Jaspamide A exhibits many interesting biological properties, including catatonic, insecticidal, anthelmintic and ichthyotoxic activities. It possesses a potent antitumor activity against 36 human solid tumor cell cultures as a consequence of its ability to interfere with actin cytoskeleton. The mechanism of action is known to be via the stabilization of cell actin filaments [U. Schmidt et al., *Tetrahedron Lett.* **1988**, 28, 1269; P. Wipf, *J. Biol. Chem.* **2000**, 275, 5163].



JHBP, juvenile hormone binding protein.

Joining chain (J chain), a small polypeptide covalently attached to polymeric, but not monomeric \rightarrow immunoglobulin (Ig) molecules, and playing an important role in the polymerization and transport of polymeric Ig across epithelial cells. For example, the J chain is involved in the assembly and stabilization of the dimeric IgA and pentameric IgM, respectively. In humans and mice, the J-chain has the function of binding Ig to the polymeric Ig receptor for transport into secretions. J-chains are characterized by a highly conserved block of residues surrounding an N-linked glycosylation site which includes eight half-cystine residues [F. E. Johansen et al., *Scand. J. Immunol.* **2000**, 52, 240].

Juvenile hormone binding protein (JHBP), a single-chain basic glycoprotein ($M_r \sim 25.9$ kDa) from *Galleria mellonella*, containing two disulfide bridges acting as key protein in juvenile hormone (JH) signal transmission. JHBP transports JH from the site of its synthesis (*corpora allata*) to target tissues, and protects JH from degradation by non-specific esterases. The binding of JH to JHBP induces a significant conformational change of the protein molecule, which might be important for signal transduction [M. Duk et al., *Eur. J. Biochem.* **1996**, 242, 741; A. J. Sok et al., *Biol. Chem.* **2005**, 386, 1].

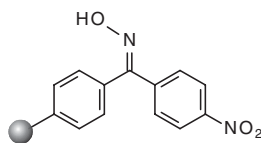
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Kahalalides, a family of several structurally unrelated cyclodepsipeptides (\rightarrow depsipeptides) isolated from the mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp., found on the island of Oahu. Each of the kahalalides A–G contains as a common feature a fatty acid, while some of the amino acid residues have the D-configuration or are dehydro amino acids. The structure of kahalalide B was confirmed by total synthesis in 2000. Kahalalide F exhibits activity against several cancer cell lines, shows antiviral and immunosuppressive activity, and is currently in Phase I clinical trials as an anticancer and antipsoriatic agent. Kahalalide A shows antimycobacterial activity, and its solid-phase total synthesis was described in 2005 [G. Goetz et al., *J. Nat. Prod.* **1997**, 60, 562; A. Lopez-Macia et al., *Tetrahedron Lett.* **2000**, 41, 9765; L. Bourel-Bonnet et al., *J. Med. Chem.* **2005**, 48, 1330].

Kailuins, 19-membered cyclodepsipeptides (\rightarrow depsipeptides) composed of six residues discovered in a Gram-negative bacterial culture (BH-107). They were named after Kailua Beach in Oahu, where the culture sample was obtained from a piece of driftwood. The kailuins A–D consist of five amino acid residues differing only in the type of β -hydroxy fatty acid moiety. They show mild cytotoxicity against three human cancers [G. G. Harrigan et al., *Tetrahedron* **1997**, 53, 1577].

Kaiser oxime resin, 4-nitrobenzophenone oxime resin, a base-labile resin widely used for the synthesis of Boc/Bzl-protected segments. Several methods have been de-

scribed for the detachment of protected segments from the resin, including hydrazinolysis, ammonolysis, or aminolysis using suitable amino acid esters. A preferred procedure to obtain the free carboxyl function of the peptide is transesterification of the peptide resin with *N*-hydroxypiperidine, followed by treatment of the resulting hydroxypiperidine ester with zinc in acetic acid. The only disadvantage of the Kaiser oxime resin is the lability towards nucleophiles [W. DeGrado, E. T. Kaiser, *J. Org. Chem.* **1982**, 47, 3258; E. T. Kaiser, *Acc. Chem. Res.* **1989**, 22, 47].



Kaiser oxime resin

Kaiser test, *ninhydrin test*, a simple and most frequently used method of *on-resin monitoring* in \rightarrow SPPS. A positive color reaction, performed with a small aliquot of the resin material, indicates unconverted amino groups. Samples containing <0.5% of unreacted amino groups can usually be detected within minutes. A modified version of the Kaiser test allows quantitative analysis [E. Kaiser et al., *Anal. Biochem.* **1970**, 34, 595; V. K. Sarin et al., *Anal. Biochem.* **1981**, 117, 147].

KALA amphipathic peptides, peptides containing the insecticide peptide sequence Lys-Ala-Leu-Ala (KALA). A synthetic both L- and D- isomer of the 30-peptide [YAA-(KALA)₆LAA] was shown to form α helices

and to lyse lipid vesicles in a pH-dependent fashion. The designed cationic 30-peptide, WEAKLAKALA¹⁰KALAKHLAKA²⁰LAKAL KACEA³⁰, with a repeating KALA sequence binds to DNA, destabilizes membranes, and mediates transfection of plasmid DNA in various cell lines [D. R. Frohlich, M. A. Wells, *Int. J. Pept. Protein Res.* **1991**, 37, 2; T. B. Wyman et al., *Biochemistry* **1997**, 36, 3008].

Kaliotoxin (KTX), GVEINVKCSG¹⁰SPQC LKPKCD²⁰AGMRFGKCMN³⁰RKCHCTPK (disulfide bonds: C⁸–C²⁸/ C¹⁴–C³³/ C¹⁸–C³⁵), a 38-peptide originally isolated from the venom of the scorpion *Androctonus mauretanicus mauretanicus*. Kaliotoxin shows 44% sequence homology with → iberiotoxin and charybdotoxin. It acts as a specific voltage-independent inhibitor of high-conductance Ca²⁺-activated K⁺ channels present in mollusk and rabbit nerve cells. KTX has a well-defined structure consisting of an α -helix and a three-stranded antiparallel β -sheet interconnected by three disulfide bonds, as determined by NMR. Interestingly, a kaliotoxin-like 37-peptide, KTX2, was isolated from *Androctonus australis* scorpion venom that shares 76% sequence homology with KTX. Furthermore, KTX3, a 37-peptide from *Buthus occitanus tunetanus* scorpion was described in 2000 [M. Crest et al., *J. Biol. Chem.* **1992**, 267, 1640; F. Laraba-Dlebari et al., *J. Biol. Chem.* **1994**, 269, 32835; A. Meki et al., *Toxicon* **2000**, 38, 105].

Kaliuretic peptide, → atrial natriuretic peptide.

Kallidin, *Kinin 10*, H-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg¹⁰-OH, a tissue peptide hormone belonging to the → kinins. Kallidin is released from the low- and high-molecular-weight kininogens by tissue kallikrein (→ kallikrein-kinin system).

It acts in similar manner to → bradykinin, and it is easily converted to bradykinin by proteolytic cleavage of the N-terminal lysine catalyzed by aminopeptidases.

Kallikrein-kinin system (KKS), a complex system in plasma and tissue for generating → bradykinin (BK) and kallidin peptides, respectively, in humans. Plasma → kallikrein forms BK from high-molecular-weight kininogen (HMWK), whereas tissue kallikrein forms → kallidin from HMWK and low-molecular-weight kininogen (LMWK). Bradykinin peptides may also be generated by aminopeptidase-catalyzed cleavage of kallidin peptides. Since a portion of kininogens is hydroxylated on Pro³ of the BK-(1–9) sequence, hydroxylated kinins, e.g., [Hyp³]bradykinin and [Hyp³]kallidin, result from kallikrein cleavage. The latter have similar biological activity as non-hydroxylated kinins. Further components of KKS are BK-(1–8) and kallidin-(1–9), formed by carboxypeptidase (kininase I) cleavage of bradykinin and kallidin, respectively, which are also bioactive. The neutral endopeptidase 24.11 (NEP) and → angiotensin-converting enzyme (ACE) catalyze formation of the inactive kinin peptides BK-(1–7) and kallidin-(1–8). Kinin formation *in vivo* is partly controlled by an endogenous inhibitor of the kallikrein enzymes. The function of the plasma and tissue KKS in humans can be better understood by the specific measurement of bradykinin and kallidin peptides and their metabolites [K. D. Bhoola et al., *Pharmacol. Rev.* **1992**, 44, 1; D. J. Campbell, *Clin. Exp. Pharmacol. Physiol.* **2001**, 28, 1060].

Kallikreins, a family of serine proteases from which *human tissue kallikreins*, **hKs**, represent the largest contiguous cluster of protease genes in the human genome. The hKs (EC 3.4.21.35) are homologous serine

proteases which are capable of specifically cleaving LMWK (\rightarrow kallikrein-kinin system) to generate vasoactive \rightarrow kinins. The first members of this family to be studied comprised *human kallikrein 1* (hK1), *human kallikrein 2* (hK2), and *prostate-specific antigen* (PSA, hK3). The first kallikrein was discovered in human urine as early as 1926; four years later it was also detected in pancreas (Greek "*kallikreas*", pancreas), and given the name for this family. hK1 is an acidic glycoprotein ($M_r \sim 46$ kDa) synthesized as a zymogen (prokallikrein). The latter can be activated by trypsin, thermolysin, and human plasma kallikrein *in vitro*. The gene encoding hK2 was first isolated from a human genomic library, and overexpression of the entire hK2 preprotein has been achieved in *E. coli*. Until now, hK2 ($M_r \sim 22$ kDa) has not been isolated from natural sources. PSA, also named *semenogelase*, is a serine protease with chymotrypsin-like activities. This single-chain glycoprotein ($M_r \sim 26.5$ kDa; 237 aa) is synthesized as a proenzyme with similarities to those of tissue kallikreins. PSA is one of the most abundant prostate-derived proteins in the seminal fluid. In patients with carcinoma of the prostate, the serum PSA levels increase, and analysis of this level is used both for diagnosing and monitoring patients with prostate carcinoma. During the past decade, the kallikrein family has expanded to include 15 genes, and the newly identified kallikreins share significant similarities to the three members described above. An important inhibitor of tissue kallikreins is \rightarrow kallistatin. *Plasma kallikreins* (EC 3.4.21.34) generate bradykinin peptides from HMWK (\rightarrow kallikrein-kinin system). Plasma kallikrein is an endopeptidase that cleaves at P1 Arg (preferred) and Lys bonds. The proenzyme of plasma kallikrein is prekallikrein (PK), which must be converted to the active en-

zyme by activated coagulation Factor XII (\rightarrow Hageman factor). The main inhibitors of plasma kallikreins are C1 inhibitor, $\rightarrow \alpha_2$ -macroglobulin, and antithrombin III [K. D. Wuepper, C. G. Cochrane, *J. Exp. Med.* **1972**, 135, 1; M. Paliouras et al., *Biol. Chem.* **2006**, 387, 643].

Kallistatin, a human tissue kallikrein (\rightarrow kallikreins) inhibitor and an additional member of the \rightarrow serpin superfamily that inhibits human tissue kallikrein. The translated sequence of kallistatin ($M_r \sim 58$ kDa) shares about 45% sequence identity with, for example, human α_1 -antichymotrypsin, protein C inhibitor, and α_1 -antitrypsin. The unique reactive site P1-P1' of kallistatin is Phe-Ser. Kallistatin occurs in the plasma at a average level of 13.5 mg L^{-1} . The recombinant kallistatin produced in *E. coli* is very similar to the native inhibitor in its biochemical properties, despite the lacking glycosylation [K. X. Chai et al., *J. Biol. Chem.* **1993**, 268, 24498; J. L. Chao et al., *J. Lab. Clin. Med.* **1996**, 127, 612].

Kassinakinin S, FIPVTLLALH¹⁰KIKEKLNa, a novel histamine-releasing 17-peptide amide from frog (*Kassina senegalensis*) skin. It is a product from the defensive skin secretion of the African running frog. This peptide was found to be a potent histamine secretagogue in a rat peritoneal mast cell model system [T. Chen et al., *Biochem. Biophys. Res. Commun.* **2005**, 337, 474].

Kassinatuerin-1, GFMKYIGPLI¹⁰PHAVK AISDL²⁰Ia, a 21-peptide amide first isolated from the skin of the African running frog *Kassina senegalensis*. It shows a broad spectrum of antimicrobial activity, but its therapeutic potential is limited by its relatively strong hemolytic activity against human erythrocytes. The peptide adopts an amphipathic α -helical conformation in a membrane-mimetic solvent (25% TFA).

The antimicrobial and cytolytic properties of kassinatuerin-1 and its L- and D-Lys-substituted analogues have been investigated [B. Matutte et al., *Biochem. Biophys. Res. Commun.* **2000**, 268, 433; J. M. Conlon et al., *Peptides* **2005**, 26, 2104].

Kassinin, DVPKSDQFVG¹⁰Lma, a 12-peptide amide belonging to the → tachykinin family. Kassinin was isolated from methanol extracts of the skin of the African frog *Kassina senegalensis* in 1977. It causes contraction of smooth muscle preparations at an activity of only 0.5% compared with → substance P. The aqueous- and lipid-induced structure of kassinin has been studied using 2D ¹H-NMR [A. Anastasi et al., *Experientia* **1977**, 33, 857; R. C. Grace et al., *J. Biomol. Struct. Dyn.* **2001**, 18, 611].

Katacalcin (KC), PDN sequence, PDN-21, DM SSDLERDH¹⁰RPHVSMQPNA²⁰N, the C-terminal flanking 21-peptide of the → calcitonin precursor. KC belongs to a group of peptides that are encoded by the *calc-1* gene and also include → calcitonin and procalcitonin N-terminal cleavage peptide (N-ProCT). The biological functions of KC or N-ProCT are unknown. It has been reported that KC regulates human CD14⁺ peripheral blood mononuclear cell (PBMC) migration through signaling events involving protein kinase A-dependent cAMP pathways. Besides mature calcitonin (CT), katacalcin is formed during processing of the precursor in C cells. Since medullary thyroid carcinoma (MTC) is the only known condition in which plasma CT concentrations are consistently and significantly increased, the measurement of katacalcin or serum CT is generally used as a marker for this tumor. Assays based on katacalcin and CT not only help in the diagnosis of MTC but also reflect the extent of tumor removal, and are useful in detecting early recurrence. Reports concerning the potent

calcium-lowering activity of katacalcin have not yet been confirmed [I. MacIntyre et al., *Nature* **1984**, 308, 84; F. Raue et al., *J. Mol. Med.* **1987**, 65, 82; N. C. Kaneider et al., *J. Bone Miner. Res.* **2002**, 17, 1872].

Katanosin B, → lysobactin.

kDa, kilodalton.

Kemptide, H-Leu-Arg-Arg-Ala-Ser-Leu-Gly-OH, a synthetic 7-peptide substrate related to a partial sequence of the phosphorylation site in porcine liver pyruvate kinase. Kemptide is phosphorylated *in vitro* and *in vivo* by cAMP-dependent protein kinase, and *in vitro* by protein kinase C. Recently, kemptide has been used for the development of a new class of kinase microarray for the detection of kinase inhibition [B. E. Kemp et al., *Fed. Proc.* **1976**, 35, 1384; J. Zhou, J. A. Adams, *Biochemistry* **1997**, 336, 15733; L. Sun et al., *Anal. Chem.* **2007**, 79, 773].

Kendrew, John Cowdery, (1917–1997), British biochemist and winner of the Nobel Prize in Chemistry 1962, shared with Max → Perutz, for studies of the structures of globular proteins. His research was in the field of protein structure, and was mostly centered on the X-ray analysis of → myoglobin. In 1949, he took his Ph.D at Trinity College, Cambridge, and had collaborated with Perutz at the Medical Research Council Unit for Molecular Biology at Cambridge. He was knighted in 1974 and became president of St. John's College, Oxford, in 1981.

Kentsin, H-Thr-Pro-Arg-Lys-OH, a contraceptive 4-peptide first isolated from the oviductal lumen of gravid female hamsters. It has been reported that kentsin acts centrally to produce both opioid and non-opioid effects. However, the opioid-mediated analgesic effects involve mechanisms other than direct interaction

with opioid receptors [H. A. Kent, Jr., *Biol. Reprod.* **1973**, *8*, 38; H. A. Kent, Jr., *Fertil. Steril.* **1979**, *31*, 595; D. A. Fox et al., *Peptides* **1987**, *8*, 613].

Keramamide, a group of oxazole- and thiazole-containing weakly cytotoxic cyclopeptides from the sponge *Theonella* sp. that exhibit cytotoxic, antifungal, and antioxidant activities. Members of this group are *orbiculamide A* and the *keramamides A, B, C, D*, and *E*. They contain unusual building blocks such as vinylogous and α -ketohomologous amino acids. The *keramamides F, G, H*, and *J* have similar structures, but the oxazole ring is replaced by a thiazole structure moiety [J. Kobayashi et al., *Tetrahedron* **1995**, *51*, 2525; P. Wipf, *Chem. Rev.* **1995**, *95*, 2115; T. Shioiri, R. J. Hughes, *Peptide Sci.* **2003**, *41*, 2004].

Keratinocyte growth factor (KGF), a member of the heparin-binding fibroblast growth factor family (FGF-7) showing a distinctive pattern of target-cell specificity. The natural hKGF (163 aa) shows mitogenic activity on keratinocytes and endothelial cells. KGF is involved as a specific paracrine factor in the regulation of the proliferation and differentiation of normal epithelial cells. The KGF receptor (KGFR) is a membrane-spanning tyrosine kinase isoform encoded by the *fgfr-2* gene [J. S. Rubin et al., *Cell. Biol. Int.* **1995**, *19*, 399; S. Werner, *Cytokine Growth Factor Rev.* **1998**, *9*, 153].

Keratins, a group of fibrous proteins occurring in wool, hair, hooves, claws, horns and feathers, and also in skin, connective tissues and intermediate filaments. α -Keratins occur in mammals, having around 30 various variants, whereas β -keratins are found in birds, reptiles, and in the silk of insects and arachnids. α -Keratin forms closely associated pairs of α -helices in which each pair is composed of a type I and a type II keratin chain twisted in parallel into a

left-handed coil. The ~ 30 -Å-wide protofilaments consist of two staggered and antiparallel rows of associated head-to-tail \rightarrow coiled coils. After the protofilaments dimerize to a ~ 50 -Å-wide protofibril, four of these in turn form a microfibril. α -Keratins have a high content of Cys residues (2–16%) which form disulfide bridges crosslinking adjacent polypeptide chains. Insolubility and resistance to stretching are important properties of α -keratin. α -Keratins are subdivided into “hard” or “soft” keratins, depending on high or low Cys contents. Hard keratins occur, for example, in hair, horn and nail, whereas soft keratins are found in skin and callus. The elasticity of wool fibers and hair is based on the coiled coil’s tendency to untwist after stretching, and to recover its original conformation after relaxing the external force. *Silk fibroin* ($M_r \sim 365$ kDa) is an important β -keratin, in which the sequence $-(\text{Gly-Ser-Gly-Ala-Gly-Ala})_n-$ is repeated many times. The polypeptide chains form antiparallel β -pleated sheets in which the peptide chains extend parallel to the fiber axis. The relative instability of silk to stretch, plus its great flexibility, are caused by the strong covalent bonds between the extended peptide chain and the weak van der Waals forces between the pleated sheets. Skin in higher animals contains an extensive network of *intermediate filaments (IF)* made of keratin-forming protein fibers 100–150 Å in diameter. Keratin is mainly responsible for the toughness of this protective outer covering. IF are formed from four types of fibrous polypeptide. Type I IF, which occur primarily in epithelial cells, includes two subfamilies of keratin, *acidic keratin* and *neutral* or *basic keratin* with M_r between 40 and 70 kDa [P. M. Steinert, D. A. D. Parry, *Annu. Rev. Cell. Biol.* **1985**, *1*, 41; E. Fuchs, *Annu. Rev. Cell Dev. Biol.* **1995**, *11*, 123; L. Kreplak et al., *Biophys. J.* **2004**, *87*, 640].

Kettapeptin, a cyclic hexadepsipeptide antibiotic from the azinotricin type from a terrestrial *Streptomyces* sp. The peptide is characterized by a 19-membered cyclodepsipeptide ring composed of six unusual amino acid building blocks and an acyl side chain connected via an amide bond. It exhibits significant biological activity against Gram-positive bacteria [R. P. Maskmeyer et al., *J. Antibiot.* **2006**, 59, 309].

KGF, keratinocyte growth factor.

KGF receptor peptide, HSGINSSNAE¹⁰VLALFNVTM²⁰DAGEY, a synthetic 25-peptide corresponding to the partial sequence 199–223 of the KGF receptor alternative exon. It blocks the mitogenic activity of KGF receptor (\rightarrow keratinocyte growth factor) and the interaction between KGF and its receptor [D. P. Bottaro et al., *J. Biol. Chem.* **1993**, 268, 9180].

Killer peptide (KP), H-Ala-Lys-Val-Thr-Met-Thr-Cys-Ser-Ala-Ser-OH, an engineered synthetic 10-peptide. The synthesis of KP is based on the sequence of a single-chain recombinant anti-idiotypic antibody acting as a functional mimotope of a microbicidal yeast killer toxin (KT) that exerts a strong microbicidal activity against human pathogens. Synthetic KP shows antimicrobial activity against a broad spectrum of phytopathogenic bacteria and fungi, and seems to be a promising candidate to be stably engineered in plants to confer broad-spectrum resistance to phytopathogens. In *Nicotiana benthamiana*, KP was used as a *Potato virus X* expression system [L. Polonelli et al., *Infect. Immun.* **2003**, 71, 6205; M. Donini et al., *Appl. Environ. Microbiol.* **2005**, 71, 6360].

Kinetensin, H-Ile-Ala-Arg-Arg-His-Pro-Tyr-Phe-Leu-OH, a neurotensin-related 9-peptide obtained by pepsin cleavage of human, bovine and dog plasma albumins.

It increases vascular permeability after intradermal injection into rats, and releases histamine from rat mast cells *in vitro*. Kinetensin shows sequence similarities to \rightarrow neurotensin and \rightarrow angiotensin I [M. H. Mogard et al., *Biochem. Biophys. Res. Commun.* **1986**, 136, 983; R. E. Carraway et al., *J. Biol. Chem.* **1987**, 262, 5968].

Kinetically controlled enzymatic synthesis, an approach to kinetic-control reverse proteolysis (\rightarrow protease-catalyzed peptide synthesis) that requires an acyl donor ester as carboxy component and is limited to proteases that rapidly form an \rightarrow acyl enzyme intermediate such as serine and cysteine proteases. The enzyme acts as a transferase, catalyzing the transfer of the acyl moiety to the nucleophilic amino component which reacts in competition with water with the acyl enzyme to form the desired peptide. In contrast to equilibrium-controlled synthesis, the kinetic-control approach requires much less enzyme, and the reaction time to obtain maximum product yield is significantly shorter [V. Schellenberger, H.-D. Jakubke, *Angew. Chem.* **1991**, 30, 1437].

Kinetically controlled ligation (KCL), \rightarrow chemical ligation.

King Kong Peptide, \rightarrow conotoxins.

Kininogen, \rightarrow kallikrein-kinin system.

Kinins, human peptide hormones implicated in many physiological and pathological processes, including reduction of blood pressure and regulation of sodium homeostasis, inflammation and the cardioprotective effects of preconditioning. The \rightarrow kallikrein-kinin system (KKS) of the plasma generates \rightarrow bradykinin (BK), whereas the tissue KKS is responsible for the formation of \rightarrow kallidin. The kinin action is mediated via two types of kinin receptor, the type 1 (B₁) and type 2 (B₂). B₁

receptor agonists are [DesArg⁹]bradykinin, [DesArg¹⁰]kallidin and the hydroxylated kinins (\rightarrow KKS), whereas BK, kallidin and also the hydroxylated kinins are B₂ receptor agonists. It has been reported that endogenous kinin peptides play a role in the regulation of coronary vascular tone, and in mediating the hypotensive effect of ACE inhibition. Whereas, kallidin peptides are more abundant than BK in urine, BK peptide levels are higher than kallidin peptide levels in the blood and tissues. However, the mechanisms by which are kinins produced *in vivo* are widely unknown. Members of this peptide hormone group are bradykinin (kinin 9), kallidin (kinin 10), and methionyl-lysyl bradykinin [J. E. Taylor et al., *Drug. Dev. Res.* **1989**, 16, 1; A.-M. Duncan et al., *Am. J. Physiol.* **2000**, 278, R897].

KISS-1 peptide, \rightarrow metastatin.

Kisspeptin, \rightarrow metastatin.

Knottins, a family of peptides present in *Mirabilis jalapa* seeds. The members M_j-AMP₁ and M_j-AMP₂ consist of 37 and 36 aa, respectively, differing only by four residues, and contain three disulfide bridges. Both peptides inhibit the growth of phytopathogenic fungi. Further knottins are the highly basic PAFPs which are produced by *Phytolacca americana* and consist of 38 aa, showing significant sequence similarities and the same cysteine motif as the M_j-AMP peptides [B. Cammune et al., *J. Biol. Chem.* **1992**, 267, 2228; F. Shao et al., *Biochem. Biophys. Res. Commun.* **1999**, 1430, 262].

Kulolide, a 22-membered cyclodepsipeptide (\rightarrow depsipeptides) isolated from the cephalaspidean mollusk, *Philinopsis speciosa* collected off Oahu. Among the seven residues, L-3-phenyllactic acid and (R)-2,2-dimethyl-3-hydroxy-7-octynoic acid, are

fairly unusual. An octynoic acid is also found in the \rightarrow onchidins. Kulolide exhibits activity against L1210 leukemia cells and P388 murine leukemia cells [M. T. Reese et al., *J. Am. Chem. Soc.* **1996**, 118, 11081].

Kutznerides, general structure: cyclo-[2-(1-methylcyclopropyl)-D-glycine-(2S,3aR,8aS)-6,7-dichloro-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid-D-3-hydroxy-D-glutamic acid-O-methyl-L-serine-L-piperazic acid-(S)-2-hydroxy-3,3-dimethylbutanoic acid-], depsipeptides isolated from culture supernatants of the actinomycete *Kutzneria* sp. 744. *Kutzneride 1* and *kutzneride 2* contain the 3-hydroxy-D-glutamic acid as its *threo*-isomer, whereas in *kutzneride 3* and *kutzneride 4* its *erythro*-isomer is present. Furthermore, the piperazic acid was modified to its (R)-4-chloro analogue in *kutzneride 2*, and to its C-5/N unsaturated analogue in *kutzneride 4*. The kutznerides 1–4 display moderate spore germination-inhibiting activity against several root-rotting fungi [A. Broberg et al., *J. Nat. Prod.* **2006**, 69, 97].

Kyotorphin, H-Tyr-Arg-OH, a neuroactive dipeptide first identified in the rat hypothalamus. Kyotorphin was named from the site of its discovery, Kyoto (Japan). It has a specific receptor coupled to G_i and phospholipase C and elicits [Met]enkephalin (\rightarrow enkephalins) release. Kyotorphin elicited potent nociceptive flexor responses at extremely low doses between 0.1 and 100 fmol after intraplantar injection into the hind-limb of mice. The *in-vivo* signal transduction of the nociceptive response by kyotorphin occurs via α_1 - and inositol triphosphate-mediated Ca²⁺ influx [H. Takagi et al., *Nature* **1979**, 282, 410; H. Takagi et al., *Eur. J. Pharmacol.* **1979**, 56, 265; H. Ueda, M. Inoue, *Mol. Pharmacol.* **2000**, 57, 108].

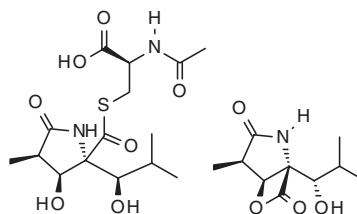
L

L1-peptides, *peptide* 18283, PNNNKIL VPK¹⁰VSGLQYRVFR²⁰, and *peptide* 18294, LYIKGSGSTA¹⁰NLASSNYFPT²⁰, derived from the HPV-16 L1-protein, are useful tools for serological detection of high-risk human papillomavirus (HR-HPV)-associated cervical carcinoma lesions [M. Urquiza et al., *Biochem. Biophys. Res. Commun.* **2005**, 332, 224].

Lac, lactic acid.

Lactacystin, a microbial product from *Streptomyces* sp. which acts as a selective and potent irreversible inhibitor of the 20S → proteasome and inhibits the cell cycle in tumor cells. Lactacystin and, particularly, the derived *clasto*-lactacystin β -lactone (also known as *omuralide*) are able, as small molecules, to inhibit irreversibly the proteolytic activity of the 20S proteasome, without affecting other proteasome activities. Radioactive lactacystin covalently binds to the β 5 subunit of the 20S proteasome. From the crystal structure of the yeast 20S proteasome-lactacystin complex it follows that lactacystin binds selectively to the β -oxygen atom of the *N*-terminal threonine in the β 5 subunit through a covalent ester bound. The acylating species is omuralide, which is formed by eliminating *N*-acetyl-L-cysteine from lactacystin. Omuralide is capable of penetrating cell membranes. Lactacystin was initially discovered as a neurite outgrowth inducer of a murine neuroblastoma cell line. The catalytic asymmetric total synthesis of (+)-lactacystin was described in 2006 [S. Omura et al., *J. Antibiot.* **1991**, 44, 113; C. E. Masse et al., *Eur.*

J. Org. Chem. **2000**, 2513; N. Fukuda et al., *J. Org. Chem.* **2006**, 71, 1220].



Lactacystin

Omuralide

α -Lactalbumin (LA), one of the most important members of the milk proteins. Human lactalbumin (123 aa; M_r ~14 kDa) occurs at a concentration of 0.14–0.6% in human milk. Generally, LA appears to occur only in mammalian milk and colostrum. α -Lactalbumin acts as a modifier protein to modify the action of galactosyl transferase to the enzyme complex lactose synthase. It promotes the binding of glucose to the enzyme complex and facilitates the biosynthesis of lactose. The crystal structure of human LA was described in 1991. Recently, it has been reported that bovine LA stimulates mucus metabolism in the gastric mucosa [K. R. Acharya et al., *J. Mol. Biol.* **1991**, 221, 571; Y. Ushida et al., *J. Dairy Sci.* **2007**, 90, 541].

β -Lactam antibiotics, a family of antibiotics containing a β -lactam ring (2-azetidinone). They are the most successful examples of natural product application and chemotherapy. *Monobactams* (name derived from *monocyclic* bacterially produced β -lactam antibiotics) are β -lactam antibiotics, with only the lactam ring such

as aztreonam and nocardicin A. The majority of β -lactam antibiotics have a second ring condensed to the β -lactam ring with basic types *penam*, *cepham*, *carbapenam*, and *clavan*. The β -lactam antibiotics inhibit the biosynthesis of bacterial cell walls. The most important groups of β -lactam antibiotics are the penicillins and cephalosporins. Each group has yielded medically useful products, and has contributed to the reduction in pain and suffering of people worldwide. Starting with the discovery of penicillin, continued efforts have resulted in the improvement of these compounds in relation to potency, activity against resistant pathogens, breadth of antibacterial spectrum, stability, and pharmacokinetic properties. Advances have also been made on structural and regulatory biosynthetic genes and metabolic engineering of the pathways involved. Currently, new semisynthetic compounds are available commercially, notably those designed to combat the development of resistance [R. B. Morin, M. Gorman, *Chemistry and Biology of β -Lactam Antibiotics*, Academic Press, 1982; A. L. Demain, R. P. Elander, *Antonie van Leeuwenhoek* 1999, 75, 5].

Lactoferricin (Lfcin), a peptide derived from \rightarrow lactoferrin with antimicrobial, antiviral, antitumor, and immunological properties. The most studied Lfcins are those derived from bovine and human lactoferrin, LfcinB and LfcinH, respectively. Both peptides are highly positively charged, but there is a striking difference in both the length of the peptide and the amino acid sequence. **LfcinB**, FKRRWQWRM¹⁰KKLGAPSITC²⁰VRRAF (disulfide bridge: C³–C²⁰), a 25-mer corresponding to the partial sequence 17–41 of bovine lactoferrin, which forms a loop structure through an intramolecular disulfide bond. **LfcinH**, GRRRRSVQWC¹⁰AVSQPE

ATKC²⁰FQWQRNMRKV³⁰RGPPVSCIKR⁴⁰DSPIQCIQA (disulfide bridges: C²⁰–C³⁷/C¹⁰–C⁴⁶), is a bicyclic 49-mer forming an analogous 18-membered loop similar to that in LfcinB. Lfcins are released both in the gastrointestinal tract by gastric pepsin, as well as at the site of infection stomach through proteolytic cleavage of bovine and human lactoferrin, respectively [J. L. Gifford et al., *Cell. Mol. Life Sci.* 2005, 62, 5373].

Lactoferrin (LF), an iron-binding protein ($M_r \sim 80$ kDa), occurs predominantly in the secreted fluids of mammals such as tears, milk, saliva, bronchial mucus and seminal plasma, and is also stored in the secondary granules of polymorphonuclear leukocytes. The three-dimensional structure of LF is very similar to that of other members of the \rightarrow transferrin family except for a unique, highly positively charged N-terminal sequence segment. Although the physiological functions of LF have yet to be completely solved, it plays a multifunctional role in host defense. LF reversibly binds two atoms iron. Originally, the antimicrobial properties of intact LF were believed to be related to its iron-scavenging capabilities. However, further studies have shown that potent antimicrobial properties reside in the basic N-terminal region which is not involved in iron binding. The peptide \rightarrow lactoferricin can be released from LF through pepsin cleavage in the stomach [K. Shimazaki et al. (Eds.), *Lactoferrin: Structure, Function, and Applications*, Elsevier Science, New York, 2000; D. Caccavo et al., *J. Endotoxin Res.* 2002, 8, 403].

Lactogenic hormone, \rightarrow prolactin.

β -Lactoglobulin, the major whey protein of ruminant species. This \rightarrow globulin is also content of the milks of many, but

not all, species. β -Lactoglobulin ($M_r \sim 37$ kDa) consists of two subunits, and shows structural similarity to the retinol-binding protein of blood plasma. It is a member of the \rightarrow lipocalin family, most of which bind small hydrophobic ligands and may act as specific transporters, as does serum retinol-binding protein. Bovine β -lactoglobulin binds several ligands, including cholesterol and vitamin D₂.

Lactorphins, \rightarrow milk protein-derived opioid peptides.

Ladder sequencing, an approach to peptide sequencing that combines ladder-generating chemistry with MS. *N-terminal ladder sequencing* requires a modified \rightarrow Edman degradation procedure in which in every step the peptide is incompletely degraded to yield continuously a mixture of one amino acid-shortened peptides. Such a peptide ladder results when Edman degradation with PITC is performed in the presence of 5% phenyl isocyanate (PIC), a terminating reagent. The content of phenylcarbamoyl peptides increases to a statistical mixture. Analysis of the mixture using MALDI-MS allows for direct sequence determination from the successive mass differences of the peptide ladder. *C-terminal ladder sequencing* is based on the same principle. The ladder can be formed by carboxypeptidase digestion or using the \rightarrow Schlack-Kumpf method combined with MALDI-MS analysis of the truncated peptides [B. T. Chait et al., *Science* **1993**, 262, 89; M. Bartlett-Jones et al., *Rapid Commun. Mass Spectrom.* **1994**, 8, 737; B. Thiede et al., *Eur. J. Biochem.* **1997**, 244, 750].

Laminins, a family of glycoproteins providing an integral part of the structural scaffolding of basement membranes in almost

every animal tissue. Each member of the laminins is a heterotrimer assembled from α , β , and γ chain subunits, secreted and incorporated into cell-associated extracellular matrices. Laminins are multidomain, heterotrimeric and glycosylated molecules ($M_r \sim 800$ – 1000 kDa). The α -helical coiled-coil domain of the long arm is involved in the specific assembly of the three chains, and is the only domain composed of multiple chains. In the terminal region of the long arm reside sites for receptor-mediated cell attachment and promotion of neurite outgrowth. Up until 2007, 15 laminins had been identified, which differ in the isoforms of the three chains that assemble into the cross-shape molecules observed by electron microscopy. In 2005, a simplification of the laminin nomenclature was presented. According to the new identification system, Arabic numerals are used based on the α , β , and γ chain numbers. For example, the laminin with the chain composition $\alpha 5\beta 1\gamma 1$ is termed laminin-511, and not laminin-10. Furthermore, all modules are now termed “domains”. The laminins are capable of self-assembly, and bind to other matrix macromolecules. They have unique and shared cell interactions mediated by \rightarrow integrins, dystroglycan, and other receptors. Based on those interactions, laminins contribute to cell differentiation, cell shape and movement, maintenance of tissue phenotypes, and promotion of tissue survival. From the characterization of genetic disruptions in humans, mice, flies, and nematodes it follows that the different laminin subunits play developmental roles in diverse cell types, affecting differentiation from blastocyst formation to the post-natal period [R. Timpl, P. Ekblom, *The Laminins*, CRC Press, **1996**; H. Colognato, P. D. Yurchenco, *Dev. Dyn.* **2000**, 218, 213; M. Aumailley et al., *Matrix Biol.* **2005**, 24, 326; T. Zimmermann,

F. J. Blanco, *J. Biomol. Struct. Dyn.* **2007**, *24*, 413].

Lan, lanthionine.

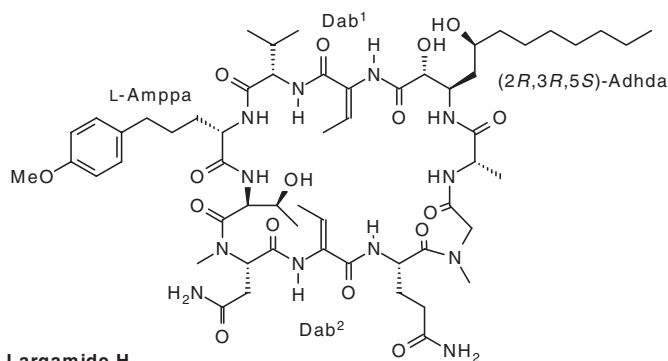
Lanreotide, → somatostatin.

Lantibiotics, a class of ribosomally synthesized, post-translationally modified peptides of 19 to 38 residues, containing unusual amino acids, such as α,β -didehydro amino acids and lanthionine. The unusual amino acid lanthionine is composed of two alanine residues connected across a thioether linkage that connects their β -carbons in a similar fashion as the amino acid cystine connects two alanine residues across a disulfide bridge. The amino acid lanthionine is present in the name of the lantibiotics, which is derived from "lanthionine-containing antibiotic peptides". They belong to the subgroup of → bacteriocins, and are produced by a wide variety of Gram-positive bacterial strains. The amino acids lanthionine and 3-methylanthionine are generated via post-translational modification (conjugate addition of a Cys residue to an α,β -didehydro amino acid). The building blocks lysinoalanine, β -hydroxy-aspartate, D-alanine, 2-oxobutyrate, pyruvate, lactate, S-aminovinyl-D-cysteine, and S-aminovinyl D-methylcysteine occur less frequently. The post-translational modifications present in lantibiotics are unique in Nature and are essential for their biological activity. The gene organization for the biosynthetic machinery is performed in clusters, including information for the antibiotic propeptide, the modification enzymes and accessory functions, e.g., special proteases and ABC transporter, immunity factors, and regulatory peptides. According to Jung, the lantibiotics are subdivided into two types: Type A (→ nisin, → subtilin, → epidermin, → gallidermin, → pep5); and type B (→ cin-

namycin, → ancovenin, → duramycins). Type A lantibiotics are elongated, helical amphiphiles with 20 to 34 residues bearing a net positive charge. They were believed to form short-lived pores in the membrane of susceptible bacteria. Nisin has been used for food preservation for many years. Type B lantibiotics are more compact, form globular structures, and generally interrupt a variety of membrane-derived enzyme functions. Several lantibiotics have been shown to interfere with peptidoglycan biosynthesis by binding to lipid II, but this activity is not confined to the type A lantibiotics [G. Jung, H.-G. Sahl (Eds.), *Nisin and Novel Lantibiotics*, ESCOM, Leiden, **1991**; A. Guder et al., *Biopolymers (Pept. Sci.)* **2000**, *55*, 62; P. D. Cotter et al., *Curr. Prot. Pept. Sci.* **2005**, *6*, 61; C. Chatterjee et al., *Chem. Rev.* **2005**, *105*, 633].

LAP, leucine aminopeptidase.

Largamides, a family of depsipeptides, termed largamides A–G, and a new cyclic peptide, largamide H, isolated from the marine cyanobacterium *Oscillatoria* sp. Largamides A–C are characterized by the unusual building block senecioic acid, while largamides B and C contain in addition the rare 2-amino-5-(4'-hydroxyphenyl)pentanoic acid (Ahppa) and the novel 2-amino-6-(4'-hydroxyphenyl)hexanoic acid (Ahpha), respectively. Largamides D–G contain as unusual building blocks 3-amino-6-hydroxy-2-piperidone acid (Ahp) and the rare Ahppa unit. Largamide H is a cyclic peptide displaying a new 2,5-dihydroxylated β -amino acid moiety, a methoxylated derivative of Ahppa, and two residues of 2,3-dehydro-2-aminobutanic acid (Dab). The largamides D–G act as chymotrypsin inhibitors [A. Plaza, C. A. Bewley, *J. Org. Chem.* **2006**, *71*, 6898].



Largamide H

Large-scale peptide synthesis, procedures for the industrial production of peptides. The term “large-scale” is relatively subjective however, and may be defined as ranging from kilograms to metric tonnes. Although the chemistry does not differ markedly between large-scale manufacturing processes and those used under laboratory conditions, the development of an economic, efficient and safe procedure makes high demands. First, special requirements imposed by regulatory authorities must be fulfilled. Reactors and other equipments used for large-scale synthesis must fulfill special requirements (→ peptide production plant). Environmental and economic aspects also determine the selection of reagents and solvents used in industrial processes. Strategy and tactics are quite different between small-scale synthesis in the laboratory and industrial synthesis. Although many protected amino acid derivatives are available commercially, minimum protection schemes are preferred for large-scale syntheses. For economic reasons, it is detrimental to use more than two equivalents of activated amino acids, and reagents and reactants should be used in amounts close to stoichiometry. In the coming years, large-scale synthesis from more than 100 kg up to a multi-tonne scale will prove to be a major challenge. The production of nearly

4000 kg of → T20 a year underlines the importance of large-scale peptide synthesis [L. Andersson et al., *Biopolymers* **2000**, 55, 227; T. Vorherr et al., *Chimia* **2005**, 59, 25].

LD₅₀, lethal dose 50%.

LDL, low-density lipoprotein.

LD-MS, laser desorption mass spectrometry.

LDToF, laser desorption time-of-flight.

LDV sequence, a recognition sequence (-Leu-Asp-Val-) of the vascular cell adhesion molecule-1 (VCAM-1).

Lectins, *agglutinins*, *hemaagglutinins*, usually plant-derived proteins or glycoproteins that recognize and bind specifically to carbohydrates and cell-surface carbohydrate moieties. Based on differences in molecular structure, biochemical properties, and carbohydrate-binding specificity, plant lectins are usually considered a complex and heterogeneous group of proteins. With the *legume lectins*, the *chitin-binding lectins* composed of → hevein domains, the *type 2 ribosome-inactivating proteins*, and the *monocot mannose-binding lectins*, four major plant lectin families have been classified. Furthermore, the jacalin-related lectins, the

amaranthin family, and the Cucurbitaceae phloem lectins are now recognized as separate subgroups. It has been described that plant lectins inhibit fungal conidial germination, alter germ tubes, and inhibit hyphal growth. Lectins are known to protect the plant from fungal infection. *Wheat germ agglutinin (WGA) lectin*, for example, has an affinity for *N*-acetylglucosamine and binds to chitin-containing fungal walls. It interferes with chitin formation in the synthesis of fungal cell walls, and thus protects the plant from infection. *Urticola dioica agglutinin (UDA)*, produced from the stinging nettle is a usually heat- and acid-resistant single-chain fungistatic lectin ($M_r \sim 8.5$ kDa) with high sequence similarities of WGA. UDA inhibits the hyphal growth of several phytopathogenic fungi. Some well-known lectins are \rightarrow *ricin*, *concanavalin A* from the jack beans, consisting of four subunits with 238 aa each, and *vicilin*, a glycoprotein containing 0.2% glucosamine and 1% mannose. Because certain lectins are capable of agglutinating erythrocytes and other cell structures, they are also called phytohemagglutinins. Investigations on *animal lectins* reached maturity during the late 1990s. For example, animal lectins are involved in cell-cell or cell-matrix interactions [I. J. Goldstein, C. E. Hayes, *Adv. Carbohydr. Chem. Biochem.* **1978**, 35, 127; H. J. Gabius, *Eur. J. Biochem.* **1997**, 243, 543; E. J. M. van Damme et al., *Crit. Rev. Plant Sci.* **1998**, 17, 575].

Lepirudin, [*Leu*¹,*Thr*²]-63-desulfatohirudin, (Refludan[®], Berlex Laboratories, USA and Canada, Pharmion[®], all other countries) a recombinant \rightarrow hirudin (65 aa; $M_r \sim 6.9$ kDa) first approved for the treatment of heparin-induced thrombocytopenia (HIT). Later, a new indication was found in the treatment of unstable angina. *Desirudin* dif-

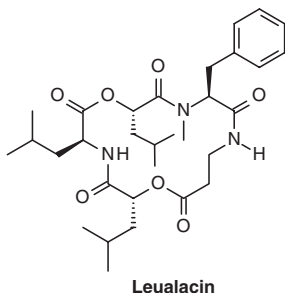
fers from lepirudin only in the first two *N*-terminal residues (Val¹, Val²), and it plays a definite role in thrombosis prophylaxis. Lepirudin directly inhibits the active site pocket and the fibrinogen binding site of free and clot-bound thrombin [A. Greinacher, N. Lubenow, *Circulation* **2001**, 103, 1479].

Leptin, a single-chain proteohormone ($M_r \sim 16$ kDa) exhibiting a wide range of effects in the regulation of body weight. It is the protein product of the obese gene (*ob* gene) secreted from white adipose tissue cells [*leptos* (Greek): thin, small]. Leptin is a satiety hormone that acts directly through its hypothalamus receptors to regulate a large number of molecules implicated in energy homeostasis. The reduction of body weight is primarily the result of centrally mediated effects on food intake, insulin sensitivity and adipose tissue metabolism, energy expenditure, and apoptosis. A variety of leptin effects are mediated via synthesis and release of neuropeptide effector molecules, e.g., \rightarrow neuropeptide Y, \rightarrow melanin-concentrating hormone, \rightarrow agouti-related protein, \rightarrow glucagon-like peptides, \rightarrow neurotensin, α -MSH (\rightarrow melanotropin), \rightarrow corticoliberin. Leptin receptors are localized ubiquitously in the body, but the general role of leptin is currently not fully understood. The receptors belong to the cytokine class I receptor family. The *db/db* genotype seems to code for a deficient leptin receptor protein. Administration of mouse rec. leptin to *ob/ob* mice corrects both over-eating and obesity. Furthermore, leptin reduces appetite and weight of mice with diet-induced obesity. The orexigenic peptide \rightarrow ghrelin antagonizes leptin action through the activation of the hypothalamic NY/Y1 receptor pathway. Nowadays, it is clear that leptin also has direct and indirect actions on bone. For example, it

promotes proliferation and differentiation in a variety of osteoblast models *in vivo* [Y. Zhang et al., *Nature* **1994**, 372, 425; I. R. Reid, J. Cornish, *Calcif. Tissue Int.* **2004**, 74, 313; U. Meier, A. M. Gressner, *Clin. Chem.* **2004**, 50, 1511; M. N. Della-Fera, C. A. Baile, *Peptides* **2005**, 26, 1782].

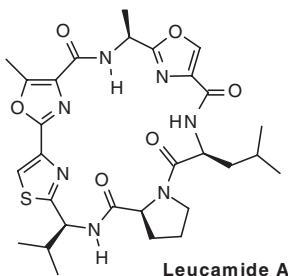
Leu, leucine.

Leualacin, a cyclic pentadepsipeptide from the fungus *Hapsidospora irregularis*. Leualacin is a Ca^{2+} -blocking agent which is structurally completely different from clinically used compounds such as benzodiazepines, dihydropyridines, and verapamil derivatives. It displayed potent calcium channel activity at levels comparable to the calcium channel antagonists nitrendipine and diltiazem [K. Hamano et al., *J. Antibiot.* **1992**, 45, 899; U. Schmidt, J. Langner, *J. Chem. Soc., Chem. Commun.* **1994**, 2381; K. L. McLaren, *J. Org. Chem.* **1995**, 60, 6082].



Leucamide A, a bioactive cyclic hexapeptide first isolated from the Australian marine sponge *Leucetta microraphis* and structurally confirmed by total synthesis. It contains an unique mixed 4,2-bis-heterocycle tandem pair consisting of methyloxazole and thiazole subunit showing moderate cytotoxicity toward several tumor cell lines [S. Kehraus et al., *J. Org.*

Chem. **2002**, 67, 4989; W. Wang, F. Nan, *J. Org. Chem.* **2003**, 68, 1636].



Leuchs, Hermann (1879–1945), German chemist and discoverer of the \rightarrow *N*-carboxy anhydrides of amino acids. He carried out the work for his doctoral thesis under the direction of Emil \rightarrow Fischer on the synthesis of serine and glucosamine. In 1902, he received his D. Phil. degree and achieved independent status from 1904 onwards, Privatdozent (1910) and associate professor (1914). He turned down offers of full professorships at the Universities of Graz and Braunschweig, which would have improved his position, in favor of a personal full professorship at the Berlin Institute. He ended his life in the final days of World War II [F. Kröhnke, "*Hermann Leuchs*", *Chem. Ber.* **1952**, 85, LV].

Leuchs's anhydride, \rightarrow *N*-carboxy anhydride.

Leucine (Leu, L), α -aminoisocaproic acid, $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{COOH}$, $\text{C}_6\text{H}_{13}\text{NO}_2$, M_r 131.17 Da, a proteinogenic amino acid.

Leucokinins, a group of structurally related insect neuropeptides originally isolated from head extracts of the Madeira cockroach *Leucophaea maderae*. They stimulate gut motility and fluid secretion by Malpighian tubule in insects. *Leucokinin I*, H-Asp-Pro-Ala-Phe-Asn-Ser-Trp-Gly-NH₂, and three other members of

this group (*Leucokinin II–Leucokinin IV*) are 8-peptide amides with both identical residues in position 1 and the same C-terminal tripeptide sequence. They increase motility of the isolated hindgut of the cockroach. Synthetic leucokinins show biological activity in a different insect and in a different tissue. Further members of the leucokinins are *leucomyosuppressin* (*LMS*), pGlu-Asp-Val-Asp-His-Val-Phe-Leu-Arg-Phe¹⁰-NH₂, and *leucopyrokinin* (*LPK*), pGlu-Thr-Ser-Phe-Thr-Pro-Arg-Leu-NH₂. Leucokinins and pyrokinin exhibit an inhibitory effect on the release of digestive enzymes from the insect midgut [J. R. Nachmann et al., *Biochem. Biophys. Res. Commun.* **1986**, 137, 936; J. van Brunt, *Biotechnology* **1987**, 5, 31; G. M. Coast, *Peptides* **1996**, 17, 327; S. Harshini et al., *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **2002**, 132, 353].

Leucomyosuppressin, → leucokinins.

Leucopyrokinin, → leucokinins.

Leucosulfakinins, tyrosine-sulfated neuropeptides isolated from the head of the cockroach *Leucophaea maderae*. *Leucosulfakinin I*, EEFEDY^SGHMR¹⁰Fa, and *Leucosulfakinin II*, <ESDDY^SGHMR¹⁰a (Y^S: SO₃H) resemble each other and show some similarities to mammalian → cholecystokinin and → gastrin, but they do not belong to the CCK/gastrin family due to the discrepancies between the C-terminal tetrapeptide amide sequence [R. J. Nachman et al., *Science* **1986**, 234, 71; R. J. Nachman et al., *Biochem. Biophys. Res. Commun.* **1986**, 140, 357; R. Predel et al., *Eur. J. Biochem.* **1999**, 263, 552].

Leu-enkephalin, → enkephalins.

Leukemia inhibitory factor (LIF), a glycoprotein acting as growth and differentiation

regulator with pleiotropic activity in several adult and embryonic systems. Target cells of LIF are monocytes, macrophages, and their precursors. It promotes the entry of hematopoietic stem cells into the cell cycle. The LIF receptor is structurally related to the IL-6 signal transducer, gp130. LIF was originally isolated as an inhibitor of mouse M1 myeloid leukemia cells. LIF and → oncostatin M share 25% sequence homology [M. Tomida et al., *J. Biol. Chem.* **1984**, 259, 10978; D. P. Gearing et al., *EMBO J.* **1991**, 10, 2839].

Leukocyte interferon, IFN- α , → interferons.

Leukokinin, → tuftsin.

Leukokinins, peptides containing 20–25 amino acid residues formed by the action of acid proteases found in leukocytes, cancer cells, and ascites fluids on the protein substrate leukokininogen. The leukokinins are extremely potent in causing increased vascular permeability and hypotensive blood pressure changes [L. M. Greenbaum et al., *Inflammation Res.* **1978**, 8, 80].

Levitide, <EGMIGTLTSK¹⁰RIKQa, a 14-peptide amide from the skin secretions of the South African frog *Xenopus laevis* acting as a neuropeptide [L. Poulter et al., *J. Biol. Chem.* **1988**, 263, 3279].

LH, luteinizing hormone.

LHRH, acronym of luteinizing hormone-releasing hormone, → gonadotropin-releasing hormone.

Liberins, IUPAC-IUB designation for releasing hormones and releasing factors. The suffix *-liberin* describes the corresponding releasing hormone of the hypothalamus, such as → corticoliberin.

Light-directed spatially addressable parallel synthesis, a method for the parallel

synthesis of peptides (\rightarrow combinatorial peptide synthesis). It relies on a photolithographic technique originating from microchip technology. It is combined with the solid-phase synthesis of peptides using temporary \rightarrow photolabile protecting groups such as Nvoc. Amino-functionalized glass plates are employed as the solid support for this technology, and suitable photo-lithographic masks allow for a spatially controlled photo deprotection of the Nvoc-protected amino terminus at a spatial resolution of $50 \times 50 \mu\text{m}$. An appropriate choice and layout of the lithographic mask provides up to 10 000 different peptides per cm^2 . The exact positioning of the lithographic techniques safeguards correct identification of the immobilized peptide of the screening in a biological test system [S. P. A. Fodor et al., *Nature* **1993**, 364, 555].

Linker, \rightarrow handle.

Lipid transfer proteins, a family of homologous antifungal peptides containing eight disulfide-linked cysteines produced by some plants. For example, onion seeds (*Allium cepa*, L) produce the lipid transfer peptide ACE-AMP₁, which inhibited *F. oxysporum* [B. P. A. Cammune et al., *Plant Pathol.* **1996**, 109, 445].

Lipocalin family, a large group of small extracellular proteins characterized by great diversity in the sequence, but most of them sharing three characteristic conserved sequence motifs. The latter are termed *kernel lipocalins*, whereas the *outlier lipocalins* share only one or two motifs. The crystal structures are highly conserved and comprise a single eight-stranded, hydrogen-bonded, antiparallel β -barrel bearing an internal ligand-binding site. Members of the lipocalin family are capable of binding a range of small hydrophobic molecules. The

lipocalins exhibit great functional diversity, with functions in retinol transport, invertebrate cryptic coloration, olfaction and pheromone transport, and prostaglandin biosynthesis. The lipocalins are part of a larger protein superfamily, the \rightarrow calycins [D. R. Flower et al., *Biochim. Biophys. Acta* **2000**, 1482, 9].

Lipopeptides, peptides modified with lipid residues which are preferentially bound at the thiol function of cysteine or at the α -amino group of *N*-terminal amino acids. The α -subunits of heteromeric \rightarrow G proteins and non-tyrosine receptor kinases contain *N*-myristoylated *N*-terminal glycine residues together with *S*-palmitoylation of a neighboring cysteine residue. Lipid moieties are necessary to recruit and anchor peptides and proteins to the membrane. Furthermore, it has been postulated that lipidation of proteins represents an event in signal transduction. The synthesis of lipid-modified peptides is not easy to perform as all coupling and deprotection reactions must be carried out under very mild conditions [S. Moffet et al., *EMBO J.* **1993**, 12, 349; D. Kadereit et al., *Chem. Eur. J.* **2001**, 7, 1184].

Lipophilic segment coupling, a combined solid-phase/solution-phase approach which circumvents solubility problems in solution-phase segment condensation. Lipophilic segments are synthesized by Fmoc/Bu^t SPPS using maximum protection chemistry on a resin bearing a highly acid-labile 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB) handle. Due to the sufficient solubility of the resulting protected segments in *N*-methylpyrrolidone, the segment condensations can be performed in this solvent using \rightarrow TBTU as coupling reagent and reaching completion within a few minutes [B. Riniker et al., *Tetrahedron* **1993**, 49, 9307].

Lipoproteins, non-covalent conjugates consisting of lipids and proteins occurring, for example, in cellular membranes, cell cytoplasm and blood plasma, and involved in the transport and distribution of water-insoluble lipids in body fluids. The protein components of lipoproteins are termed *apolipoproteins* or *apoproteins*. Apolipoproteins form amphipathic helices that coat lipoprotein surfaces. Human lipoproteins consist of at least nine apolipoproteins (A-I, A-II, B-48, B-100, C-I, C-II, C-III, D, E). The major classes of lipoproteins in human blood plasma are divided into *chylomicrons* (density $<0.95 \text{ g cm}^{-3}$; major apolipoprotein: A-I, A-II, B-48, C-I, C-III, E), *very low-density lipoproteins*, VLDL (density: $<1.006 \text{ g cm}^{-3}$; major apolipoproteins: B-100, C-I, C-II, C-III, E), *intermediate density lipoproteins*, IDL (density: $1.006\text{--}1.019 \text{ g cm}^{-3}$; major apolipoproteins: B-100, C-III, E), *low-density lipoproteins*, LDL (density: $1.019\text{--}1.063 \text{ g cm}^{-3}$; major apolipoprotein: B-100), and *high-density lipoproteins*, HDL (density: $1.063\text{--}1.210 \text{ g cm}^{-3}$; major apolipoproteins: A-I, A-II, C-I, C-II, C-III, D, E). Chylomicrons transport externally supplied triacylglycerols and cholesterol from the intestines to the tissues. VLDL, IDL and LDL are responsible for the transport of endogenous triacylglycerols and cholesterol from the liver to the tissues, whereas HDL transport endogenous cholesterol from the tissues to the liver. An excess of plasma LDL promotes atherosclerosis, which is also correlated with a low concentration of HDL [J. P. Kane, *Curr. Opin. Struct. Biol.* **1991**, 1, 510; M. Rosseneu (Ed.), *Structure and Function of Apolipoproteins*, CRC Press, Boca Raton, FL, **1992**; D. Atkinson, *Curr. Opin. Struct. Biol.* **1992**, 2, 482; R. M. Lawn, *Sci. Am.* **1992**, 266, 54; K. Skalen et al., *Nature* **2002**, 417, 750].

Lipotropic hormone, \rightarrow lipotropin.

Lipotropin, *lipotropic hormone*, **LPH**, a polypeptide hormone from the hypophysis stimulating the mobilization of lipids from lipid depots. β -LPH (91 aa; $M_r \sim 10 \text{ kDa}$) is biosynthetically formed from the precursor \rightarrow proopiomelanocortin (PMOC). β -LPH is released from PMOC in the anterior and intermediate lobes of the pituitary gland, whereas in the intermediate lobe only β -LPH is split to γ -LPH (corresponds to β -LPH 1–58) and \rightarrow β -endorphin [A. F. Bradbury et al., *Biochem. Biophys. Res. Commun.* **1976**, 69, 950; J. Bogard et al., *J. Biol. Chem.* **1995**, 270, 23038].

Liprolog®/Humalog®, *insulin lispro*, an engineered form of human \rightarrow insulin in which the partial sequence -Pro²⁸-Lys²⁹- has been reversed. This manipulation led to an insulin variant that exists as monomer at physiological concentrations and consequently has a faster onset, but shorter duration of action, due to enhanced absorption after subcutaneous administration [E. Ciszak et al., *Structure* **1995**, 3, 615].

Liquid-phase sequencer, *spinning cup sequencer*, an automated equipment for N-terminal sequence analysis of peptide and proteins (\rightarrow Edman degradation). The analysis material is spread by centrifugal forces as a thin film on the inner wall of a spinning cup. The reagents and solvents are fed automatically to the bottom of the glass cup through a valve assembly and a special feeding line. The extracting solvents reach a groove in the cup, from where they are removed through an effluent line. The truncated peptide remains in the reaction vessel [P. Edman, G. Berg, *Eur. J. Biochem.* **1967**, 1, 80].

Liquid-phase peptide synthesis (LPPS), a hybrid approach between solution-phase and solid-phase synthesis combining the inherent advantages of both approaches.

The application of a soluble polymeric support material is characterized by the advantage of homogeneous reaction conditions which may overcome some disadvantages of SPPS. Polyethylene glycol (PEG) as the polymeric support and C-terminal-protecting group is particularly suitable because of its solubility properties. In LPPS, as in SPPS, the growing peptide chain remains attached to the polymeric material throughout the synthesis. Deprotection and coupling reactions take place in homogeneous solution. The purification of intermediates is performed by ultrafiltration or crystallization. The protected peptidyl-PEG is washed extensively in order to remove low-molecular-weight byproducts and impurities, followed by monitoring of the synthetic intermediates, particularly by NMR techniques. However, LPPS protocols based on Boc chemistry are laborious and were not used widely until the development of combinatorial synthesis approaches. In 2002, the versatile protection strategy based on the Fmoc group was adapted to LPPS [E. Bayer, M. Mutter, *Nature* **1972**, 237, 512; M. Mutter, E. Bayer, *Angew. Chem. Int. Ed.* **1974**, 13, 88; P. M. Fischer, D. I. Zheleva, *J. Peptide Sci.* **2002**, 8, 529].

Liraglutide, a long-lasting human GLP-1 analogue (\rightarrow glucagon-like peptides) obtained by derivatization of GLP-1 with a fatty acid. Treatment as monotherapy significantly improves glycemic control and lowers body weight, without risk of hypoglycemia in patients with \rightarrow non-insulin-dependent diabetes mellitus [K. D. Degn et al., *Diabetes* **2004**, 53, 1187; T. Vilsboll et al., *Expert Opin. Invest. Drugs* **2007**, 16, 231].

Litorin, pGlu-Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH₂, a member of the \rightarrow ranatensin family. Litorin was isolated

from the skin of the Australian frog *Litoria aurea*. Litorin shows similar activities to \rightarrow ranatensin. *Rohdei-litorin*, pGlu-Leu-Trp-Ala-Thr-Gly-His-Phe-Met-NH₂, has been isolated from the skin of *Phyllomedusa rohdei*, and displayed a greater affinity for rat urinary bladder receptors [V. Erspamer, P. Melchiorri, *Trends Biochem. Sci.* **1980**, 1, 391; D. Barra et al., *FEBS Lett.* **1985**, 182, 53].

Liver cell growth factor, \rightarrow glycyl-L-histidyl-L-lysine.

Lividins, antimicrobial peptide homologues from the skin secretion of the Chinese frog, *Rana (Odorrana) livida*. The lividins 1–4 are found to be structural homologues of known antimicrobial peptide families from *Rana* frogs [M. Zhou et al., *Peptides* **2006**, 27, 2118].

Locustakinin, H-Ala-Phe-Ser-Ser-Trp-Gly-NH₂, a 6-peptide amide from *Locusta migratoria*. Locustakinin is a myotropic neuropeptide with sequence similarity to cockroach \rightarrow leucokinins [L. Schoofs et al., *Regul. Pept.* **1992**, 37, 49; G. M. Coast, *Peptides* **1996**, 17, 327].

Long-acting natriuretic peptide, \rightarrow atrial natriuretic peptide.

LPH, lipotropic hormone.

LPPS, liquid-phase peptide synthesis.

LPS, lipopolysaccharide.

LPXRFamide peptide family, a member of the hypothalamic \rightarrow RFamide superfamily. The peptides of this family are present in the brains of vertebrates, such as mammals, amphibians, and fish. They possess a LPXRFamide (X = L or Q) motif at their C-termini in all investigated animals. These peptides were found to be localized in the hypothalamus and brainstem areas, and to regulate pituitary hormone release.

The first identified peptide of this family was → gonadotropin-inhibitory hormone [K. Ukena, K. Tsutsui, *Mass Spectrom. Rev.* **2005**, *24*, 469].

Luliberin, → gonadoliberin.

Lunasin, SKWQHQQDSC¹⁰RKQLQGVNLT²⁰PCEKHIMEKI³⁰**QGRGDDDDDD**⁴⁰DD, a 43-peptide characterized by a → RGD-sequence (bold) and an unusual acidic C-terminus comprising nine aspartic acid residues. It has been reported that lunasin is a novel cancer-preventive soy peptide with efficacy against chemical carcinogens and oncogens, as demonstrated in mammalian cells and in a mouse skin cancer model [B. O. de Lumen, *Nutrition Rev.* **2005**, *83*, 16].

Lunatusin, an antifungal peptide ($M_r \sim 7$ kDa) isolated from the seeds of Chinese lima bean (*Phaseolus lunatus* L.). The trypsin-stable peptide exerted an antifungal activity towards various fungal species, and also inhibited proliferation in the breast cancer cell line MCF-7 [J. H. Wong, T. B. Ng, *Peptides* **2005**, *26*, 2086].

Lung surfactant protein C, *lung surfactant-associated protein C*, **SP-C**, FGIPC^{*}C^{*}PVHL¹⁰KRLIVVVVV²⁰VLVVVVIVGA³⁰LLMGL (C^{*} is S-palmitoylated), a 35-lipopeptide with two palmitoylated cysteine residues in the N-terminal part. SP-C constitutes about 1% of the lung surfactant mass, and is expressed by only one cell type in the body, the alveolar type II epithelial cell of the lung. Human SP-C is synthesized as a 197 aa proSP-C. Two-thirds of the 35-peptide resides in the transmembrane domain, whereas the remaining N-terminal portion is located in the cytosol. The very hydrophobic SP-C is the smallest of the surfactant proteins. The hydrophobic properties are based on 28 aliphatic residues and two additional fatty

acyl chains. The poly-valine part forms an α -helix which perfectly matches the size of a fluid bilayer. It has been reported that, in agreement with the predicted β -strand conformation of a poly-valine segment, helical SP-C unfolds and transforms into β -sheet aggregates and amyloid fibrils within a few days in aqueous organic solvents. SP-C fibril formation and aggregation have been associated with lung disease [J. Johansson et al., *Biochemistry* **1994**, *33*, 6015; J. Perez-Gil, K. M. Keough, *Biochim. Biophys. Acta* **1998**, *1408*, 303; J. Johansson et al., *Cell. Mol. Life Sci.* **2004**, *61*, 326].

Luteinizing hormone, → lutropin.

Luteinizing hormone-releasing hormone, → gonadoliberin.

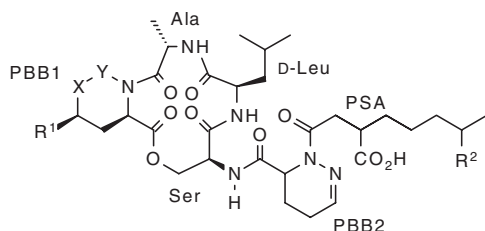
Luteotropin, → prolactin.

Lutropin, *luteinizing hormone*, **LH**, a heterodimeric glycoprotein that belongs to the mammalian → gonadotropins. Human LH ($M_r \sim 23$ kDa) consists of an α subunit (96 aa), which is identical with those of → follitropin (FSH), → thyrotropin, → chorionic gonadotropin, and a β -chain (121 aa). The secretion of LH is regulated by → gonadoliberin. Together with FSH, LH stimulates growth, the synthesis of sex hormones, and spermatogenesis [N. B. Schwartz, *Can. J. Physiol. Pharmacol.* **1995**, *73*, 675].

LVP, lysine vasopressin.

LWamide, → metamorphosin.

Lydiamycins, cyclodepsipeptides (→depsipeptides) isolated from the fermentation broth of *Streptomyces lydicus* (strain HKI0343). Lydiamycins A–C contain Ala, Leu, Ser, piperazic acid building block 1 (PBB1), dehydropiperazic acid building block 2 (PBB2), and 2-pentylsuccinic



	R ¹	R ²	-X-Y-
Lydiamycin A	H	H	-CH ₂ -NH-
Lydiamycin B	OH	H	-CH ₂ -NH-
Lydiamycin C	H	H	-CH=NH-
Lydiamycin D	H	OH	-CH ₂ -NH-

Lydiamycins

acid (PSA). They exhibit antimycobacterial properties. [X. Huang et al., *Angew. Chem. Int. Ed.* **2006**, 45, 3067].

Lymphokines, → interleukins.

Lymphotactin, → chemokines.

Lynbyabellins, 18-membered cyclodepsipeptides (→ depsipeptides) isolated from the marine cyanobacterium *Lyngbya majuscula*. The characteristic structural features of lynbyabellin A and B are their thiazole and thiazoline units. Lyngbyabellin A shows moderate cytotoxicity against human nasopharyngeal KB cells and human colon adenocarcinoma LoVo cells. Lyngbyabellin B exhibits toxicity to brine shrimp, and activity against *Candida albicans* [H. Luesch et al., *J. Nat. Prod.* **2000**, 63, 611; K. Milligan et al., *J. Nat. Prod.* **2000**, 63, 1440].

Lys, lysine.

Lysine (Lys, K), α,ϵ -diaminocaproic acid, H₂N-(CH₂)₄-CH(NH₂)-COOH, C₆H₁₄N₂O₂, M_r 146.19 Da, a proteinogenic amino acid.

Lysobactin, *katanosin B*, a cyclodepsipeptide isolated both from bacteria (*Lysobacter* sp.) and from a strain related to the genus *Cytophaga*. It has excellent *in-vitro* activity against a wide range of Gram-positive bacteria which are associated with life-threatening infections, including multiresistant variants such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The structure and total synthesis has been described [F. Sarabia et al., *Curr. Med. Chem.* **2004**, 11, 1309; F. von Nussbaum et al., *Angew. Chem. Int. Ed.* **2007**, 46, 2039].

M

MA, mixed anhydride.

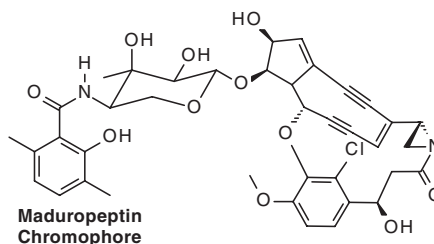
Mab, monoclonal antibody.

α_2 -Macroglobulin, α_2 -antiplasmin, a glycoprotein of the α_2 -globulin fraction acting as an endogenous inhibitor of mechanistically different proteases. α_2 -Macroglobulin consists of four identical subunits ($M_r \sim 720$ kDa). It binds tightly to a number of proteases such as \rightarrow plasmin, \rightarrow thrombin and chymotrypsin but, unlike other protease inhibitors, it does not block the active sites of the enzymes. For example, α_2 -macroglobulin forms an irreversible equimolar complex with plasmin that prevents it from binding to \rightarrow fibrin. Generally, the interaction of α_2 -macroglobulin with the appropriate proteases results in the formation of receptor recognition regions on α_2 -macroglobulin which allow the binding of the α_2 -macroglobulin-protease complex on various cells, especially on macrophages for elimination from the plasma. In humans, the average plasma concentration of α_2 -macroglobulin is 220–380 mg per 100 mL. The human α_2 -macroglobulin receptor has been purified and characterized, and contains high-affinity calcium binding sites that are important for receptor conformation and ligand recognition. It has been reported that α_2 -macroglobulin is genetically associated with \rightarrow Alzheimer's disease, based on its ability to mediate the clearance and degradation of A β , the major component of \rightarrow amyloid- β deposits [S. K. Moestrup et al., *J. Biol. Chem.* **1990**, 265, 12623; D. Blaker

et al., *Nature Genet.* **1998**, 19, 357; Z. Qiu et al., *J. Neurochem.* **1999**, 73, 1393].

Macrophage (CSF), \rightarrow colony-stimulating factors.

Maduropeptin (MDP), an antitumor-acting chromoprotein isolated from the culture medium of *Actinomadura madurae*. Maduropeptin consists of an endiin-containing chromophore and an acidic stabilizing protein ($M_r \sim 32$ kDa). The chromophore forms a labile 9-membered endiin ring without any homology to those of similar endiin-containing chromoproteins such as \rightarrow neocarzinostatin, macromomycin, or kedarcidin. The maduropeptin chromophore shows antibacterial and cytotoxic activities itself. MDP exhibits potent inhibitory activity against Gram-positive bacteria and tumor cells and strong *in-vivo* antitumor activity in P388 leukemia and B16 melanoma-implanted mice. It cleaves dsDNA *in vitro* at specific biologically critically DNA sequences, whereas the protease-like apoprotein stabilizes and solubilizes the chromophore. Furthermore, maduropeptin catalyzes *in vitro* the degradation of histones to low-molecular-weight peptides [M. Hanada



et al., *J. Antibiot. (Tokyo)* **1991**, 44, 403; N. Zein et al., *Biochemistry* **1995**, 34, 11591; A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, 39, 2103].

Magainins, a class of → antimicrobial peptides synthesized in the skin glands of frogs and other amphibians. They are active *in vitro* against a variety of bacteria, fungi, and protozoa. These amphibian-derived peptides are characterized by helical, amphiphilic structure resulting in high membrane affinity. Magainins with 20 to 25 residues are shorter than → cecropins, but share the overall features of charge distribution, helicity and amphiphilic properties. The 23-peptides *magainin 1*, GIGK FLHSAG¹⁰KFGKAFVGEI²⁰MKS, and *magainin 2*, [Lys¹⁰,Asn²²]magainin 1, from the South African clawed frog (*Xenopus laevis*) and other magainins are α-helical ionophores which dissipate ion gradients in membranes, causing lysis. Magainins 1 and 2 interact strongly with phospholipids, such as phosphatidylglycerol, but not with zwitterionic phospholipids, for example, yolk phosphatidylcholine. Furthermore, they interact with Gram-negative bacterial lipopolysaccharide (LPS) and lipid A. It has been reported that magainin 2 binds to the heteropolysaccharide portion of the LPS molecule. Magainin 2 and its synthetic analogues are able to rapidly and irreversibly lyse hematopoietic and solid tumor cells with a relative cytotoxic potency that parallels their antibacterial efficacy and at concentrations which are relatively non-toxic to well-differentiated cells. *MSI-78*, GIGKFLK KAK¹⁰KFGKAFVKIL²⁰KKa, a synthetic analogue based on the magainin consensus sequence, has been developed as a drug for the topical treatment of Gram-positive infections. Another analogue, termed *pexiganan acetate*, has obtained approval for the treatment of diabetic

foot ulcers [M. Zasloff, *Proc. Natl. Acad. Sci. USA* **1987**, 84, 5449; R. A. Cruciani et al., *Proc. Natl. Acad. Sci. USA* **1991**, 88, 3791; D. Hirsh et al., *Biochemistry* **1996**, 35, 12733; A. J. De Lucca et al., *Ann. Agric. Environ. Med.* **1996**, 3, 37].

Mahogany, a single-pass transmembrane protein that modulates the activity of → agouti protein and → agouti-related protein (AGRP). It is an ancillary protein of the → melanocortin system. Mahogany is expressed primarily in the brain, especially in the hypothalamus, and in the skin. It is involved in mammalian coat coloration [T. M. Gunn et al., *Nature* **1999**, 398, 152].

Maillard reaction, a reaction of the carbonyl group of reducing oligosaccharides with the amino group of amino acids or amines. The primarily formed N-substituted glycosylamine is converted to a Schiff base. Subsequent cyclization and Amadori rearrangement yields the typical derivative which causes discoloration of the formulation. The brown color developed in many foods during storage is due to products of the Maillard reaction [M. J. Hageman, *Drug. Dev. Ind. Pharm.* **1988**, 14, 2047].

Major proglucagon fragment (MPCGF), → glucagon.

Mal, maleoyl.

MALDI-MS, matrix-assisted laser desorption/ionization mass spectroscopy.

MALDI-ToF, matrix-assisted laser desorption/ionization time-of-flight.

Malformins, heterodetic cyclic pentapeptides with antibiotic and cytotoxic action. *Malformin A₁*, cyclo-(D-Cys-D-Cys-Val-D-Leu-Xaa-) (disulfide bond: D-Cys¹-D-Cys²; Xaa = Ile), is produced by *Aspergillus niger*. Further members of this group are *malformin B₁* (Xaa = alle), *malformin B₂* (Xaa

= Val), and *malformin C* (Xaa = Leu). Malformins cause malformation of the roots of cereals and other higher plants [M. Bodanszky, G. L. Stahl, *Proc. Natl. Acad. Sci. USA* **1974**, *71*, 2791; J. M. Herbert et al., *Biochem. Pharmacol.* **1994**, *48*, 1211].

Mammalian tachykinins, a family of \rightarrow tachykinin peptides traditionally classified as neurotransmitters that include \rightarrow substance P (SP), \rightarrow neurokinins (NKA and NKB), two elongated versions of NKA, \rightarrow neuropeptide γ (NP γ) and \rightarrow neuropeptide K (NPK), \rightarrow hemokinin 1 (HK-1) and \rightarrow endokinins A–D. They act as neurotransmitters, paracrine or endocrine factors, neuroimmunomodulators, and have also immune and pro-inflammatory actions. Furthermore, mammalian tachykinins are involved in vasodilation, plasma extravasation, smooth muscle contraction, secretion, neural excitation, and processing of sensory information. The biological actions are mediated via three known mammalian tachykinin receptors, NK₁, NK₂, and NK₃ [N. M. Page et al., *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 6245; N. M. Page, *Peptides* **2005**, *26*, 1356; L. Liu, E. Burcher, *Peptides* **2005**, *26*, 1369].

Mammothropin, \rightarrow prolactin.

Mannopectimycins, cyclic glycopeptide antibiotics produced by *Streptomyces hygroscopicus* LL-AC98. Mannopectimycins α and β lacking isovaleryl substitution and the disaccharide moiety, respectively, had only poor antibacterial activity, in contrast to the peptides γ , δ , and ϵ , among which the member ϵ was the most active component against methicillin-resistant staphylococci and vancomycin-resistant enterococci [M. P. Singh et al., *Antimicrob. Agents Chemother.* **2003**, *47*, 62].

Maspin, a protein (375 aa; M_r ~42 kDa) with N-terminal methionine, C-terminal

valine and eight cysteines. It is a member of the \rightarrow serpins. The cDNA of maspin was isolated from a normal human mammary epithelial cell library. In invasive breast carcinomas, the gene of maspin is down-regulated. Maspin is located in the cell membrane and extracellular matrix, and has been shown to have tumor suppressor activity. It does not behave as a classical inhibitory serpin against any known target protease. It has been suggested that the tumor suppressor activity of maspin may depend in large part on its ability to inhibit angiogenesis; this raises the possibility that maspin may be an excellent lead for the development of drugs that modulate angiogenesis [Z. Zou et al., *Science* **1994**, *263*, 526; M. Zhang et al., *Nature Med.* **2000**, *6*, 196].

Mast cell degranulating peptide (MCDP), IKCNCKRHVI¹⁰KPHICRKICG²⁰KNa (disulfide bonds: C³–C¹⁵/C⁵–C¹⁹), a cationic 22-peptide amide. MCDP is a component of the bee venom which contains several biologically active non-peptide substances, as well as two more major peptides, the hemolytic peptide \rightarrow melittin, the neurotoxic peptide \rightarrow apamin, together with a number of minor peptides. Like apamin, MCDP blocks Ca²⁺-dependent K⁺ channels in neurons. MCDP causes mast cell degranulation and histamine release at low concentrations, and has anti-inflammatory activity at higher concentrations [E. M. Dotimas et al., *Biochim. Biophys. Acta* **1987**, *911*, 285; W. E. Steinmetz et al., *Peptide Res.* **1994**, *7*, 77; A. Buku, *Peptides* **1999**, *20*, 415].

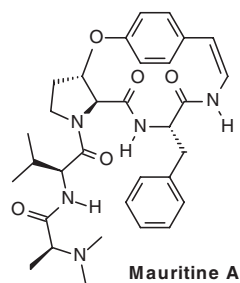
Mastoparan, INLKALAALA¹⁰KKILa, a 14-peptide amide found in the venom of wasps. Mastoparan degranulates mast cells and induces the release of catecholamines and serotonin from adrenal chromaffin cells or platelets. *Mastoparan C*, [Leu^{1,7},Val⁹]mastoparan, and crabolin

are constituents of the venom of European hornets. Like \rightarrow mellitin, mastoparan shows hemolytic activity, and forms artificial ion channels in guest cell membranes. *Eumenine mastoparan-AF*, EMP-AF, INLL KIAKGI¹⁰IKSLa, was isolated from the venom of the solitary wasp *Anterhynchium flavomarginatum micado*, the most common eumenine wasp found in Japan. Besides the degranulation and hemolytic activity, EMP-AF also affects neuromuscular transmission in the lobster walking leg preparation [Y. Hirai et al., *Chem. Pharm. Bull. (Tokyo)* **1979**, 27, 1942; A. Argiolas, J. J. Pisano, *J. Biol. Chem.* **1984**, 259, 10106; C. Hider, *Endeavour, New Series* **1988**, 12, 60; K. Konno et al., *Toxicon* **2000**, 38, 1505].

Matrix Gla protein (MGP), a γ -carboxyglutamic acid(Gla)-containing protein belonging to the family of extracellular mineral-binding proteins, expressed in several tissues with high accumulation in bone and cartilage. Besides \rightarrow osteocalcin, also named *bone Gla protein (BGP)*, bovine MGP (79 aa) was the second Gla-containing protein in bone, and contains 80% of the Gla occurring in bone. Human MGP (84 aa; $M_r \sim 10.5$ kDa) is a vitamin K-dependent extracellular matrix protein that binds Ca^{2+} ions and is involved in the prevention of vascular calcification. It contains five Gla residues and a disulfide bond ($\text{C}^{54}-\text{C}^{60}$). The total chemical synthesis of hMGP was described in 2001 [P. A. Price et al., *Biochem. Biophys. Res. Commun.* **1983**, 117, 765; T. M. Hackeng et al., *Protein Sci.* **2001**, 10, 864].

Mauritines, Mauritines A–F, cyclopeptide alkaloids isolated from the root bark of the African trees *Ziziphus mauritiana* Lam. The mauritines A–F are active against the Gram-positive bacterium *Bacillus subtilis*. The structure of mauritine A was determined by X-ray crystal analysis. The first total synthesis of mauritine A was per-

formed using cycloetherification methodology in 2000, followed by total synthesis of all members of the mauritines in 2005 [R. Tschesche et al., *Tetrahedron Lett.* **1972**, 13, 2609; T. Laib et al., *Tetrahedron Lett.* **2000**, 41, 7645; P. Cristau et al., *Chem. Eur. J.* **2005**, 11, 2668].



Max Bergmann-Kreis, an association of peptide chemists from German-speaking countries. Since 1980, annual meetings have been held that are subject to a confidentiality agreement signed by all who attend. The encouragement of research in peptide chemistry is the most important aim of this association. Peptide chemistry is also promoted through two awards, the *Max Bergmann Gold Medal* for distinguished contributions to the field, and the *Friedrich Weygand Prize* for excellent PhD theses or postdoctoral work.

Maximins, antimicrobial peptides from the skin secretions of Chinese red belly toad *Bombina maxima*. Peptides of the first group *maximins 1–5* (maximin 1: GIGTK ILGGV¹⁰KTALKGALKE²⁰LASTYANa) are 27-peptides structurally related to \rightarrow bombinin-like peptides. Besides their antimicrobial activity, they show cytotoxicity against tumor cells, and also spermicidal action. In addition, maximin 3 possesses anti-HIV activity. The second group comprises *maximins H1–H3* (maximin H1: ILGPVISTIG¹⁰GVLGGLLKNLa²⁰) which

are homologous to bombinin H peptides. *Maximins* S peptides are deduced by random sequencing from a constructed *Bombina maxima* skin cDNA library, and can be grouped into maximin S1 (14 aa) and maximin S2–S5 peptides, all of which have 18 aa. *Maximin* 9, GIGRKF LGGV¹⁰KTTFRCGVKD²⁰FASKHLYa, contains a free Cys¹⁶ which seems to be important for its antimycoplasma activity [R. Lai et al., *Peptides* **2002**, 23, 427; T. Wang et al., *Biochem. Biophys. Res. Commun.* **2005**, 327, 945; W.-H. Lee et al., *FEBS Lett.* **2005**, 579, 4443].

MBHA resin, 4-methoxybenzhydramine resin, a solid support for the synthesis of C-terminal peptide amides using Boc/Bzl chemistry [G. R. Matsueda, J. M. Stewart, *Peptides* **1981**, 2, 45].

MBP, maltose-binding protein.

Mbs, 4-methoxybenzenesulfonyl.

MCDP, mast cell degranulating peptide.

MCH, melanin-concentrating hormone.

MD, molecular dynamics.

MDP, maduropeptin.

Me, methyl.

Melanin-concentrating hormone (MCH), DFDMLRCMLG¹⁰RVYRPCWQV (hMCH; disulfide bond: C⁷–C¹⁶), a cyclic 19-peptide from the mammalian hypothalamus. MCH was originally isolated from salmon pituitary glands (DTMRCMVGRV¹⁰YRPCWEV, disulfide bond: C⁵–C¹⁴). In lower vertebrates, salmon MCH alters pigmentation by inducing the aggregation of melanin granules in melanophores. The sequence of hMCH was found to be the same as that of the rat and mouse peptide. The physiological role of MCH in

higher vertebrates has not been fully elucidated, but it may act as a neuromodulator and hypophysiotropic agent in the secretion of → corticotropin, → growth hormone, and α-MSH (→ melanotropin). There is evidence that the hypothalamic MCH is involved in feeding behavior and also regulates the stress axis and emotion. Transgenic mouse models and pharmaceutical studies have indicated that MCH signaling is a potential target for treatment of obesity, metabolic syndrome, anxiety, and depression. The first MCH receptor was reported to be an orphan G protein-coupled receptor (MCH-R1), while in 2001 a second human MCH receptor (MCH-R2) was identified by *in-silico* data mining in the human genome. Both receptors share only 36% sequence homology, which indicates only a remote evolutionary relationship. The cyclic peptide fragment hMCH (7–16) is necessary, but not sufficient, for maximum activity. The flanking residues Arg⁶ and Trp¹⁷ are required for agonist potency. Especially, Met⁸, Arg¹¹, and Tyr¹³ contribute to potent response in receptor binding and functional studies. Exchange of Arg⁶, Leu⁹, Gly¹⁰, or Gln¹⁸ may generate peptides with decreased receptor affinity and efficacy towards MCH-R2 [H. Kawauchi et al., *Nature* **1983**, 305, 321; J. M. Vaughan et al., *Endocrinology* **1989**, 125, 1660; D. Qu et al., *Nature* **1996**, 380, 243; J. Chambers et al., *Nature* **1999**, 400, 261; A. W. Sailer et al., *Proc. Natl. Acad. Sci. USA* **2001**, 98, 7564; A. N. Eberle, *Peptides* **2004**, 25, 1585; T. Shimazaki, *CNS Drugs* **2006**, 20, 801].

Melanocortin peptides, *melanocortins*, *melanocyte-stimulating hormone*, **MSH**, *melanotropin*, a peptide hormone produced in the pars intermedia of the hypophysis under the control of → melanoliberin and → melanostatin. Species lacking the

pars intermedia (e.g., chicken, whale, porpoise) produce it in the neurohypophysis. Furthermore, MSH is formed by neurons of the central nervous system. Three different MSH sequences are parts of the biosynthetic precursor protein → proopiomelanocortin (POMC), and are released during the processing of POMC in the intermediate lobe. All three peptides have been highly conserved during evolution, but their exact biological function in mammals is still largely obscure. They contain the melanocortin core sequence MEHFRW (in γ -MSH E is substituted by G) that is necessary for the biological actions. α -MSH, Ac-SYSMEHFRWG¹⁰KPVa (rat), is the most potent naturally occurring melanocortin peptide. The biological actions are mediated via → melanocortin receptors. α -MSH exerts pleiotrophic functions, including the modulation of a wide range of inflammatory stimuli; this would be consistent with a cytoprotective role for this hormone in protecting skin cells from exogenous stress, as would occur following UV exposure or exposure to agents inducing inflammation or oxidative stress. α -MSH also modulates both cutaneous and uveal melanoma cell behavior. It has the potential to retard metastatic spread by reducing cell migration and invasion, and is also capable of reducing the ability of the immune system to detect tumor cells by down-regulating adhesion molecules that would normally assist in immune cell interaction with melanoma cells. The acetyl group is important for melanotropic activity. Furthermore, α -MSH shows central effects on memory and thermal regulation. In frogs and certain lizards, the release of α -MSH from the pars intermedia of the pituitary causes a dark-colored background which results in the dispersion of melanin granula in the melanophores. The linear analogue [Nle⁴,D-Phe⁷] α -MSH has greatly

increased potency and prolonged duration of activity in various bioassays. For example, it causes increased pigmentation in the yellow mouse after reabsorption through the skin. Further research has been directed towards analogues with potential clinical use in the treatment of pigmentary disorders and melanoma. Superpotent analogues of α -MSH have been described, for example, *melanotan I* (MTI), Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH₂, and *melanotan II* (MTII), Ac-Nle-c[Asp,His,D-Phe,Arg,Trp,Lys]-NH₂, which have been tested clinically for investigations on tanning of the skin (MTI) and for the diagnosis and treatment of male erectile dysfunction (MTII). Human β -MSH is an 18-peptide, DEGPYRMEHF¹⁰RWGSPPKD, which shows the same biological activity as α -MSH in the Anolis skin test, but β -MSH from other species has lower activity. Rat β -MSH differs from human β -MSH in four positions (Ala¹, Asp², Val⁷, Asn¹⁴). Various species contain two different β -MSH peptides. The same is true for a third MSH peptide found in the N-terminal part of POMC. Three different species of γ -MSH generally described: γ_1 -MSH, YVMGHFRWDR¹⁰Fa (rat), γ_2 -MSH, TVMGHFRWER¹⁰FG (rat), γ_3 -MSH, YVMGHFRWDR¹⁰FGPRNSSSAG²⁰GSAQ (rat), and [Lys]- γ_3 -MSH (rat). γ_3 -MSH contains the sequence up to the next dibasic site at the N-terminus of the joining peptide [J. I. Harris, A. B. Lerner, *Nature* **1957**, 179, 1346; A. Eberle, *Melanotropins: Chemistry, Physiology and Mechanisms*, Karger, Basel, **1988**; V. J. Hruby et al., *Ann. N. Y. Acad. Sci.* **1993**, 680, 51; I. Gantz, T. M. Fong, *Am. J. Physiol. Endocrinol. Metab.* **2003**, 284, E468; S. C. Harmer, A. B. Bicknell, *Peptides* **2005**, 26, 1944; P. C. Eves et al., *Peptides* **2006**, 27, 444; M. E. Hadley, R. T. Dorris, *Peptides* **2006**, 27, 921].

Melanocortin receptors (MCR), G protein-coupled receptors preferentially linked to cAMP generation through the stimulatory G protein G_s and adenylate cyclase. To date, five melanocortin receptors (MC1R–MC5R) have been identified and cloned. MC1R is expressed by cutaneous melanocytes, where it has a dominant function in determining skin and hair pigmentation by \rightarrow melanocortin peptides, especially by α -MSH. However, MC1R is also found in other cell types in the skin such as keratinocytes, fibroblasts, endothelial cells, and antigen-presenting cells. MC1R is also expressed in leukocytes, where it mediates the anti-inflammatory and immunomodulatory properties of the melanocortins. MC2R is the classical adrenocortical ACTH receptor (\rightarrow corticotropin), and is only activated by ACTH. It has no affinity to α -, β - and γ -MSH. MC3R is found in many areas of the CNS, and also in several peripheral tissues such as gastrointestinal tract, placenta, and kidney. All of the melanocortin peptides are practically equipotent at MC3R, although γ -MSH shows the greatest affinity at this receptor. MC4R occurs predominantly in the CNS, but it has been reported that MC4R is also involved in sexual function and feeding behavior. MC5R is expressed in low levels in a wide variety of tissues such as adrenal gland, adipocytes, leukocytes, and many others. Its distribution in the CNS is very limited. Interestingly, \rightarrow agouti protein and \rightarrow agouti-related protein are endogenous antagonists of the melanocortin peptides with marked MCR subtype specificity [K. G. Mountjoy et al., *Science* **1992**, 257, 1248; J. E. Wikberg et al., *Pharmacol. Res.* **2000**, 42, 393].

Melanocortin system (MCS), a complex physiological system involved in pigmentation, inflammation, steroidogenesis, en-

ergy homeostasis, analgesia, immunomodulation, temperature control, cardiovascular regulation, neuromuscular regeneration, and sexual function. MCS consists of: (i) the \rightarrow melanocortin peptides α -, β - and γ -melanocyte-stimulating hormone (α -, β -, γ -MSH) and \rightarrow corticotropin (ACTH); (ii) a family of five \rightarrow melanocortin receptors; and (iii) the endogenous melanocortin antagonists \rightarrow agouti protein and \rightarrow agouti-related protein (AGRP). Additionally, two ancillary proteins, \rightarrow mahogany and \rightarrow syndecan-3, have been discovered which modulate the activity of the melanocortin peptides [J. E. Wikberg et al., *Pharmacol. Res.* **2000**, 42, 393; I. Gantz, T. M. Fong, *Am. J. Physiol. Metab.* **2003**, 284, E468].

Melanocyte-stimulating hormone, \rightarrow melanocortin peptides.

Melanoliberein, *melanotropin-releasing hormone*, **MRH**, *melanotropin-releasing factor*, **MRF**, a hypothalamic peptide stimulating the release of melanocyte-stimulating hormone (\rightarrow melanocortin peptides). The hexapeptide fragment of \rightarrow oxytocin, H-Cys-Tyr-Ile-Gln-Asn-Cys-OH, has been suggested for MRH.

Melanostatin, *melanotropin release-inhibiting hormone*, **MRIH** or **MIH**, *melanotropin release-inhibiting factor*, **MIF**, a hypothalamic peptide inhibiting the release of melanocyte-stimulating hormone (\rightarrow melanocortin peptides). The C-terminal tripeptide amide, H-Pro-Leu-Gly-NH₂, of \rightarrow oxytocin has been suggested as a structural proposal for melanostatin. Melanostatin inhibits the release of α -MSH in the hypophysis. The analogue [N-Me-D-Leu²]MRIH, named *pareptide*, increases the L-DOPA-induced behavior pattern. It shows antidepressant activity and has been used for the treatment of Parkinson's disease.

Melanotan, melanotan I and II, → melanocortin peptides.

Melanotropin, → melanocortin peptides.

Mellitin, GIGAVLKVL^T¹⁰TGLPALISW^I²⁰KRK^RQ^Q, a 26-peptide amide which comprises about 50% of the dried bee venom. It is synthesized as part of the 70 aa prepro-mellitin. Removal of the signal sequence (21 aa) provides pro-mellitin. The enzymatic release from the precursor occurs outside the venom gland cells. The hemolytic and surface tension-decreasing activities of mellitin are based on the distribution of hydrophobic residues in the *N*-terminal part, and the hydrophilic residues in the *C*-terminal part. The resulting tenside character is probably a prerequisite for the pharmacological and biochemical action [R. C. Hider, *Endeavour New Series* **1988**, 12, 60].

MeO, methoxy.

Merrifield resin, → chloromethyl resin.

Merrifield, R. Bruce (1921–2006), American biochemist and winner of the Nobel Prize in Chemistry 1984 for his development of an ingenious new method for synthesizing peptides (→ solid-phase peptide synthesis) and other biopolymers. This methodology revolutionized biochemical research and stimulated progress in molecular biology, medicine and pharmacology. The Merrifield synthesis has had a significant impact in various areas beyond peptide chemistry, including the synthesis of oligonucleotides, solid-phase organic synthesis, and combinatorial chemistry. Bruce Merrifield graduated from the University of California at Los Angeles in 1943, and received his Ph.D. in biochemistry in 1949. In the same year he joined the staff of the Rockefeller Institute for Medical Research (now Rockefeller

University). In 1957, Merrifield became an assistant professor and in 1966 was appointed to the chair of biochemistry, a position which he held until his retirement in 1992. He was named John D. Rockefeller Jr. Professor in 1983 [B. Merrifield, *Bruce Merrifield: Life During a Golden Age of Peptide Chemistry: The Concept and Development of Solid-Phase Peptide Synthesis*, Oxford University Press, **1993**; T. K. Sayer, *Chem. Biol. Drug Design* **2006**, 67, 383].

Merrifield synthesis, an alternative name for → solid-phase peptide synthesis (SPPS) in honor of the inventor of this ingenious concept [R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, 85, 2149].

Merrifield tactics, → Boc/Bzl-protecting chemistry scheme used in → solid-phase peptide synthesis (SPPS).

Mes, mesityl.

Met, methionine.

Metallacyclopeptides, artificial analogues of naturally occurring peptides with the potential for application in medicinal chemistry. Metal coordination of two suitable ligands in a peptide structure is the requirement for the formation of metallamacrocycles. Different metal ligand units can be attached to peptides. The addition of an appropriate metal ion can lead to the formation of a metallacyclopeptide which is characterized by the fixation of a special conformation. Random coil peptides can be rigidified by complex formation, and secondary structures – including α -helices or β -sheets – can also be stabilized. General approaches towards metallacyclopeptides as metal-stabilized cyclopeptide mimetics, or as part of larger secondary structures, have been described which may contribute to the design and synthesis of artificial

proteins in the future [M. Albrecht, P. Stortz, *Chem. Soc. Rev.* **2005**, 34, 496].

Metallopeptidases, a family of \rightarrow peptidases. The peptide bond to be cleaved is mediated by a water molecule which is activated by a divalent metal cation, usually Zn^{2+} but sometimes Co^{2+} or Mg^{2+} . In order to assist the attack of a water molecule, the metal ion provides a strong electrophilic "pull". The metallopeptidase has a water molecule coordinated to the fourth tetrahedral site. Besides the metal ion the other ligands are two histidine building blocks and a glutamic acid residue, as in thermolysin and carboxypeptidase A. The metallopeptidases can be divided in two groups, depending on the number of metal ions necessary for catalysis. In many cases only one zinc ion is required, but often two metal ions act co-catalytically. All the enzymes which contain cobalt or manganese require two metal ions, but zinc-dependent enzymes are also known in which two zinc ions act in a co-catalytic manner. Currently, it is known that enzymes containing co-catalytic metal ions are exopeptidases, whereas those with one catalytic metal ion belong to the exopeptidases or endopeptidases. His, Glu, Asp or Lys are known metal ligands in metallopeptidases. Together with the metal ligand, a Glu residue is very often engaged in the catalytic process. In the leucyl aminopeptidase, Lys or Arg fulfill this function.

Metalloproteins, proteins with bound metal ions. To this family of transport and storage proteins belong, e.g., \rightarrow ferritin, \rightarrow transferrin, \rightarrow iron-sulfur proteins, \rightarrow metallothioneins [D. P. Ballou, *Metalloproteins*, Princeton University Press, **1999**; A. Messerschmidt et al. (Eds.), *Handbook of Metalloproteins*, Vols. 1–4, John Wiley & Sons, **2001–2004**].

Metallothioneins (MT), highly conserved metal ion-binding proteins. The name MT was first used in 1957 to describe a protein from equine cortex containing large amounts of sulfur and cadmium. Until now, structurally related proteins have been identified in diverse organisms, mostly associated with Zn^{2+} and Cu^+ (or Cd^{2+} if Cd^{2+} -intoxicated). MT sequester excess amounts of certain metal ions, varying for the structurally distinct polypeptides and proteins in all vertebrates, invertebrates, and fungi. Functions in the regulation of gene expression have been proposed for some MT, especially those in higher eukaryotes with Zn^{2+} . Animal MT genes respond to endogenous factors, including a variety of hormones, second messengers, cytokines and growth factors, in addition to trace-metal levels. *Class III metallothioneins* are characterized by the presence of poly(γ -glutamyl-cysteinyl)glycine (found in Cd^{2+} -intoxicated plant cells) or other γ -glutamyl isopeptides in which Gly is either absent or substituted with β -alanine; these compounds were first termed cadystins. Mammalian MT are composed of ~ 61 aa with a high content of Cys (20–35%) which coordinate seven divalent metal ions (or 12 monovalent ions such as Cu^+) in two distinct metal clusters. They contain no aromatic amino acids, and the locations of the Cys residues are invariant. Proteins from any phyla with such a primary structure are designated *class I metallothioneins*. Low- M_r Cys-rich metal-binding proteins with a Cys residue distribution different to that in mammalian MT are termed *class II metallothioneins* [J. H. R. Kägi, *Methods Enzymol.* **1991**, 205, 613; K. Wüthrich, *Methods Enzymol.* **1991**, 205, 502; N. J. Robinson et al., *Biochem. J.* **1993**, 295, 1; R. D. Palmiter, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 8428].

α -Methylphenacyl resin, a photolabile polymeric support suitable for solid-phase synthesis of protected segments, but only compatible with the Boc/Bzl approach [S. S. Wang, *J. Org. Chem.* **1976**, 41, 3258].

Metorphamide, *adrenorphin*, H-Tyr-Gly-Gly-Phe-Met-Arg-Arg-Val-NH₂, an 8-peptide amide found in bovine brain and adrenal tissue. The sequence of metorphamide corresponds to bovine pro-enkephalin precursor-(206–213). Furthermore, metorphamide is similar in sequence to bovine adrenal medulla peptides. It shows high affinity to λ opioid receptors [H. Matsuo et al., *Nature* **1983**, 305, 721; M. Sonders, E. Weber, *J. Neurochem.* **1987**, 49, 671].

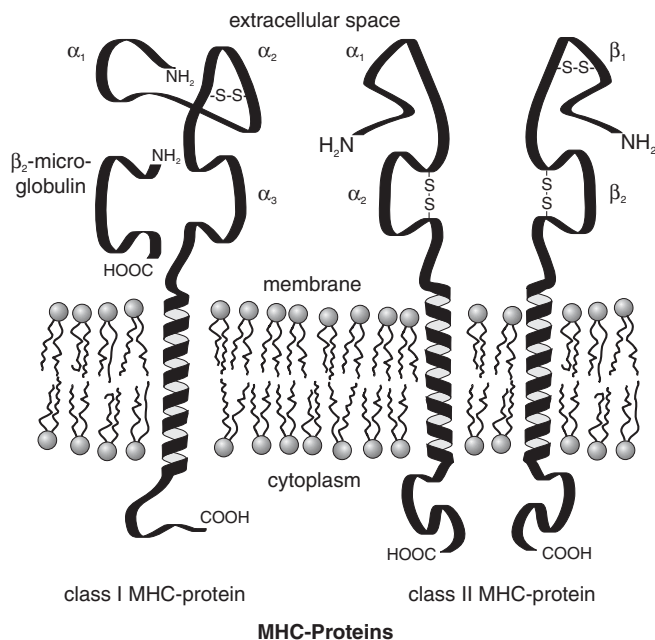
MGP, matrix Gla protein.

MHC, major histocompatibility complex.

MHC molecules, \rightarrow MHC proteins.

MHC proteins, *MHC molecules*, surface glycoproteins strongly associated with either self or foreign peptides. They are membrane-bound proteins encoded by the major histocompatibility complex (MHC; *histo* refers to tissue). With the *Class I MHC proteins* and the *Class II MHC proteins*, two principal classes of MHC molecules were recognized long before the native function was understood. They act as antigen-presenting markers by which the immune system is able to distinguish body cells from invading antigens (Class I MHC proteins), and immune system cells from other cells (Class II MHC proteins). They are integral membrane glycoproteins with the biological function to bind, in the endoplasmic reticulum, short peptides that are heterogeneous in size (usually 12- to 26-mers) and result from degraded proteins, and expose them to the cell surface for recognition

by CD4⁺ T-cell receptors. In order to indicate their function in discriminating between “own” and “foreign”, the products of the MHC gene cluster are also termed antigens. *Class I MHC molecules* (~ 350 aa; $M_r \sim 44$ kDa) are folded into five domains: a C-terminal cytoplasmic domain (~ 30 aa), a transmembrane domain (~ 40 aa), and three external domains (~ 90 aa each, designated $\alpha_3, \alpha_2, \alpha_1$). The Class I MHC proteins are also invariably associated (1:1) with an extracellular, non-glycosylated small protein, termed β_2 -microglobulin (β_{2m}) (\rightarrow microglobulins), which does not span the membrane, and is separately encoded by a gene of a different chromosome. The α_3 domain and β_{2m} , the closest located to the membrane, are both homologous to an \rightarrow immunoglobulin domain. *Class II MHC proteins* are heterodimeric transmembrane glycoproteins and consist of an α chain ($M_r \sim 33$ kDa) and a β chain ($M_r \sim 28$ kDa). Each (~ 230 aa) of the two chains forms two conserved immunoglobulin-like domains (α_1, α_2 and β_1, β_2 , respectively). Class I MHC proteins occur on most cells, whereas Class II MHC molecules are found on macrophages and B lymphocytes. The peptide fragments are presented to the T-cell receptor either via a Class I or Class II MHC molecule. As a rule, Class I MHC molecules present peptides to CD8 (predominantly cytotoxic) T cells, and Class II MHC molecules to CD4⁺ (mainly helper) T cells. The genes encoding MHC proteins form a gene superfamily, since they have domains that are structurally similar to those in immunoglobulins and T-cell receptors. Perfusion chromatography is suitable for the very rapid purification of Class I and Class II MHC proteins [P. J. Bjorkman et al., *Nature* **1987**, 329, 512; P. J. Bjorkman, P. Parham, *Annu. Rev. Biochem.* **1990**, 59, 253; L. D. Barber, P. Parham, *Annu. Rev. Cell. Biol.* **1993**, 9, 163; L. J. Stern, D. C.



Wiley, *Structure* **1994**, 2, 245; P. J. Lehner, P. Cresswell, *Curr. Opin. Immunol.* **1996**, 8, 59; P. Malik, P. Strominger, *J. Immunol. Methods* **2000**, 234, 83; I. Stefanova et al., *Nature* **2002**, 420, 429].

Microcins (Mcc), a family of low-molecular-weight antibiotic peptides (<10 kDa) produced by Gram-negative Enterobacteriaceae strains (such as *Escherichia coli*). Mcc are distinguished by their size from protein antibiotics (>20 kDa) → bacteriocins such as colicins, cloacins. The structures of Mcc range from unmodified linear peptides to extensively modified peptides with, e.g., a heterocyclic backbone structure. Mcc are divided into two subgroups: class I Mcc are post-translationally modified (e.g., MccB17, MccJ25, MccD93), while class II are unmodified peptides (MccV, MccE492, MccH47, MccL, Mcc24) and share several common properties with class IIa bacteriocins: absence of modified amino

acids, double-glycine type leader peptides, secretion mediated by ABC transporter, and antibacterial activity at the bacterial cytoplasmic membrane. The structural genes encoding microcins are very similar to → lantibiotics. Mcc are translated as precursor peptides with leader peptide and pro-peptide sequences. The exception is MccC7, which does not possess a leader peptide. Mcc genes are found within gene clusters encoding proteins for the maturation of the Mcc. MccB17 is the best-studied among the more than 20 family members. Oxazole and thiazole rings in MccB17 (M_r 3 kDa; 43 aa) are formed by post-translational modifications of Ser, Cys, and Gly in the precursor peptide. More than two-thirds of the total amino acid residues of MccB17 consist of glycine. The biological actions of Mcc are widely diverse; some Mcc act at the cytoplasmic membrane, leading to depolarization with consequences for microbial energetics, others inhibit enzyme

activities of, e.g., DNA gyrase, RNA polymerase, etc. MccC7 inhibits protein biosynthesis. MccB17 is an inhibitor of DNA gyrases. MccE492 (M_r 6 kDa) is structurally and functionally related to bacteriocins of Gram-positive bacteria, and depolarizes cytoplasmic membranes [R. James, C. Lazdunski, F. Pattus (Eds.), *Bacteriocins, Microcins and Lantibiotics*, Springer, Berlin, Heidelberg, New York, **1992**; G. I. Videnov et al., *Angew Chem. Int. Ed.* **1996**, 35, 1506; Y. M. Li et al., *Science* **1996**, 274, 1188; R. W. Jack, G. Jung, *Curr. Opin. Chem. Biol.* **2000**, 4, 310; A. M. Pons et al., *Biochimie* **2002**, 84, 531].

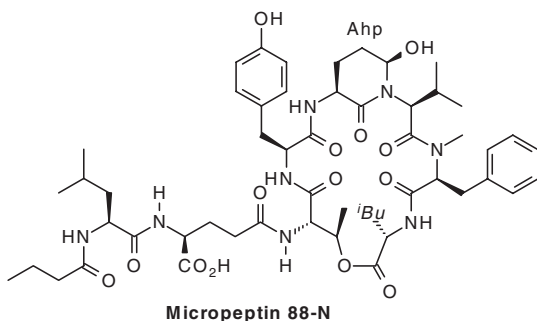
Microcystins, originally described as cyanoginins, a main class of \rightarrow cyanobacterial peptides from the genera *Microcystis*, *Planktothrix*, and *Anabaena*. These cyclic 7-peptides are especially characterized by (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda), dehydroalanine and D-amino acids (D-Glu, D-erythro-2-methyl-isoaspartate, D-Ala), with a high variability in positions 2 and 4. *Nodularins* are cyclic 5-peptides containing an Adda moiety, and show much similarity to microcystins [D. P. Botes et al., *J. Chem. Soc., Perkin Trans.* **1984**, 2311; M. Welker, H. von Döhren, *FEMS Microbial Rev.* **2006**, 30, 530].

Microginins, a main class of \rightarrow cyanobacterial peptides from *Microcystis*, *Planktothrix*, and *Nostoc*. The linear peptides vary in length from four to six amino acids, contain a C-terminal 3-amino-2-hydroxy-decanoic acid moiety (Ahda), and two tyrosine units at the C-terminus. The first member was isolated from the freshwater blue-green alga *Microcystis aeruginosa* (NIES-100), and is an inhibitor of \rightarrow angiotensin-converting enzyme [T. Okino et al., *Tetrahedron Lett.*

1993, 34, 501; M. Welker, H. von Döhren, *FEMS Microbial Rev.* **2006**, 30, 530].

Microglobulins, proteins with low molecular weight belonging to the \rightarrow globulins. α_1 -Microglobulin is a glycoprotein (183 aa) of the blood plasma, with binding affinity to other proteins. It shows sequence homology to \rightarrow β -lactoglobulin and the retinol-binding protein. The non-glycosylated β_2 -microglobulin (99 aa; $M_r \sim 11.8$ kDa) shows similarity to the \rightarrow immunoglobulins. It occurs in association with the lymphocyte antigen CD1. Furthermore, it is a component of immunoglobulin Fc receptors of the gastric epithelia of newborn children. β_2 -Microglobulin is the non-covalently bound light chain component of the major histocompatibility complex I (\rightarrow MHC proteins). Its three-dimensional structure is based on an antiparallel β -barrel fold with immunoglobulin domain topology. β_2 -Microglobulin is involved in the development of DRA (Dialysis-Related Amyloidosis), an amyloid deposition disease occurring in humans [C. Rosano et al., *Biochim. Biophys. Acta* **2005**, 1753, 85].

Micropeptins, cyclodepsipeptides (\rightarrow depsipeptides) isolated from cultures of cyanobacterium *Microcystis aeruginosa*. *Micropeptin* 90, isolated from the cultured freshwater blue-green alga *Microcystis aeruginosa* (NIES-90), inhibits \rightarrow plasmin and trypsin, with IC_{50} s of 0.1 and $2.0 \mu\text{g mL}^{-1}$, respectively, but not papain, chymotrypsin, or elastase. Micropeptin 90 contains the unusual building blocks of 3-amino-6-hydroxy-2-piperidone, and N-methyl-L-tyrosine. The amino group of Thr is acylated with glyceric acid 3-O-sulfate. Further micropeptins are *micropeptin* 103 (from *Microcystis virides* (NIES-103)), 478-A and B and A90720 acting as potent serine protease inhibitors. In



2005, with *micropeptins* 88-N and 88-Y, two new members of 3-amino-6-hydroxy-2-piperidone (Ahp)-containing cyclodepeptides from the cyanobacterium *Microcystis aeruginosa* (NIES-88) acting as chymotrypsin inhibitors were isolated [K. Ishida et al., *Tetrahedron Lett.* **1995**, 36, 3535; M. Namikoshi, K. L. Rinehart, *J. Ind. Microbiol.* **1996**, 17, 373; H. Yamaki et al., *J. Nat. Prod.* **2005**, 68, 14].

Micro reactor, a device consisting of a network of micron-sized channels connected to a series of reservoirs containing chemical reagents and products to form the complete device with overall dimensions of a few centimeters. The miniaturization of chemical reactors offers many fundamental and practical advantages, in particular the environmental benefits. The first example of multi-step peptide synthesis in a micro reactor was described using simple model reactions [P. Watts et al., *Tetrahedron* **2002**, 58, 5427; S. J. Haswell, P. Watts, *Green Chemistry* **2003**, 5, 240].

Microviridins, the largest class of the → cyanobacterial peptides characterized by a tricyclic structure. The main peptide ring consists of seven amino acids with an ester bond between the β-carboxy group of Asp¹⁰ and the hydroxy function of Thr⁴, an

isopeptide bond between Lys⁶ and Glu⁷ and a side chain of variable length. All amino acids are in L-configuration, and the only non-proteinogenic unit is the N-terminal acetyl moiety [M. O. Ishitsuka et al., *J. Am. Chem. Soc.* **1990**, 112, 8180; M. Welker, H. von Döhren, *FEMS Rev.* **2006**, 30, 530].

Microwave-assisted synthesis, the application of microwave energy for improving peptide synthesis. Microwave irradiation is a well-known approach to the promotion of a great variety of organic reactions, and is normally used to shorten reaction times, thereby accelerating the synthesis of organic compounds. Although the details of a peptide synthesis performed in a kitchen microwave oven were published in 1991, the use of a commercial microwave oven and the lack of temperature control made the procedure not easily reproducible. Later, both for solution-phase and solid-phase peptide synthesis, rapid microwave-assisted synthesis procedures were developed. Single-mode irradiation with monitoring of temperature, pressure and irradiation power versus time has been applied in order to make the procedure reproducible. In SPPS, microwave energy allows for a higher resin substitution and a less excess of reagents to be used. The first automated microwave peptide synthesizer

(Odyssey) was presented at the American Peptide Symposium in 2003 [A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; S.-T. Chen et al., *J. Chin. Chem. Soc.* **1991**, 38, 85; M. Erdelyi, A. Gogoll, *Synthesis* **2002**, 1592; V. V. S. Babu, R. V. R. Rao, *Ind. J. Chem.* **2005**, 44B, 2328; M. A. Fara et al., *Tetrahedron Lett.* **2006**, 47, 1011; S. Monroc et al., *SYNLETT* **2006**, 1311].

Midkine (MK), a basic, cysteine-rich protein ($M_r \sim 13$ kDa) containing five intramolecular disulfide bonds. MK is a retinoic acid response cytokine, mostly expressed in embryonic tissues. It shares 50 % identity with \rightarrow pleiotrophin which, together with MK, forms the \rightarrow midkine family. MK has neurotrophic activities and mitogenic effects on fibroblastic cell lines. Furthermore, it enhances plasminogen activator and plasmin activity in tissue repair and angiogenesis. It has also been reported to have a strong survival-promoting activity in constant light-induced retinal degeneration, and intense expression in the brain during the early stages of experimental cerebral infarction. MK promotes the survival and outgrowth of neurite from embryonic neuronal cells. In humans, a truncated MK was expressed specifically in tumor/cancer tissues. In addition, a novel truncated form of MK transiently expressed during normal mouse embryonic development was discovered. MK is also involved in regulation of the renin-angiotensin pathway in mouse aorta. The first three disulfide bonds in the highly basic protein comprise an N-terminal domain linked by a short peptide bridge to the C-terminal domain containing the remaining two disulfide bonds. MK (121 aa) was chemically synthesized applying the maximum protection strategy by Sakakibara and coworkers in 1996 [J.-I. Tsutsui et al., *Biochem. Biophys. Res. Commun.* **1991**, 176, 792; H. Muramatsu et al., *Biochem. Biophys. Res. Commun.* **1994**, 203, 1131; T. Inui et al., *J. Peptide Sci.* **1996**, 2, 28; Q. Chen et al., *Biochem. Biophys. Res. Commun.* **2005**, 330, 1230; L. Ezquerro et al., *Biochem. Biophys. Res. Commun.* **2005**, 333, 636].

Midkine family, a novel growth factor family consisting of \rightarrow midkine and \rightarrow pleiotrophin. Both members of this family signal strikingly similar functional responses *in vitro* due to the over 50% identity of the amino acid sequence. They stimulate proliferation of different cell types in culture, such as fibroblasts, endothelial and epithelial cells. Significance of the midkine family in angiotensin II signaling has been recently reported [T. Muramatsu, *Int. J. Dev. Biol.* **1993**, 37, 183; L. Ezquerro et al., *Biochem. Biophys. Res. Commun.* **2005**, 333, 636].

MIF, melanotropin release-inhibiting factor.

MIH, melanotropin release-inhibiting hormone.

MIH, melanotropin release-inhibiting hormone.

Milk protein-derived opioid peptides, a group of opioid peptides derived from milk proteins which belong to the \rightarrow exorphins. The \rightarrow β -casomorphins were the first discovered peptides of this family. α -Casein exorphins, also termed *casoxins*, are derived from bovine α -casein. α -Casein exorphin (1–7), H-Arg-Tyr-Leu-Gly-Tyr-Leu-Glu-OH, corresponds to the partial sequence 105–111 of bovine α_s -casein, and a fragment shortened by the C-terminal Glu show moderate typical opioid properties *in vitro*. *Casoxin D* (1–7), H-Tyr-Val-Pro-Phe-Pro-Phe-OH, released upon peptic-chymotryptic digestion of a human casein, corresponds to human α_s -casein (158–164), and was reported to act as an opioid antagonist. From tryptic and peptic

digests of bovine κ -casein preparations, two peptides have been isolated showing low opioid antagonist properties. *Bovine casoxin* (1–6), H-Ser-Arg-Tyr-Pro-Ser-Tyr-OMe, a 6-peptide methyl ester, could be regarded as a low-affinity μ - and κ -selective opioid receptor antagonist. Furthermore, specific fragments of α -lactalbumin (α -lactorphin, H-Tyr-Gly-Leu-Phe-NH₂) and β -lactoglobulin (β -lactorphin, H-Tyr-Leu-Leu-Phe-NH₂), bearing *N*-terminal Tyr residues have been synthesized and act as μ -opioid receptor ligands with low potency. *Human lactoferrins A, B, and C*, peptides with six, five, and seven residues, isolated from the peptic digest of human \rightarrow lactoferrin, are μ -opioid receptor-selective antagonists with moderate potency. It has also been reported that milk opioid-derived peptides may be involved in defense against noxious agents, and could have dietary and health applications [H. Teschemacher et al., *Biopolymers* **1997**, 43, 99; H. Meisel, R. J. FitzGerald, *Br. J. Nutr.* **2000**, 84, 27; A. Trompette et al., *J. Nutr.* **2003**, 133, 3499; H. Teschemacher, *Curr. Pharm. Design* **2003**, 9, 1331].

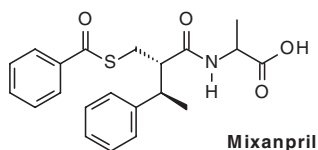
Mio- and Dio-Fmoc, monoisooctyl-Fmoc and diisooctyl-Fmoc, base-labile protecting groups derived from the \rightarrow Fmoc group with improved solubility in organic solvents. Mio-Fmoc is the acronym of 2-(2-ethylhexyl)-fluorenyl-9-methoxycarbonyl, while Dio-Fmoc stands for 2,7-bis(2-ethylhexyl)-fluorene-9-methoxycarbonyl [P. Weissig et al., *Synlett* **2006**, 2235].

Mismatch sequences, undesired side products based on incomplete conversion in SPPS. Mismatch sequences arise when acylation or deprotection are incomplete and one or more amino acid components are skipped in the chain elongation. They may also be formed when the amino acid sequence is correct, but acylation of nucle-

ophilic side-chain functionalities, for example, occurs after partial deblocking.

Mitocalcin, a mitochondrial Ca²⁺-binding protein with EF-hand and coiled-coil domains encoded by the *mitocalcin* gene. Mitocalcin is widely expressed in mouse tissues, especially in neurons co-localized with mitochondria but not in glial cells. Mitocalcin may play roles in neuronal differentiation and function via the control of mitochondrial function [M. Tominaga et al., *J. Neurochem.* **2006**, 96, 292].

Mixanpril, *N*-[(2*S*,3*R*)-2-benzoylthiomethyl-3-phenylbutanoyl]-L-alanine, a dual inhibitor for the neutral endopeptidase-24.11 (NEP) and the \rightarrow angiotensin-converting enzyme (ACE). The orally administrable mixanpril is important for the treatment of high blood pressure and cardiac defects [S. Turcaud et al., *Bioorg. Med. Chem. Lett.* **1995**, 5, 1893].



Mixed anhydride method, a procedure of peptide coupling using reactive species resulting from the carboxylic moiety of a *N*-acylated amino acid and alkyl chlorocarbonates (alkyl chloroformates), especially isobutyl chlorocarbonate (isobutyl chloroformate), that readily reacts with an amino component. The nucleophilic amino component attacks the carboxy group of the amino acid component, with formation of the desired peptide derivative and release of the unstable isobutyl carbonic acid which immediately decomposes into carbon dioxide and isobutanol [J. Meienhofer, in: *The Peptides: Analysis, Synthesis, Biology*,

Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York, 1979, 263].

MK, midkine.

Mmt, 4-methoxtrityl.

Moa, 6-methyloctanic acid.

Mob, 4-methoxybenzyl.

Molecular chaperones, *protein-folding helper proteins*, a diverse set of abundant and ubiquitous protein families required for the correct folding, assembly, transport, and degradation of other proteins within the cell. Most of the molecular chaperones are \rightarrow heat shock proteins. The molecular chaperones regulate several important cellular processes; for example, they enhance the efficiency of the *de-novo* protein folding and promote the refolding of proteins that have become misfolded as a result of cellular stress. It is important to note that chaperones only transiently stabilize and mediate folding or assembly of unfolded protein substrates, and are not present in the native protein. Furthermore, they target misfolded proteins and prevent protein aggregation in all cell types. In the case that molecular chaperones cannot repair misfolded proteins, chaperone-mediated targeting results in selective degradation. A major cellular pathway for protein catabolism important for the housekeeping and turnover of many regulatory proteins is the ubiquitin-proteasome pathway (\rightarrow proteasome) in which degradation by the proteasome occurs by conjugation of multiple \rightarrow ubiquitin moieties to the substrate protein and degradation of the tagged protein by the 26S proteasome of misfolded proteins. The CHIP protein (carboxy terminus of HSC70-interacting protein, \rightarrow heat shock proteins) binds HSC70 or Hsp70 in the mammalian cytosol and attenuates the Hsp40-

stimulated ATPase and refolding activities of Hsp70. Principally, it acts as an E3 ligase to facilitate the transfer of a polyubiquitin chain to misfolded proteins. Another important pathway for intracellular protein degradation is the lysosome-mediated autophagy that involves an acidic cellular compartment, the lysosome vacuole. One form of autophagy is mediated by chaperones. Hsp70 contributes to the delivery of proteins to lysosomes. The Hsp70 family of chaperones covers three different biochemical functions: the ATPase activity; the secondary amide peptide bond *cis/trans* isomerase (APase) activity; and the unfolded polypeptide chain-binding capability. The structures and modes of action of the molecular chaperone families are significantly diverse. There are several chaperone systems carrying out a multitude of functions, all aimed towards insuring the proper folding of target proteins. They can assist in the efficient folding of newly synthesized proteins, and can also promote the disaggregation of preformed protein aggregates. Efficient folding of many newly synthesized proteins depends on assistance from the molecular chaperones in preventing misfolding and aggregation within the crowded environment of the cell. Especially, nascent chain-binding chaperones, including Hsp70, \rightarrow trigger factor and prefoldin, stabilize elongating chains on ribosomes in a non-aggregated state. In *E. coli* cytoplasm there are four main chaperone systems. (1) *Ribosome-associated trigger factor*, which assists in the folding of the nascent chain and also exhibits enzymatic activity as a \rightarrow peptidyl prolyl *cis/trans* isomerase. (2) The *Hsp70 system*, consisting of DnaK (Hsp70), its cofactor DnaJ (Hsp40), and the nucleotide exchange factor GrpE which recognizes polypeptide chains in an extended conformation. (3) The *Hsp60 system*, built of GroEl (Hsp60)

and its cofactor GroES (Hsp10), is involved in the folding of compact intermediates with exposed hydrophobic surfaces. (4) The *Clp* ATPases, which belong to the Hsp100 family of heat shock proteins, are capable of unfolding proteins and disaggregating preformed aggregates to target them for degradation. Molecular chaperones regulate several other cellular processes, such as vesicle fusion, signal transduction, and apoptosis. They are also important as a defense tool against misfolded, aggregation-prone proteins, and belong to the most potent suppressors of neurodegeneration known for animal models of human diseases, such as → Alzheimer's disease, Parkinson's disease, Huntington's disease, familial amyotrophic lateral sclerosis, and polyglutamine (polyQ) expansion diseases. More details on the six main families of chaperones are given under → heat shock proteins [J. Ellis, *Nature* **1987**, 328, 378; M. J. Gething, J. Sambrook, *Nature* **1992**, 355, 33; R. I. Morimoto, A. Tissieres, C. Georgopoulos, *The Biology of Heat-Shock Proteins and Molecular Chaperones*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, **1994**; F. U. Hartl, *Nature* **1996**, 381, 571; D. E. Feldman, J. Frydman, *Curr. Opin. Struct. Biol.* **2000**, 10, 26; F. U. Hartl, M. Hayer-Hartl, *Science* **2002**, 295, 1852; S. Walter, J. Buchner, *Angew. Chem. Int. Ed.* **2002**, 41, 1098; J. C. Young et al., *Nat. Rev. Mol. Cell. Biol.* **2004**, 5, 781; A. Y. Yam et al., *J. Biol. Chem.* **2005**, 280, 41252; P. J. Muchowski, J. L. Wacker, *Nature Rev. Neurosci.* **2005**, 6, 11].

Monatin, 4-hydroxy-4-(indol-3-ylmethyl) glutamic acid, a high-intensity sweet, natural compound. Monatin was isolated from the roots of *Schlerochiton ilicifolius*, a spiny-leaved hardwood shrub growing in South Africa. The synthesis of the four

stereoisomers showed that not the natural stereoisomer 2*S*,4*S* but rather the 2*R*,4*R* stereoisomer was the sweetest of the series [R. Vleggar et al., *J. Chem. Soc., Perkin Trans I* **1992**, 3095; A. Bassoli et al., *Eur. J. Org. Chem.* **2005**, 2518].

Monellin, an intensively sweet protein from the West African berries *Dioscoreophyllum cumminsii*. On a weight basis, monellin is several thousand times more potent in sweetness than sucrose. It consists of two non-covalently associated polypeptide chains, A and B, with 44 and 50 residues, respectively. According to the X-ray crystal structure, the natural protein consists of an anti-parallel β -sheet with five strands and an α -helix. Single-chain monellin (SCM), an engineered 94 aa polypeptide, has been proven to be as sweet as the native two-chain molecule, and is more stable in both high-temperature and acidic environments compared to the native monellin [T. Mizukoshi et al., *FEBS Lett.* **1997**, 413, 409; S.-Y. Lee et al., *Biochemistry* **1999**, 38, 2340].

Monitoring on-resin, → on-resin monitoring.

Monobactams, → β -lactam antibiotics.

Monoclonal antibodies (MAb), from a pharmaceutical point of view a group of natural drugs with the ability to mimic their natural function in an organism, but without inherent toxicity. The first monoclonal antibody marked for therapeutic purposes was Orthoclone (OKT3) launched by Ortho Biotec for acute kidney transplant rejection in 1986. However, first-dose reactions and antimurine antibodies remain drawbacks in clinical application. Near-human clinical MAb, called "chimerized" or "humanized" antibodies have been created by fusing mouse variable domains to human constant domains in order to retain binding specificity while simultaneously reducing

the portion of the mouse sequence. The first example of an approved chimeric antibody was ReoPro (Abciximab) from Centocor, an anticoagulant, which was registered at the end of 1994 in the USA. Zenapax is a complementary-determining region (CDR) grafted MAb targeted to the interleukin-2 (IL-2) receptor on T cells for use in preventing transplant rejection. Antibodies and antibody derivatives constitute more than 25% of the pharmaceutical proteins currently under development, and there is no doubt that the immune system is an excellent target for new therapeutic efforts [G. Galfre, C. Milstein, *Methods Enzymol.* **1981**, 73, 3; T. J. Vaughan et al., *Nature Biotechnol.* **1998**, 16, 535; M. A. van Dijk, J. G. J. van den Winkel, *Curr. Opin. Chem. Biol.* **2001**, 5, 368; M. Z. Lin et al., *Clin. Cancer Res.* **2005**, 11, 129; A. P. Levene et al., *J. R. Soc. Med.* **2005**, 98, 146; R. M. Sharkey, D. M. Goldenberg, *CA Cancer J. Clin.* **2006**, 56, 226].

Montanastatin, cyclo-(D-Hiv-D-Val-Lac-Val)₂, a member of the → depsipeptides isolated in only low yield from a culture of the soil-dwelling eubacteria *Streptomyces anulatis* collected in Montana together with → valinomycin. Montanastatin is a cyclic “dimer” of the sequence shown in brackets, whereas valinomycin is a cyclic “trimer”. Due to the smaller ring size, montanastatin shows none of the antimicrobial activity exhibited by valinomycin [G. R. Pettit et al., *Bioorg. Med. Chem.* **1999**, 7, 895].

Moore, Stanford (1913–1982), American biochemist and winner of the Nobel Prize for Chemistry in 1972 (shared with → Anfinsen and → Stein) for his contribution to the understanding of the connection between chemical structure and catalytic activity of the active center of the ribonuclease molecule. He received his Ph.D in organic

chemistry at the University of Wisconsin in 1938, and one year later joined the → Bergmann laboratory at the Rockefeller Institute for Medical Research in New York. The development of quantitative chromatographic methods for amino acid analysis, their automation, and the utilization in the researches of protein chemistry led to the Nobel Prize for Moore and Stein.

Morphiceptin, H-Tyr-Pro-Phe-Pro-NH₂, a physiological active 4-peptide amide obtained from bovine → casein by enzymatic digestion, exhibiting the highest opioid activity within the → β-casomorphins. It is highly selective for the μ receptor. Furthermore, morphiceptin has been reported to inhibit oxidation of the cytochrome P450 substrate and spontaneous firing of the locus coeruleus. Recently, the enzyme-catalyzed synthesis of morphiceptin using → dipeptidyl peptidase IV (DP IV) has been described [K. J. Chang et al., *Science* **1981**, 212, 75; Y. R. Yang et al., *Eur. J. Pharmacol.* **1999**, 372, 229; N. A. Hosea et al., *Biochemistry* **2000**, 39, 5929; T. Ora et al., *J. Agric. Food Chem.* **2005**, 53, 6112].

Morphine-modulating neuropeptides, peptides found in relatively high concentrations in the periaqueductal gray matter and dorsal spinal cord of the mammalian nervous system. Known members are A-18-Fa, AGEGLSSPFW¹⁰ SLAAPQRFa, and → neuropeptide FF. Both peptides are capable of attenuating the analgesic effect of morphine [H. Y. T. Yang et al., *Proc. Natl. Acad. Sci. USA* **1985**, 82, 7757; C. B. Goodman et al., *Peptides* **1996**, 17, 389].

Motilin (Mot), FVIFTYGE¹⁰QRMQE KERNK²⁰GQ, a 22-peptide hormone belonging to the → ghrelin family. Motilin stimulates the contraction of smooth muscle in the gastrointestinal tract. Motilin was originally isolated from porcine gut,

and is mainly expressed and secreted by enterochromaffin cells of the small intestine. The sequence of motilin is highly conserved among species. Motilin is released from pro-motilin, besides motilin-associated peptides (MAP). Sequence comparison indicates that motilin and both → motilin-related peptide (MTLRP) and → ghrelin share partial homology. Mot, MTLRP and ghrelin not only share structural properties regarding both the ligands as well as their G protein-coupled receptors, but also elicit comparable central and peripheral effects [J. C. Brown et al., *Can. J. Physiol. Pharmacol.* **1971**, 49, 399; Z. Itoh, *Peptides* **1997**, 18, 593].

Motilin-related peptide (MTLRP), GSSFLSPEHQ¹⁰KAQQRKES, the amino-terminal 18-peptide sequence of the prepro-motilin-related peptide encoded by the mouse cDNA m46. MTLRP and → motilin share 22% identity and 39% similarity. Furthermore, there are also structural similarities to → ghrelin [C. Tomasetto et al., *Gastroenterology* **2000**, 119, 395].

MPGF, acronym for major proglucagon fragment, → glucagon.

MPS, multiple peptide synthesis.

MRF, melanotropin-releasing factor.

MRH, melanotropin-releasing hormone.

MRIH, melanotropin release-inhibiting hormone.

MS, mass spectrometry.

MS de-novo sequencing, peptide and protein sequencing (→ sequence analysis) by mass spectrometry. This analytic technique dates back more than 30 years, first in combination with → Edman degradation and later on its own. Starting from sector mass spectrometers or triple quadrupoles with

electron ionization, the technical developments have led first to “soft” ionization techniques, particularly electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI). Today, other types of mass spectrometer are available, such as ion traps, time-of-flight (ToF) devices and Fourier transform ion cyclotron resonance (FTICR) instruments, and more efficient derivatization reactions have been developed. Last, but not least, the great improvements in software now enables the automatic descrambling of mass spectra by computers, significantly reducing the time and effort required for manual interpretation of the data [K. Bieman, *J. Am. Soc. Mass. Spectrom.* **2002**, 13, 1254; J. Laskin, J. H. Futrell, *Mass Spectrom. Rev.* **2003**, 22, 158; J. Liska, A. Shevchenko, *Methods Mol. Biol.* **2003**, 211, 221; W. Zhang et al., *J. Am. Soc. Mass. Spectrom.* **2003**, 14, 1012; K. B. Standing, *Curr. Opin. Struct. Biol.* **2003**, 13, 595; I. Jorge et al., *Proteomics* **2005**, 5, 222].

MS/MS, tandem mass spectrometry.

MSH, melanocyte-stimulating hormone (melanotropin).

MSI-78, → magainins.

Mtb, 2,4,6-trimethoxybenzenesulfonyl.

MTLRP, motilin-related peptide.

Mtr, 2,3,6-trimethyl-4-methoxybenzenesulfonyl.

Mts, 2,4,6-trimethylbenzenesulfonyl.

Mukaiyama reaction, a redox condensation approach to peptide synthesis. A disulfide (2,2'-dipyridyldisulfide) reduction combined with a phosphine (triphenylphosphine) oxidation provides the driving force for the condensation of the carboxy component with the amino component [T. Mukaiyama et al., in: *The Peptides: Analysis, Synthesis, Biology*, Volume 2, E. Gross,

J. Meienhofer (Eds.), Academic Press, New York, 1980, 383].

Multipin synthesis, an effective, low-cost, simultaneous \rightarrow multiple peptide synthesis technology (\rightarrow combinatorial peptide synthesis) originated as an immunological tool for epitope mapping. This approach has traditionally been performed on plastic pins arranged in an 8×12 microtiter plate format, thus permitting the simultaneous synthesis of sets of 96 peptides. A "pin" consists of a radiation-grafted polypropylene "crown" fitted to an inert polypropylene "stem". Originally, the peptides were prepared in a non-cleavable format on the crown surface for epitope mapping applications. Later, most peptides synthesized by the multipin approach have been prepared on cleavable linkers. The development of the basic technology has permitted the synthesis of peptides at scales of about $25 \mu\text{mol}$ per modular grafted surface, thereby changing the scope from a screening tool to the actual synthesis of micromolar quantities of peptides. Compared to the early days of multipin synthesis during the mid-1980s, the latest designs have reached over a 1000-fold increase in loading and reactions, performed at much higher rates [H. M. Geysen et al., *Proc. Natl. Acad. Sci. USA* **1984**, 81, 3998; H. M. Geysen et al., *Proc. Natl. Acad. Sci. USA* **1985**, 82, 178; N. J. Ede, *J. Immunol. Methods* **2002**, 267, 3].

Multidrug transporter, a transmembrane protein that exports cytotoxic substances from the cell. The principle of multidrug resistance of a cell relies on target inactivation, target alteration, prevention of drug influx, and active export of drugs. P-glycoprotein, a member of the ATP binding cassette (ABC) superfamily, acts as an ATP-driven transporter for anticancer agents.

Multiple peptide synthesis (MPS), the simultaneous (parallel) synthesis of a multitude of peptide sequences (\rightarrow combinatorial peptide synthesis), irrespective of the chain length and amino acid composition. Over the past two decades, MPS of large numbers of peptides – both as discrete members of sets or as mixtures – has become an important tool in molecular immunology and the drug discovery approach. The \rightarrow multipin synthesis and the \rightarrow teabag method, both developed during the mid-1980s, were the first tools of multiple peptide synthesis in parallel, and represented the "dawn" of combinatorial peptide synthesis. At the start of the 1990s there followed the \rightarrow split and mix, \rightarrow one bead-one peptide methods and the \rightarrow light-directed, spatially addressable parallel synthesis as strategies for the synthesis of peptides resulted in combinatorial chemistry. The \rightarrow spot synthesis is, like the multipin method, suited for the synthesis of peptides in minute quantities, and utilizes a planar sheet of cellulose as the polymeric support. Various other parallel handling techniques have subsequently found their inspiration from the original contributions such as peptide synthesis on glass slides, cotton, polymeric films, disks, and membranes. Fully automated instruments for multiple simultaneous peptide synthesis have been constructed and are now commercially available [R. H. Berg et al., *J. Am. Chem. Soc.* **1989**, 111, 8024; S. B. Daniels et al., *Tetrahedron Lett.* **1989**, 30, 4345; S. P. A. Fodor et al., *Science* **1991**, 251, 767; J. Eichler et al., *Peptide Res.* **1991**, 4, 296; G. Jung, A. G. Beck-Sickinger *Angew. Chem. Int. Ed.* **1992**, 31, 367; Z. Wang, R. A. Laursen, *Peptide Res.* **1992**, 5, 275; M. Schmidt et al., *Bioorg. Med. Chem. Lett.* **1993**, 3, 441; H. Gausepohl et al., *Peptide Res.* **1992**, 5, 315; K. Luo et al., *Proc. Natl. Acad. Sci. USA* **1995**, 92, 11761; R.

A. Houghten et al., *J. Med. Chem.* **1999**, 42, 3743; N. Hird et al., *Tetrahedron* **1999**, 55, 9575; H. Wenschuh et al., *Biopolymers* **2000**, 55, 188; N. J. Ede, *J. Immunol. Methods* **2002**, 267, 3; J. Hachmann, M. Lebl, *Biopolymers (Pept. Sci.)* **2006**, 84, 340].

Mutt, Viktor, (1923–1999) one of the pioneers of neuropeptide research. He was born in Estonia, and went during the Second World War to Sweden where he started his scientific studies at the Karolinska Institute on heparin, and later → secretin. Subsequently he purified → cholecystokinin and pancreozymin. During his scientific lifetime, he isolated and purified a large number of peptides and determined their structures. Later, in recognition of his great achievements, he succeeded to the chair in Biochemistry at the Karolinska Institute. In 1983, he discovered → galanin, today a well-known gastrointestinal peptide. He was a great and modest scientist who never wanted to be in the limelight.

MVD, mouse vas deferens.

Myelin basic protein (MBP), a protein (hMBP: $M_r \sim 18.5$ kDa) generated by various post-translational modifications. It belongs to a family of similar proteins. Human MBP contains two immunodominant epitopes: (1) MBP-(84–102) and (2) MBP-(139–153). In multiple sclerosis (MS), an inflammatory demyelinating disease of the human CNS, the immunodominant epitope has been localized to MBP-(70–89) and MBP-(83–97). For this reason, this sequence region of the molecule might have special significance for the disease. A proteolytic cleavage of MBP is generally assumed to be the mechanism for epitope generation. It has been reported that MBP-component 1 (MBP-C1) from MS tissue undergoes autocatalytic cleavage, providing a major cleavage pep-

tide which contains the immunodominant epitope MBP-(84–89) [G. Martino et al., *Eur. J. Immunol.* **1991**, 21, 2971; C. A. D'Souza et al., *Biochemistry* **2005**, 44, 12905].

Myelopeptides (MP), bone marrow immunoregulatory peptides, bioregulatory peptide mediators of bone marrow origin. Several MP have been isolated from the supernatant of porcine bone marrow cell cultures. Two members (MP-1 and MP-2) have been synthesized. MP-1, H-Phe-Leu-Gly-Phe-Pro-Thr-OH, shows immunoregulatory activity, and MP-2, H-Leu-Val-Val-Tyr-Pro-Trp-OH, neutralizes the inhibitory effect of leukemia cells on the functional activity of T lymphocytes. MP-1 and MP-2 are identical to sequence fragments 33–38 of the α -chain and 31–36 of the β -chain of → hemoglobin, respectively [R. V. Petrov et al., *Biosci. Rep.* **1995**, 15, 1; R. V. Petrov et al., *Biopolymers* **1997**, 43, 139].

Myoglobin, an oxygen-binding protein preferentially occurring in skeletal muscle. Myoglobin consists of a single chain (153 aa; $M_r \sim 17$ kDa) and a heme that is tightly wedged in a hydrophobic pocket. The eight helices of myoglobin are linked by short peptide segments, forming an ellipsoidal molecule. The heme group binds O_2 . The function of myoglobin is to store and transfer oxygen, i.e., from → hemoglobin to the respiratory enzymes [S. E. V. Phillips, *J. Mol. Biol.* **1980**, 142, 531; M. F. Perutz, *Trends Biochem. Sci.* **1989**, 14, 42].

Myosin, an essential protein component of contractile muscle together with → actin. Myosins are eukaryotic actin-dependent molecular motors with high importance for a wide range of functions such as muscle contraction, vision, hearing, cell motility, and host cell invasion of apicomplexan parasites. Myosin forms almost entirely the

vertebrate thick filaments, and consists of six highly conserved polypeptide chains: two *heavy chains* (each $M_r \sim 230$ kDa), two pairs of *light chains*, termed *essential light chain* (ELC, each $M_r \sim 20$ kDa), and *regulatory light chain* (RLC, each $M_r \sim 20$ kDa). Myosin consists of a long fibrous α -helical tail formed by the C-terminal halves of the heavy chains, and two globular heads associated with one of each type of ELC and RLC. The fibrous part forms a left-handed parallel coiled coil ~ 1600 Å in length which ends in the two globular heads. The single form of myosin exists only at low ionic strengths, whereas under physiological conditions myosin aggregates to natural thick filaments consisting of several hundred myosin molecules packed end-to-

end of their rod-like tails in a regular, staggered fashion. The myosin heavy chain is acting as an ATPase, promoting muscle contraction by hydrolysis of ATP to ADP and P_i . The heavy chains consist of distinct head, neck, and tail domains, and have been previously categorized into 18 different classes based on phylogenetic data. This classification has been recently updated [W. F. Harrington, M. E. Rodgers, *Annu. Rev. Biochem.* **1984**, 53, 35; H. M. Warrick, J. A. Spudich, *Annu. Rev. Cell. Biol.* **1987**, 3, 379; I. Rayment et al., *Science* **1993**, 261, 50; B. J. Foth et al., *Proc. Natl. Acad. Sci. USA* **2006**, 103, 3681].

Myosuppressin, \rightarrow schistoFLRFamide, \rightarrow FMRFamide-related peptides.

N

NADH, nicotinamide adenine dinucleotide (reduced).

NADPH, nicotinamide adenine dinucleotide phosphate (reduced).

Nanobiotics, → peptide-based nanotubes.

Native chemical ligation, → chemical ligation.

Natrin, a protein toxin ($M_r \sim 25$ kDa) isolated from *Naja atra* venom belonging to the cysteine-rich secretory proteins (CRISP). It can induce a further contractile response in the endothelium-denuded thoracic aorta of mouse which has been contracted by a high- K^+ solution. Furthermore, natrin can block the high-conductance Ca^{2+} -activated potassium (BK_{Ca}) channel in a concentration-dependent manner [J. Wang et al., *Biochemistry* **2005**, *44*, 10145].

Natriuretic peptides (NP), *cardiac natriuretic peptides*, a group of six peptides produced by atrial cardiocytes in the heart of mammals exerting natriuretic-diuretic, vasorelaxant and other actions lowering blood pressure and controlling electrolyte homeostasis. Members of this group are the → atrial natriuretic peptide (ANP) and three peptide hormones containing in the pro-ANP-(1–98): *long-acting natriuretic peptide* (LANP), *vessel dilator*, and *kaliuretic peptide* (→ atrial natriuretic peptide), the → brain natriuretic peptide (BNP) or B-type natriuretic peptide, and the → C-type natriuretic peptide (CNP). ANP and BNP are synthesized primarily in the heart muscle cells of the atria (atrial cardiocytes), and also in comparatively smaller amounts in

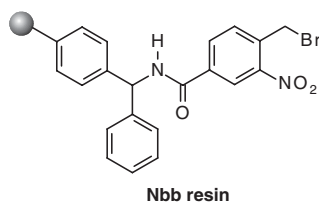
the heart ventricles and in non-cardiac areas, including the CNS, kidneys, and gonads. CNP is synthesized in the vascular endothelium. ANP and BNP are responsible for the reduction of cardiac preload and afterload and the modulation of cardiovascular growth. The biological effects are mediated via specific natriuretic peptide receptors (NPR) on the surface of the target cells. The receptor NPR-A, a guanylyl cyclase-coupled receptor widely distributed within the body, including vascular smooth muscle, kidneys, adrenal glands, brain and heart, mediates the biological actions of both ANP and BNP. NPR-B, a second guanylyl cyclase-coupled receptor, is responsible for CNP signaling. These NPRs consist of three domains: an extracellular ligand-binding domain; a short transmembrane domain; and an intracellular domain acting as a docking site for other proteins. Agonist binding to NP receptors causes an increase in intracellular cGMP that interacts with cGMP-dependent protein kinases (PKGs), cGMP-regulated cyclic nucleotide phosphodiesterases, and cGMP-gated ion channels. PKGs mediate in part the vasorelaxant effect of NP on vascular smooth muscle cells, whereas cGMP-gated ion channels are inhibited by ANP. Last, but not least, cGMP-regulated phosphodiesterases mediate regulation of cardiac function, phototransduction, and adrenal steroidogenesis. NPR-C is acting as a clearance receptor for all three NP, and is found most abundantly in the glomerular and vascular structures of the kidney, and also in the adrenal glands, brain, lungs, in all four cardiac chambers, and in the vascular

wall. In humans, the genes *Nppa* and *Nppb* encoding AFP and BNP are located on the distal short arm of chromosome 1. NP have been shown not only to be powerful prognostic markers in the setting of heart failure, but also to play an important role as a target for therapy. The measurement of plasma NP levels is an important tool in the diagnosis of chronic heart failure (CHF) and acute coronary syndromes. Furthermore, the therapeutic use of ANP and BNP has opened an active area of inquiry, either by the application of the NP themselves or by preventing their degradation. Especially, long-acting analogues of ANP and BNP should have a high potential in the treatment of chronic CHF and essential hypertension. The recently reported new function of NP in the regulation of lipid metabolism offers interesting aspects in the field of diabetes, obesity, and cardiovascular diseases. Natriuretic peptides have been also tested for their efficacy in the treatment of congestive heart failure, renal failure and cancer [T. G. Flynn et al., *Biochem. Biophys. Res. Commun.* **1983**, 117, 859; K. Kangawa et al., *Biochem. Biophys. Res. Commun.* **1984**, 118, 131; A. J. de Bold et al., *Natriuretic Peptides*, in: *Handbook of Physiology: The Endocrine System*, Vol. III: *Endocrine Regulation of Water and Electrolyte Balance*, J. C. S. Fray, M. H. Goodman (Eds.), p. 377, American Physiological Society, Oxford University Press, **2000**; M. Forero McGrath et al., *Trends Endocrinol. Metab.* **2005**, 16, 469; G. A. Wright, A. D. Struthers, *Heart* **2006**, 92, 149; C. Moro, M. Berlan, *Fund. Clin. Pharmacol.* **2006**, 20, 41; D. L. Vesely, *Clin. Exp. Pharmacol. Physiol.* **2006**, 33, 169].

Nazumamide A, a 4-peptide isolated from a marine sponge *Theonella* sp. along with \rightarrow theonellamide F containing α -aminobutyric acid as its C-terminal and

the 2,5-dihydroxybenzoyl moiety as its N-terminal building block. It has been found to be a potent inhibitor of \rightarrow thrombin [N. Fusetani et al., *Tetrahedron Lett.* **1991**, 32, 7073; T. Shioiri, Y. Hamada, *Synlett* **2001**, 184].

Nbb resin, 3-nitro-4-bromomethylbenzhydrylamido polystyrene, obtained by attaching the 4-bromomethyl-3-nitrobenzoic acid handle to benzhydrylamine resin. Nbb resin is fully compatible with the Boc/Bzl CSPPS (\rightarrow convergent solid-phase peptide synthesis) which allows for the detachment of a protected segment by irradiation [D. H. Rich, S. K. Gurwara, *J. Chem. Soc., Chem. Commun.* **1973**, 610; N. Kneib-Cordonier et al., *Int. J. Pept. Protein Res.* **1990**, 35, 527].



Nboc, 2-nitrobenzyloxycarbonyl.

NBS, N-bromosuccinimide.

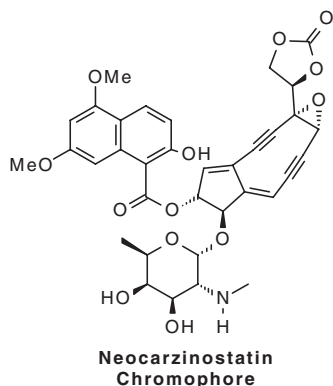
NBz, 4-nitrobenzyl.

2-Nbz, 2-nitrobenzyl.

NCA, α -amino acid N-carboxyanhydride.

NCL, native chemical ligation.

Neocarzinostatin, a polypeptide antibiotic from *Streptomyces carzinostaticus* with strong anticancer activity. Neocarzinostatin consists of an enediyne chromophore non-covalently associated to a peptide chain with 113 residues ($M_r \sim 10.7$ kDa). Neocarzinostatin has potential importance for the therapy of leukemia and both stomach and pancreatic cancer [A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, 39, 2103].



Neoefraeptins, *neoefraeptin A*: Ac-Pip-Aib-Pip-Iva-Aib-Leu- β -Ala-Gly-Acc-Aib-Pip-Gly-Leu-Iva-aX, a group of peptides with insecticidal activity isolated from the fungus *Geotrichum candidum*. All 12 neoefraeptins (A–I, L–N) contain the very rare amino acid 1-amino-cyclopropane-carboxylic acid (Acc), and some of them (F, I, L, M) also contain (2*S*,3*S*)-3-methylproline instead of pipecolic acid (Pip) in position 11. Further unusual building blocks are isovaline (Iva) and the C-terminal amide moiety X = 2,3,4,6,7,8-hexahydro-1-pyrrolo[1,2- α]pyrimidine. Neoefraeptins show a close sequence similarity to the \rightarrow efraeptins [A. Fredenhagen et al., *J. Antibiot.* **2006**, 59, 2006].

Neoendorphins, opioid peptides derived from the precursor protein pro-dynorphin (pro-enkephalin B). α -*Neoendorphin*, H-Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys¹⁰-OH, corresponds to the partial sequence of human and porcine pro-dynorphin (175–184), and contains the sequence of β -neoendorphin ([desLys¹⁰]- α -endorphin). Both neoendorphins show potent activity in the guinea pig ileum assay [K. Kangawa et al., *Biochem. Biophys. Res. Commun.* **1981**, 99, 871; N. Minamino et al., *Biochem. Biophys. Res. Commun.* **1981**, 99, 864].

Neosiphoniamolide A, an 18-membered cyclodepsipeptide (\rightarrow depsipeptides) with structural similarity to \rightarrow geodiamolides.

Nerve growth factor (NGF), a protein factor involved in a variety of biological processes, such as cell differentiation and survival, growth cessation, and apoptosis in neurons. NGF is one of the most intensively studied protein growth factors, having first been discovered more than 50 years ago. It is the prototype of the larger family of neurotrophins. NGF stimulates the proliferation and differentiation of cells of ectodermal and mesodermal origin. The activity had been identified both in tumor tissues by Levi-Montalcini in 1951, and eight years later by Cohen in various snake venoms, one year before its identification in mouse submandibular glands by Cohen. In the submandibular tissue, mouse NGF consists of a 7S complex of three subunits (α , β , γ) and 1–2 g atoms of zinc, but this complex does not occur in other mouse tissues and in other species. The tightly associated β dimer acts as the active principle of NGF. The α and γ subunits actually inhibit the hormone action, and must be dissociated for the manifestation of biological activity. The β -protomer is formed from a larger precursor by limited proteolysis. NGF has a tertiary structure based on a cluster of three cystine disulfides and two very extended, but distorted, β -hairpins. NGF binds as a dimer to the NGF receptor from which at least two cell-surface receptor types are expressed in a variety of neural and non-neural cells, TrkA and p75. TrkA is a receptor with tyrosine kinase activity that forms a high-affinity binding site for NGF. It stimulates the proliferation and differentiation of its target cells by inducing autophosphorylation of the receptor tyrosine kinase, followed by activation of the tyrosine kinase to bind to and/or

phosphorylate specific tyrosine residues on other cytoplasmic signaling proteins [R. Levi-Montalcini, V. Hamburger, *J. Exp. Zool.* **1951**, 116, 233; S. Cohen, *Proc. Natl. Acad. Sci. USA* **1960**, 46, 302; R. A. Bradshaw et al., *Protein Sci.* **1994**, 3, 1901].

NESP, → chromogranins.

Neu, neuraminic acid.

Neudesin, a secreted protein with neurotrophic activity in primary cultured mouse neurons, but not with mitogenic activity in mouse astrocytes. The activity is mediated via the activation of mitogen-activated protein (MAP) and the phosphatidylinositol-3 kinase pathways. Besides mouse neudesin (171 aa), human neudesin with 172 aa (~91% sequence identity) was also identified [I. Kimura et al., *J. Neurosci. Res.* **2005**, 79, 287].

NeuNac, N-acetylneuraminic acid.

Neuregulins (NRGs), a family of structurally related growth factors that regulate cell survival, proliferation, differentiation, and organ formation. The peptides originally described as *neu differentiation factor* (NDF), *heregulins*, *glial growth factors* (GGF), *acetylcholine receptor-inducing activity* (ARIA), and *sensory and motor neuron-derived factor* (SMDF), are now considered to be NRGs. They are all encoded by the NRG-1 gene and share an EGF-like domain, which is sufficient and necessary for biological activity. NRGs interact with ErbB receptors (receptor tyrosine kinases), and there is evidence for involvement of NRG signaling in the pathogenesis of schizophrenia and breast cancer [D. L. Falls, *Exp. Cell. Res.* **2003**, 284, 14].

Neurohypophyseal hormones, peptide hormones secreted from the neurohypophysis, the posterior lobe of the pituitary, which is anatomically distinct from the adenohy-

pophysis. It secretes → oxytocin and → vasopressin, both of which are synthesized primarily in the hypothalamus.

Neurokinins (NK), members of the → mammalian tachykinins. They are widely distributed in the central and peripheral nervous systems, and the two neurokinins (NKA and NKB) act as neurotransmitters or neuromodulators. The biological actions on many tissues are mediated via specific G protein-coupled receptors. Among the three subtypes of NK receptors, NK₁ is the preferred receptor for → substance P. *Neurokinin A*, NKA (also known as *substance K*, *neurokinin α*, and *neuromedin L*), H-His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met¹⁰-NH₂, is the agonist for the NK₂ receptor, whereas *neurokinin B*, NKB (also known as *neurokinin β* and *neuromedin K*), H-Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met¹⁰-NH₂, mediates its action through the NK₃ receptor. Together with substance P, the NK play an important role in pain transmission, neurogenic inflammation, smooth muscle contraction, secretion, vasodilation, and activation of the immune system. The NK were isolated from porcine spinal cord extracts and synthesized by Munekata and coworkers in 1984 [E. Munekata et al., *Chem. Lett.* **1984**, 1013; K. Folkers et al., *Biochem. Biophys. Res. Commun.* **1984**, 118, 405; J. E. Maggio, *Annu. Rev. Neurosci.* **1988**, 11, 13; Z. Gao, N. P. Peet, *Curr. Medicinal Chem.* **1999**, 6, 374; C. A. Maggi, *Trends Biochem. Sci.* **2000**, 21, 173].

Neuromedin B (NMB), H-Gly-Asn-Leu-Trp-Ala-Thr-Gly-His-Phe-Met¹⁰-NH₂, a mammalian neuropeptide belonging to the → ranatensin family. Originally, NMB was purified from pig spinal cord and showed potent contractile activity against rat uterus. It has been shown to be present in the CNS, as well as in the gastrointestinal tract.

The NMB receptor is a G protein-coupled receptor with seven membrane-spanning regions. Agonist binding activates several intracellular signaling cascades, e.g., phospholipase activation, protein kinase C activation, and calcium mobilization leading to the expression of several genes, DNA synthesis, as well as cellular effects such as secretion. The pharmacological effects of NMB are smooth muscle contraction, exocrine and endocrine secretions of gastrointestinal tissues, pancreas and pituitary, various central effects and in-vitro effects. Interestingly, NMB also mediates its action through the receptor of the \rightarrow gastrin-releasing peptide, which is another bombesin-like peptide in mammals. The N-terminally extended forms, NMB-30 and NMB-32, show similar activities to NMB [N. Minamino et al., *Biochem. Biophys. Res. Commun.* **1983**, 114, 541; H. Ohki-Hamazaki, *Prog. Neurobiol.* **2000**, 62, 297].

Neuromedin C (NMC), H-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met¹⁰-NH₂, a bombesin-like peptide identified in porcine spinal cord. It exhibits a potent stimulant effect on the smooth muscle of rat uterus. NMC shows sequence identity with the C-terminal part 18-27 of \rightarrow gastric-inhibitory polypeptide and sequence homology with the C-terminus of \rightarrow bombesin. The name NMC was coined since it is closely related to \rightarrow neuromedin B [N. Minamino et al., *Biochem. Biophys. Res. Commun.* **1984**, 119, 14; G. Gasmi et al., *J. Peptide Res.* **1997**, 49, 500].

Neuromedin N (NN), H-Lys-Ile-Pro-Tyr-Ile-Leu-OH, a 6-peptide with a similar biological profile to \rightarrow neurotensin (NT) isolated from porcine spinal cord. It exhibited a contractile activity on guinea pig ileum. NN is synthesized as part of a larger precursor which also contains neurotensin (NT) and neurotensin-like peptide. In the brain, pro-

cessing of pro-NT/NN gives rise to NN and NT, whereas in the gut processing leads mainly to the formation of NT and *large NN*, a large peptide ending with the NN sequence at its C-terminus. NN together with NT are released upon the depolarization of brain tissues. After food ingestion, intestinal NT and large NN are secreted into the circulation. There is evidence that both NN and NT bind with similar affinities to the three NT receptor subtypes. Large NN has been shown to have NT-like activity on intestinal preparations, although its pharmacological properties have not yet been elucidated in detail [N. Minamino et al., *Biochem. Biophys. Res. Commun.* **1984**, 122, 542; P. R. Dobner et al., *Proc. Natl. Acad. Sci. USA* **1987**, 84, 3516; J.-P. Vincent et al., *Trends Pharmacol. Sci.* **1999**, 20, 302].

Neuromedin S (NMS), a neuropeptide of different chain length with potent anorexigenic and circadian rhythm-modulating properties. NMS was identified and isolated from human, rat, and mouse brain tissues in 2005, and shows structural similarities to \rightarrow neuromedin U. Rat NMS-36, LPRLHTDSR¹⁰MATIDFPKKD²⁰PTTSLGRPFF³⁰LF RPRNa, has been shown to be an endogenous ligand for two orphan G protein-coupled receptors, FM-3/GPR66 and FM-4/TGR-1. The latter have been identified as neuromedin U receptor type 1 and type 2, respectively. Intracerebroventricular (i.c.v.) administration of NMS decreases food intake in rats more potently and persistently than is observed with the same dose of neuromedin U. NMS analogues NMS-17, DSSGIVGRPF¹⁰FLFRPRNa, and NMS-33, FLFQFSRAKD¹⁰PSLKIGDSSG²⁰IVGRPFFLFR³⁰PRNa, were isolated from the dermal venoms of Eurasian bombinid toads. When comparing the sequences of toad NMS-17 and NMS-33, human NMS-33, mouse NMS-36 and rat NMS-36,

the defining NMS motif is clearly a completely conserved C-terminal 11-peptide amide (marked in *italics*) [K. Mori et al., *EMBO J.* **2005**, *24*, 325; T. Ida et al., *Endocrinology* **2005**, *146*, 4217; T. Chen et al., *Biochem. Biophys. Res. Commun.* **2006**, *345*, 377].

Neuromedin U (NMU), (U derived from uterus), p-NMU-8, H-Tyr-Phe-Leu-Phe-Arg-Pro-Arg-Asn-NH₂, p-NMU-25, FKVDE EFQGP¹⁰IVSQNRRYFL²⁰FRPRNa, a neuropeptide of different chain length first isolated from the spinal cord of the pig. NMU was detected in various vertebrates, e.g., pig, human (hNMU-25: FRVDEEF QSP¹⁰FGSRSRGYFL²⁰FRPRNa), rat, dog, chicken, rabbit and frog, showing a classical brain-gut distribution. Additionally, NMU possesses peripheral actions, e.g., adrenocortical function, modification of intestinal ion transport, and splanchnic blood flow. A significant reduction in food intake (anorexigenic effect) was found after intracerebroventricular (i.c.v.) administration to rats. Furthermore, elevations in body temperature and heart rate, as well as augmentation of stress responses, complete the spectrum of actions. The C-terminal 5-peptide amide (marked in *italics*) is completely conserved among the neuromedins. In 2000, NMU-23 was isolated from the defensive skin secretion of the Australian tree frog, *Litoria caerulea*. This NMU analogue exhibits full NMU agonist activity in preparations of rat uterine and human urinary bladder smooth. Rat-NMU-23, YKVNEYQGPV¹⁰APSGGFFLFR²⁰PRNa, was recovered from the gastrointestinal tract. It exerts two-fold potent uterus-stimulating activity in comparison to pig NMU-25. p-NMU-8 is some times unstable in the biological fluids used for bioassay. The reason for this may be a partial decomposition of the

C-terminal Asn-NH₂ via the formation of an aminosuccinimide intermediate [N. Minamino et al., *Biochem. Biophys. Res. Commun.* **1988**, *156*, 355; A. L. Salmon et al., *J. Biol. Chem.* **2000**, *275*, 4549; R. Hanada et al., *Nat. Med.* **2004**, *10*, 1067; P. H. Jethwa et al., *Am. J. Physiol. Endocrinol. Metab.* **2005**, *289*, E301; T. Kawai et al., *Chem. Pharm. Bull.* **2006**, *54*, 659; T. Chen et al., *Biochem. Biophys. Res. Commun.* **2006**, *345*, 377].

Neuropeptide γ (NP γ), DAGHGQISHK¹⁰RHKTDSEFVGL²⁰Ma, a member of the \rightarrow mammalian tachykinins. NP γ is encoded on the prepro-tachykinin gene TAC1. The differential inclusion or exclusion of exon 4 into γ and β TAC1 allows the formation of two extended NKA peptides, either NP γ or \rightarrow neuropeptide K. NP γ was discovered in an extract of the rabbit intestinal tract. It corresponds to γ -prepro-tachykinin-(72–92). NP γ has been reported to be the most potent contractile tachykinin in human isolated bronchus, acting through a “non-classical” NK2 receptor [R. Kage et al., *J. Neurochem.* **1988**, *50*, 1412; E. Burcher et al., *Neuropeptides* **1991**, *20*, 79].

Neuropeptide 26RFa, VGTALGSLAE¹⁰ELNGYNRKKG²⁰GFSRFa, a 26-peptide amide isolated from a brain extract of the European green frog *Rana esculenta*. 26RFa is the only member of the family of \rightarrow RFamide peptides that possesses a C-terminal FRFa motif, which suggests it to be a member of a new subfamily of vertebrate RFamide peptides. Comparison of the primary structure of frog 26RFa with those deduced from mammalian prepro-26RFa indicates that the sequence of this peptide has been strongly conserved in various vertebrate species, for example, 84% identity between frog and ox sequences. 26RFa has been reported to be a

potent stimulator of appetite in mammals. Other data suggest that this neuropeptide exerts various neuroendocrine regulatory functions at the pituitary and adrenal levels [N. Chartrel et al., *Peptides* **2006**, 27, 1110].

Neuropeptide F (NPF), PDKDFIVNPS¹⁰ DLV LDNKAAL²⁰RDYLRQINEY³⁰FAIIGR PRFa, a 39-peptide amide first isolated from the flatworm *Moniezia expansa*. NPF shows sequence homology with members of the vertebrate → neuropeptide Y (NPY) family. NPF from the terrestrial tubellarian, *Atrioposthia triangulata*, is a 36-peptide showing C-terminal sequence homology with NPF from *Moniezia expansa* [A. G. Maule et al., *Parasitology* **1991**, 102, 309; W. J. Curry et al., *Comp. Biochem. Physiol. C* **1992**, 101, 269].

Neuropeptide FF (NPFF), H-Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH₂, a member of the → RFamide peptide family. NPFF was originally detected in the bovine brain by using antisera directed against the molluscan peptide → FMRFamide. With NPFF₁ and NPFF₂, two G protein-coupled receptors have been characterized as specific NPFF receptors that are related to the → neuropeptide Y and orexin receptor family. NPFF is a peptide with pleiotropic functions in the mammalian CNS, including feeding processes, cardiovascular regulation, opiate interactions, pain modulation, insulin release, and electrolyte imbalance. *In vivo*, NPFF administered intrathecally (i.t.) shows pro-opioid activity, but administered intracerebroventricularly (i.c.v.) produces anti-opioid activity. Recently, the identification of transcriptional regulators of NPFF gene expression have been reported [H.-Y. T. Yang et al., *Proc. Natl. Acad. Sci. USA* **1985**, 82, 7757; P. Panula et al., *Neurobiology* **1996**, 48, 461; N. Vyas et al., *Peptides* **2006**, 27, 990; J. M. Nystedt et al., *Peptides* **2006**, 27, 1020].

Neuropeptide K (NPK), DADSSIEKQV¹⁰ ALLKALYGHG²⁰QISHKRHKTD³⁰SFVGL Ma, a member of the → mammalian tachykinins. NPK is, beside → neuropeptide γ (NPγ), an N-terminally extended form of Neurokinin A (NKA). NPK is encoded on the prepro-tachykinin TAC1 gene. The differential inclusion of exon 4 into βTAC1 splice transcript allows the potential formation of NPK [K. Tatemoto et al., *Biochem. Biophys. Res. Commun.* **1985**, 128, 947; N. M. Page, *Peptides* **2005**, 26, 1356].

Neuropeptide R-RFa, *Rana* RFamide, also referred to as fGRP, SLKPAANLPL¹⁰RFa, a 12-peptide amide isolated from the brain of the European green frog *Rana esculenta*, and the hypothalamus of the bullfrog *Rana catesbeiana*. R-RFa was the first amphibian → RFamide peptide to be discovered. It shares the C-terminal LPLRFamide motif with other members of this family discovered in mammals, birds, and fish. It has been reported that the physiological functions of R-RFa and other LPLRFamide peptides appear to be involved in the control of pituitary hormone secretion. In amphibians, it induces a dose-dependent increase of the GR release from cultured bullfrog pituitary cells after i.p. administration, but the release of prolactin, LH and FSH *in vitro* and *in vivo* has not been affected [A. Koda et al., *Endocrinology* **2002**, 143, 411; N. Chartrel et al., *Peptides* **2006**, 27, 1110].

Neuropeptide S (NPS), SFRNGVGTGM¹⁰ KKTSFQRAKS²⁰, an arousal-promoting 20-peptide transmitter. Since the N-terminal residue of NPS in all species is always serine (S), the name neuropeptide S was coined. The NPS receptor (NPSR) shares moderate homology with other members of the G protein-coupled receptor (GPCR) supergene family. The highest

degree of similarity is reported with \rightarrow oxytocin or \rightarrow vasopressin receptors. NPS is involved in sleep-wakefulness regulation. Its primary structure is highly conserved among vertebrates. DNA sequences corresponding to parts of the NPS precursor were available from human, chimpanzee, macaque, dog, bovine, mouse, elephant, rat, rabbit, guinea pig, chicken, opossum and frog (*Xenopus tropicalis*). NPS promotes arousal and reduces anxiety-like behavior in rats and mice [Y. L. Xu et al., *Neuron* **2004**, 43, 487; R. K. Reinscheid, Y. L. Xu, *FEBS J.* **2005**, 272, 5689].

Neuropeptide W (NPW), WYKHVASPRY¹⁰HTVGRAAGLL²⁰MGLRRSPYLW³⁰ (hNPW), a 30-peptide first isolated from the porcine hypothalamus as an endogenous ligand for the G protein-coupled receptors GPR7 and GPR8. NPW is named after the tryptophan residues (W) at the N- and C-termini of the peptide. NPW is highly conserved among species. Rat NPW differs from the human peptide by only one amino acid in position 17 (Ser instead of Ala). NPW is present in antral G cells of rat, mouse, and human stomach [Y. Shimomura et al., *J. Biol. Chem.* **2002**, 277, 35826; M. S. Mondal et al., *J. Endocrinol.* **2006**, 188, 49].

Neuropeptide Y (NPY), *neuropeptide tyrosine*, YPSKPDNPGE¹⁰DAPAEDLARY²⁰YSALRHYINL³⁰ITRQRYa (porcine), a 36-peptide amide belonging to the \rightarrow neuropeptide Y family. The name is related to the two terminal tyrosine residues. NPY is widely distributed in the central and peripheral nervous systems, and is one of the most abundant neuropeptides in the brains of vertebrates. The highest concentrations in the brain are found in the hypothalamus. NPY is processed from a 97-prepro-peptide. Five NPY receptors (\rightarrow neuropeptide Y

family) are known. Most of the vascular effects of NPY, and many of its physiological actions (e.g., anxiolysis), are mediated through the Y1 receptor. The Y1 receptor (glycoprotein, $M_r \sim 70$ kDa) is distributed in various tissues, including brain, heart, kidney, and gastrointestinal tract. The function of Y1 in the regulation in food intake is still controversial, although Y1 antagonists can inhibit NPY-induced feeding. On the other hand, the Y5 receptor subtype seems to play a role in NPY-induced feeding, as shown by studies involving knock-out-animals, antisense knock-down, and Y5-selective agonists. After cloning the Y receptors and expression in mammalian cell lines, ligand-binding studies have led to the development of potent and selective agonists and antagonists for the different receptor subtypes. The essential sequence parts of NPY for receptor recognition could be determined by investigations with C- and N-terminal truncated analogues. The Y2 receptor (glycoprotein, $M_r \sim 50$ kDa) is the only Y receptor that binds NPY and also both N-terminally truncated and even shortened fragments of NPY. However, N-terminal fragments in the absence of the C-terminal part are completely inactive at all receptor subtypes. NPY inhibits the formation of cAMP which is stimulated by, e.g., forskolin or isoproterenol, and the calmodulin-stimulated phosphodiesterase. It increases intracellular Ca^{2+} concentration in vascular smooth muscle cells. Many more biological effects of NPY have been described, however [K. Tatemoto et al., *Nature* **1982**, 296, 659; T. S. Gray, J. E. Morley, *Life Sci.* **1986**, 38, 389; A. Beck et al., *FEBS Lett.* **1989**, 244, 119; L. Grundemar, S. Bloom (Eds.), *Neuropeptide Y and Drug Developments*, Academic Press, New York, **1997**; D. R. Gehlert, *Neuropeptides* **1999**, 33, 329; I. Sylte et al., *Bioorg. Med. Chem.* **1999**, 7, 2737; C. Cabrele, A. G. Beck-Sickingher,

J. Peptide Sci. **2000**, 6, 97; C. Cabrele et al., *J. Biol. Chem.* **2000**, 275, 36043; C. Cabrele et al., *Peptides* **2001**, 22, 365; A. Bettio, A. G. Beck-Sickinger, *Biopolymers (Pept. Sci.)* **2001**, 60, 420; M. M. Berglund et al., *Exp. Biol. Med. (Maywood, NJ, USA)* **2003**, 228, 217; R. Bader, O. Zerbe, *ChemBioChem* **2005**, 6, 1520].

Neuropeptide Y family, *neuropeptide tyrosine family*, *NPY family*, a peptide family consisting of → neuropeptide Y (NPY), → pancreatic polypeptide (PP) and → peptide YY (PYY). The members of this family are 36-peptide amides, and their various biological functions comprise vasoconstriction, stimulation of food intake, intestinal functions, regulation of circadian rhythms, and the release of pituitary sex hormones, amongst other effects. NPY and PYY occur in all vertebrates, and their sequences are highly conserved. PP is one of the most rapidly evolving neuroendocrine peptides known. The five receptors of the NPY family – Y1, Y2, Y4, Y5, and y6 – belong to the rhodopsin-like superfamily (class 1) of G protein-coupled receptors. The gene for the y6 receptor seems to have become non-functional during evolution, caused by a nonsense frameshift mutation in the third extracellular loop. The → Dm-NPF peptide is also related to this family. An alternative designation → PP-fold family was proposed by Rehfeld in 1998 [J. F. Rehfeld, *Physiol. Rev.* **1998**, 78, 1087; L. Grundemar, S. R. Bloom (Eds.), *Neuropeptide Y and Drug Developments*, Academic Press, San Diego, **1997**; C. Cabrele, A. G. Beck-Sickinger, *J. Peptide Sci.* **2000**, 6, 97; M. M. Berglund et al., *Exp. Biol. Med. (Maywood, NJ, USA)* **2003**, 228, 217; R. Bader, O. Zerbe, *ChemBioChem* **2005**, 6, 1520].

Neuropeptides, peptides in the range between two and about 50 amino acid

residues present throughout the CNS as well as in peripheral organs, such as pancreas, adrenal glands, and cells of the immune system. They have a pivotal function in human life because they are involved in almost all physiological processes. During the early 1970s, de Wied termed a “neuropeptide” as an endogenous substance synthesized in nerve cells and involved in nervous-system functions. However, this origin-oriented definition has since evolved to a functional one. Post-translational processing of polypeptide precursors into active neuropeptides by a common mechanism is an usual pathway for their formation. However, some neuropeptides can be produced from a single polypeptide. Additionally, neurons with the same gene encoding a protein are capable of releasing different neuropeptides due to differences in the way that each neuron processes the polypeptide. With very few exceptions, almost all receptors are coupled to → G proteins characterized by seven membrane-spanning α -helices. At present, molecular biology procedures have been used to discover new neuropeptides. For example, the subtractive hybridization approach led to the discovery of the → orexins. Furthermore, orphan G protein-coupled receptors have been used as targets for the identification and isolation of their endogenous ligands, e.g., → nociceptin for the opioid N/OFQ receptor. Additional information and summarized literature are provided for → endogenous opioid peptides [D. de Wied, *Excerpta Med. Int. Congr. Ser.* **1974**, 359, 653; E. R. Kandel, J. H. Schwartz, T. M. Jessel (Eds.), *Principles of Neural Sciences*, McGraw-Hill Medical, New York, **2000**; T. Hokfelt et al., *Lancet Neurol.* **2003**, 2, 463; R. Ubink et al., *Trends Neurosci.* **2003**, 26, 604].

Neuropeptidomics, → peptidomics [M. Svensson et al., *Anal. Chem.* **2007**, 79, 14].

Neurophysins (NP), precursor proteins and additionally transport molecules of the hormones \rightarrow oxytocin (OT) and \rightarrow vasopressin (VP). The NP (95 aa; $M_r \sim 10$ kDa) contain the sequence of OT and VP, respectively, at the N-terminal end. OT is associated with NP I, and VP with NP II. NP II contains additionally a C-terminal 39-glycopeptide with unknown function. The NP are synthesized in the hypothalamus and transported in neurosecretory vesicles down the axon to the posterior pituitary, which acts as a storage and release facility for VP and OT. The crystal structure of the neurophysin-oxytocin complex was described in 1996 [H. Land et al., *Nature* **1983**, 302, 342; R. Acher, J. Chauvet, *Biochimie* **1988**, 70, 1197; J. P. Rose et al., *Nature Struct. Biol.* **1996**, 116, 258].

Neurotensin (NT), <ELYENKPRRP¹⁰YIL (hNT), a 13-peptide from brain and intestine, originally isolated from calf hypothalamus. In analogy to many other neuropeptides, NT shows a dual function as a neurotransmitter or neuromodulator in the nervous system and as a local hormone in the periphery. Hence, it acts as a neuromodulator of dopamine transmission and of anterior pituitary hormone secretion. Furthermore, NT exerts potent hypothermic and analgesic effects in the brain. On the other hand, NT is a paracrine and endocrine modulator of the digestive tract and of the cardiovascular system of mammals. In addition, its action as a growth factor on a variety of normal and cancer cells is well documented. NT(8–13) is almost as potent as the NT itself, and displays full NT bioactivity in several systems. NT is synthesized as part of a larger precursor together with \rightarrow neuromedin N and the *neurotensin-like peptide*, H-Lys-Leu-Pro-Leu-Val-Leu-OH. Neuromedin N exhibits a similar biological activity profile to NT me-

diated by the same NT receptor subtypes. Four neurotensin receptors have been identified, two of which are G protein-coupled receptors (NTR-1, NTR-2). NTR-3 and NTR-4 are structurally different and represent entirely new types of neuropeptide receptor, as they occur primarily intracellularly and are related to yeast sorting receptors (sortilin, SorLA). NT receptor antagonists contributed to an understanding of the role of NT in antipsychotic drug actions, psychostimulant sensitization and the modulation of pain. It is assumed that NT plays a key role in stress-induced analgesia [R. E. Carraway, S. E. Leeman, *Biochem. J.* **1973**, 248, 6854; P. R. Dobner, *Cell. Mol. Life Sci.* **2005**, 62, 1946].

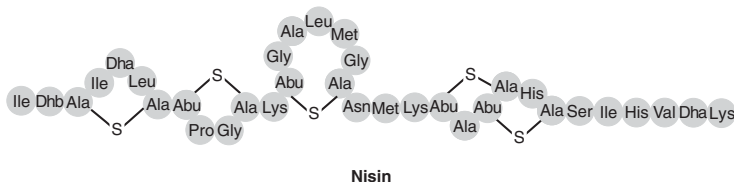
Neurotensin-like peptides, \rightarrow neurotensin.

Neurotrophins, homodimeric peptide growth factors, with \rightarrow nerve growth factor (NGF) as the prototype.

NGF, nerve growth factor.

NIDDM, non-insulin-dependent (type II) diabetes mellitus.

Nisin, the prototype and best studied Type A of \rightarrow lantibiotics. *Nisin A* is a heterodetic pentacyclic peptide (M_r 3353 Da) formed by a single lanthionine (Ala-S-Ala) and four 3-methylanthionine residues (Abu-S-Ala). In addition, nisin contains three unsaturated amino acid building blocks, 2,3-didehydroalanine (Dha) and two 2,3-didehydrobutyrines (Dhb). Starting from the N-terminal end, the rings are labeled A to E. The rings A, B, and C are all separated, whereas the rings D and C form a bicycle. *Nisin Z* is a naturally occurring variant which differs from nisin A by a single amino acid exchange (His27Asn). Nisin is produced by strains of *Lactococcus lactis*, and shows antimicrobial activity against a broad range of Gram-positive



bacteria. Nisin is used as a food additive in over 50 countries. Although, nisin was discovered during the 1940s, the complete structure was elucidated only in 1970 by E. Gross [R. W. Jack, G. Bierbaum, H.-G. Sahl, *Lantibiotics and Related Peptides*, Springer, Berlin, Heidelberg, New York, **1998**; H.-G. Sahl, G. Bierbaum, *Annu. Rev. Microbiol.* **1998**, 52, 41; G. Jung, *Angew. Chem. Int. Ed.* **1991**, 30, 1051; E. Breukink, B. De Kruijff, *Biochim. Biophys. Acta* **1999**, 1462, 223; G. Wahlström, P. E. J. Saris, *Appl. Environ. Microbiol.* **1999**, 65, 3742].

ω -Nitroarginine, an Arg derivative with the side chain protected by a nitro group. It was used for a while in peptide synthesis. The protecting group is stable towards TFA, HBr/AcOH, and alkali. However, it is prone to side reactions during acylation and cleavage [M. Bergmann et al., *Hoppe-Seyler's Z. Physiol. Chem.* **1934**, 224, 40].

4-Nitrobenzyloxycarbonyl group (pNZ), a urethane-type amino-protecting group first described as an alternative to the \rightarrow benzyloxycarbonyl group during the early 1950s. Nowadays, pNZ has been suggested as a temporary N^α -protecting group in orthogonal SPPS due to its ability to avoid diketopiperazine and aspartimide formation, and both as semipermanent and permanent protecting group of ω -amino side-chain functions [F. H. Carpenter, D. T. Gish, *J. Am. Chem. Soc.* **1952**, 74, 3818; A. Isidro-Llobet et al., *Eur. J. Org. Chem.* **2005**, 3031; *Tetrahedron Lett.* **2005**, 46, 7733; P. E. Lopez et al., *Tetrahedron Lett.* **2005**, 46, 7737].

4-Nitrophenylester (ONp), member of the \rightarrow active ester. 4-Nitrophenylester of protected amino acids can be synthesized by the \rightarrow mixed anhydride method, the \rightarrow carbodiimide method, the carbonate method, and other more specialized variants. They are crystalline compounds that may be stored in the dark at room temperature for longer periods of time, and which display high reactivity in aminolysis reactions [M. Bodanszky, in: *The Peptides. Analysis, Synthesis, Biology* (E. Gross, J. Meienhofer, Eds.), Volume 1, Academic Press, New York, **1979**, 105].

Nitrophorins (NP), nitric oxide (NO) transport proteins from the saliva of the blood-sucking insect *Rhodnius prolixus* that uses a ferric (Fe^{3+}) heme to deliver NO to the victims. Nitrophorins act as vasodilators and anti-platelet agents. At the tissue of the victim, the released NO molecule in the vicinity of the bite causes host signaling pathways that lead to vasodilation and reduced platelet aggregation. From crystal structure analysis of NP1 and NP4 it follows that the nitrophorins have a unique hemoprotein structure and are completely unlike the globins [J. M. C. Ribeiro et al., *Science* **1993**, 260, 539; J. F. Andersen et al., *Structure* **1998**, 6, 1315; E. M. Maes et al., *Biochemistry* **2005**, 44, 12690].

2-Nitroveratryloxycarbonyl group (Nvoc), 4,5-dimethoxy-2-nitrobenzyloxycarbonyl, a urethane-type, photolabile N^α -amino-protecting group. Based on its *o*-nitrobenzyl moiety, the Nvoc group is generally removed by irradiation at wavelengths

>300 nm. As well as in classical peptide synthesis, the Nvoc group has found application in → light-directed spatially addressable parallel synthesis and in the synthesis of → peptide nucleic acid (PNA) [A. Patchornik et al., *J. Am. Chem. Soc.* **1970**, 92, 6333; S. P. A. Fodor et al., *Science* **1991**, 251, 767; S. A. Robertson et al., *J. Am. Chem. Soc.* **1991**, 113, 2722; Z.-C. Liu et al., *Tetrahedron* **2005**, 61, 7967].

NK, neurokinin.

NK-lysin, a lysine-rich antimicrobial peptide first discovered in porcine cytotoxic (CTL) and natural killer (NK) lymphocytes, which exerts powerful antibacterial properties and antitumoral activity [M. Andersson et al., *EMBO J.* **1995**, 14, 1615; E. G. Davies et al., *Vet. Immunol. Immunopathol.* **2005**, 105, 163].

Nle, norleucine (α -aminocaproic acid).

NMDA, *N*-methyl-D-aspartate.

NMDA receptor, → conotoxins.

NMM, *N*-methylmorpholine.

NMR, nuclear magnetic resonance.

Nociceptin/orphanin FQ (N/OFQ), FG GFTGARKS¹⁰ARKLANQ, a 17-peptide acting as an endogenous ligand of the “orphan opioid receptor” (ORL-1, now designated NOP). NOP shares significant homology with classical opioid receptors, but does not bind classical opioid ligands. N/OFQ and NOP are found in brain and spinal cord, but also in peripheral tissues of several species, such as humans, rat and mouse, where they regulate important functions, e.g., anxiety, analgesia/hyperalgesia, depressive state, and food intake. N/OFQ shows a clear resemblance to → dynorphin A. Both peptides have six residues in common, contain a very similar *N*-terminal tetrapeptide sequence, and possess a highly positively

charged core. N/OFQ is synthesized as part of a larger precursor polypeptide together with → nocistatin which shows antinociceptive activity. N/OFQ is involved in the control of several biological activities not limited to nociception, but also including learning and memory, motivation, stress and anxiety, and the regulation of cardiovascular, hormonal, renal, and intestinal functions. Although N/OFQ acts at the molecular and cellular levels in a similar way as opioids, it binds to the NOP receptor with 500- to 1000-fold higher affinity compared to the binding affinity to the κ -opioid receptor. Dynorphin A is inactive at the NOP receptor, but is a potent agonist of the κ -opioid receptor. Both, the structural homology of the receptors and the chemical and physical similarities of the endogenous agonists, require a high degree of functional selectivity for the recognition and activation of the two receptors. From the cDNA-deduced amino acid sequences of the human NOP receptor it could be concluded that δ -, μ -, and κ -opioid receptors contain conserved regions, especially, in the transmembrane helices and cytoplasmic loops. The broad pharmacological profile of N/OFQ has initiated the development of novel non-peptidic NOP receptor ligands, antagonists and agonists which are protease-resistant and bioavailable [J.-C. Meunier et al., *Nature* **1995**, 377, 532; R. K. Reinscheid et al., *Science* **1995**, 270, 792; J.-C. Meunier et al., *Peptides* **2000**, 21, 893; R. K. Reinscheid et al., *Peptides* **2000**, 21, 901; M. H. Heinricher, *Life Sci.* **2005**, 77, 3127; M. Broccardo et al., *Peptides* **2005**, 26, 1590].

Nocistatin, TEPGLEEVGE¹⁰IEQKQLQ, an endogenous 17-peptide isolated from bovine brains and encoded by the gene for the nociceptin/orphanin FQ precursor. The 176-aa precursor protein comprises two bioactive peptides, nocistatin and →

nociceptin/orphanin FQ, which play opposing roles in the CNS. Simultaneous administration of nocistatin blocks allodynia and hyperalgesia induced by nociceptin/orphanin FQ. Nocistatin is widely present in the spinal cord and brain, and may play an important function in the CNS, including involvement in nociception, learning, and memory. Human, rat, and mouse precursors produce larger counterparts containing 30, 35, and 41 residues that all demonstrate the antinociceptive activity [E. Okuda-Ashitaka et al., *Nature* **1998**, 392, 286; E. Okuda-Ashitaka, S. Ito, *Peptides* **2000**, 21, 1101; O. Crescenzi et al., *Biopolymers* **2000**, 53, 257; G. M. Scoto et al., *Neurosci. Lett.* **2005**, 387, 126; E. H. Liu et al., *Neurosci. Lett.* **2007**, 416, 155].

NOE, nuclear Overhauser effect.

NOESY, nuclear Overhauser enhanced spectroscopy.

Non-insulin-dependent diabetes mellitus (NIDDM), *type 2 diabetes, adult-onset diabetes*, a complex disease characterized by uncontrolled hepatic glucose output and insulin resistance and impaired glucose tolerance in peripheral tissues. NIDDM is more complex in etiology than \rightarrow insulin-dependent diabetes mellitus (IDDM). Relative insulin deficiency, reduced insulin action, and insulin resistance of glucose transport in skeletal muscle and adipose tissue are distinguishing marks of this disease, which leads to the development of a range of complications including nerve damage, renal failure, blindness and the acceleration of cardiovascular disease. GLP-1 (\rightarrow glucagon-like peptides) is potentially a very attractive agent for the treatment of type 2 diabetes. Since GLP-1 must be administered parenterally and its half-life is short, a long-acting GLP-1 receptor agonist (\rightarrow exenatide) and a long-acting GLP-1 ana-

logue (\rightarrow liraglutide) have been developed as well as DPP IV inhibitors [D. E. Moller, *Nature* **2001**, 414, 821; S. A. Ross et al., *Chem. Rev.* **2004**, 104, 1255; K. B. Degn et al., *Diabetes* **2004**, 53, 1187; P. H. Geelhoed-Duijvestijm, *Neth. J. Med.* **2007**, 65, 60].

Non-proteinogenic amino acids, *non-natural amino acids*, amino acids not occurring in natural peptides and proteins. In eukaryotes, the introduction of these amino acid building blocks into proteins cannot be conducted by the natural ribosomal machinery. However, in prokaryotes biologically active peptides are synthesized by the \rightarrow non-ribosomal peptide synthesis (NRPS).

Non-natural amino acid building blocks, non-proteinogenic amino acids suitable for the incorporation into peptides and proteins for modulating structures, properties, and functions of the corresponding products. Various methods for the incorporation of these unusual building blocks into peptide and protein structures have been developed, with the aim of structure-activity investigations of bioactive peptides and the *de-novo* design of proteins. It is well known that native peptides can be directly applied as pharmacologically active compounds only to a very limited extent. The major disadvantages of using a peptide in a biological system are rapid proteolytic degradation, hepatic clearance, low membrane permeability, and absent ability to pass body barriers such as the blood-brain barrier. Therefore, chemically modified peptides with improved bioavailability and metabolic stability may be used directly as drugs. Alternatively, peptidic receptor ligands or enzyme substrates (peptide leads) may serve as starting points for the development of non-peptidic drugs. Many efforts have been

made to develop peptide-based, pharmacologically active compounds, including peptide modification (bioconjugation) and the design of \rightarrow peptidomimetics. The latter are non-peptidic compounds, whilst modified peptides (by definition) contain \rightarrow non-proteinogenic or modified amino acid building blocks. The *de-novo* design of peptides and proteins has emerged as a challenging approach to study the relationship between the structure and function of a protein. Several strategies for the incorporation of non-natural amino acid moieties into naturally peptides and proteins have been developed, from which four strategies have been widely exploited at present, which include \rightarrow bioconjugation, \rightarrow non-ribosomal peptide synthesis, \rightarrow chemical ligation, \rightarrow biochemical protein ligation, and tRNA engineering methods, and these are still undergoing further advancement and optimization [D. R. W. Hodgson, J. M. Sanderson, *Chem. Soc. Rev.* **2004**, 33, 422].

Non-ribosomal peptide synthesis (NRPS), an approach to peptide synthesis performed in prokaryotes. This process is catalyzed by large enzymes, referred to as non-ribosomal peptide synthetases (NRPS). Some of these enzymes are multimeric complexes, while others are single proteins. It has been reported that each module is composed of about 1000–1200 aa, giving a mass of the complete enzyme of $M_r \sim 2$ MDa. In contrast to ribosomal peptide synthesis in eukaryotes, NRPS produces an array of chemically diverse peptides characterized by high D-amino acid content, N-methylation, unusual heteroaromatic moieties, cyclic structures, and both N- and C-terminal-modified building blocks. Each module of the NRPS contains the necessary components for the activation and reaction of a single amino acid. The basic

module consists of an activation (A) domain, a thiolation domain (T domain), and a condensation (C) domain. In the first step of the elongation cycle a highly activated amino acid adenylate is formed from the appropriate amino acid and ATP catalyzed by the A domain. The activated acyl moiety is transferred from the A domain to the thiol of a pantothein group covalently bound to the T domain, resulting in the formation of a thioester as the active acylating agent. In following peptide bond binding step, the aminoacyl pantothenate of the T domain undergoes nucleophilic attack by the α -amino function of the amino acid bound to the T domain of the next module of NRPS. After peptide bond formation, the growing peptide chain is transferred to the T domain of the next module, mediated by the C domain of the next module. Sequential progression of the growing peptide chain from one module to the next provides a complete peptide before release by the TE domain. There are several advantages of the application of NRPS in biotechnology, including peptide bond formation in water, a lack of any protection necessities of the amino acid building blocks, epimerization domains enable selective incorporation of D-amino acids into the growing peptide chain, and finally cyclic peptides and other esoteric peptides can be obtained [S. A. Sieber, M. A. Marahiel, *Chem. Rev.* **2005**, 105, 715].

Norcysteine (Ncy), α -thiolglycine, an unnatural amino acid possessing an electronegative sulfur atom attached directly to the α -carbon atom. Ncy is an interesting building block for the introduction of shorter disulfide bridges compared with those resulting from the oxidation of the side chains of two cysteines. Both L- and D-Ncy have been introduced into GnRH

analogues [M. P. Samant, J. E. Rivier, *Org. Lett.* **2006**, 8, 2361].

Nostopeptins, cyclodepsipeptides (→ depsipeptides) isolated from the cultured freshwater cyanobacterium *Nostoc minutum*. Nostopeptin A and B contain, besides four usual amino acids with 3-amino-6-hydroxy-2-piperidone and 2-hydroxy-3-methyl-proline, two rarer building blocks. They inhibit elastase and chymotrypsin [T. Okino et al., *J. Nat. Prod.* **1997**, 60, 158].

Np, 4-nitrophenyl.

NP, neurophysin

Nps, 2-nitrophenylsulfenyl.

NPY, neuropeptide Y.

NRPS, non-ribosomal peptide synthesis.

NT, neurotensin.

NTA, *N*-thiocarboxy anhydride.

N-terminal sequence analysis, → Edman degradation.

N-terminal protein ligation, an approach towards → native protein ligation using split inteins. The protein of interest is obtained by ligation of a recombinant and a synthetic fragment. The C-terminal part is obtained by recombinant synthesis from a fusion protein containing the C-extein (C-terminal part of the target protein) and the

IntC fragment (C-terminal intein), while the N-terminal part is obtained synthetically and contains an N-extein together with the IntN-Fragment [C. Ludwig et al., *Angew. Chem. Int. Ed.* **2006**, 45, 5218].

Nu/Nu⁻, nucleophile.

Nuclear Overhauser effect (NOE), the transfer of spin polarization from one spin population to another by cross-relaxation in nuclear magnetic resonance spectroscopy. The NOE in, e.g., NOESY spectra can be used to derive distance information between two nuclei in a molecule and, hence, serves as a tool for structure elucidation.

Nucleoproteins, naturally occurring protein conjugates in which the hydroxy group of a Ser, Thr or Tyr residue is linked via a phosphodiester group to the 3'- or 5'-end of a nucleic acid. Nucleoproteins play decisive roles in important biological processes such as viral replication [V. A. Bloomfield et al. (Eds.), *Proteins and Nucleoproteins; Structure, Dynamics, and Assembly*, Rockefeller University Press, **1980**; B. A. Juodka, *Nucleosides Nucleotides* **1984**, 3, 445; M. Salas, *Annu. Rev. Biochem.* **1991**, 160, 39; L. Blanco et al., *Proc. Natl. Acad. Sci. USA* **1994**, 91, 12198].

Nva, norvaline.

Nvoc, nitroveratryloxycarbonyl.

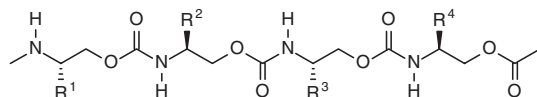
O

Obestatin, a 23-peptide amide encoded by the same gene that encodes \rightarrow ghrelin. It is derived by post-translational processing from the prohormone of ghrelin, and was first isolated and purified from the rat stomach. Obestatin shows opposing effects on food intake to ghrelin. After treatment of rats, the hormone causes suppression of food intake, inhibition of jejunal contraction, and decreased body-weight gain. Obestatin circulates in the rat plasma. It is expressed in cells of the gastric mucosa and myenteric ganglion cells, and also in Leydig cells of the testis, as verified by immunohistochemical evidence. Obestatin is biologically active on central neurons. However, until now it has not been verified whether it is also secreted from the human stomach. Obestatin binds to an orphan receptor (GPR39) which shows similarities with the \rightarrow growth hormone secretagogue receptor [J. V. Zhang et al., *Science* **2005**, 310, 985; S. L. Dun et al., *J. Endocrinol.* **2006**, 191, 481].

OCM, oncostatin M.

Octreotide, \rightarrow somatostatin.

Oligocarbamates, a class of \rightarrow pseudo-biopolymers containing a carbamate moiety instead of a peptide bond. They are stable towards proteolysis and are more hydrophobic compared to peptides; hence, they may be capable of penetrating body barriers such as the blood-brain barrier.

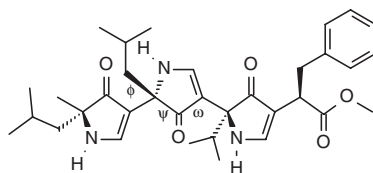


Oligocarbamates

The oligocarbamates may be considered as γ -peptide analogues bearing three skeleton atoms between the amino group and the carboxy group of one monomeric unit [C. Y. Cho et al., *Science* **1993**, 261, 1303].

Oligopeptides, peptides comprising only a small number of amino acid building blocks (Greek *oligos* = few). Formerly, peptides containing fewer than 10 amino acid residues were classified as oligopeptides.

Oligopyrrolinones, a group of pseudo-biopolymers characterized by a novel peptidomimetic principle. A strongly modified backbone is integrated in cyclic structures also containing vinylogous amino acids [A. B. Smith, III et al., *J. Am. Chem. Soc.* **1992**, 114, 10672].



Oligopyrrolinones

Omuralide, *clasto*-lactacystin β -lactone, the biologically active acylating species of \rightarrow lactacystin.

Onchidins, comprise one of the three classes of \rightarrow depsipeptides that have been isolated from mollusks. They are termed

after the taxonomic classification of the organism, *Onchidium* sp. From the same mollusks the onchitriols were isolated that show moderate anticancer activity. The onchidins comprise, with onchidin and onchidin B, two highly symmetric compounds each consisting of a 32-membered ring. Onchidin contains the β -amino acid, 3-amino-2-methyl-7-octynoic acid (Amo), and onchidin B the β -hydroxy acid, 3-hydroxy-2-methyl-7-octynoic acid (Hymo). Beside these acetylenic acids there is no difference in the structures of the onchidins. Acetylenic acids were also found in \rightarrow kulolide and maleamide C. Like \rightarrow valinomycin, onchidin forms a cyclic structure with the polar groups oriented toward the central cavity, whereas the remaining part of the molecule is relatively non-polar. This structure enables them to complex with ions, and thus act as selective ion transporters through cellular membranes. The onchidins show cytotoxic activity [R. Fernandez et al., *J. Am. Chem. Soc.* **1996**, *118*, 11635; F. F. Huerta et al., *Org. Lett.* **2000**, *2*, 1037].

Onconase (ONC), a protein ($M_r \sim 11.8$ kDa; 104 aa) from the oocytes and early embryos of the Northern leopard frog, *Rana pipiens*, which shares 30% sequence identity with ribonuclease A (RNase A). This unstable protein shows also a similar three-dimensional structure as RNase A. The active site of ONC is located in the cleft of its kidney shape, and contains the catalytic triad (His¹⁰, Lys³¹ and His⁹⁷) that is characteristic of the RNase A superfamily. ONC is currently in clinical trials for the treatment of cancer [E. Notomista et al., *Biochemistry* **2000**, *39*, 8711; J. E. Lee, R. T. Raines, *Biochemistry* **2003**, *42*, 11443].

Oncostatin M (OSM), a single-chain glycoprotein produced by macrophages and activated T lymphocytes. It is a member of the

IL-6 family of \rightarrow cytokines that is known primarily for its effects on cell growth. Human OCM shows 25% sequence homology with \rightarrow leukemia inhibitory factor (LIF). Both share a functional high-affinity receptor that is composed of gp130 and a LIF receptor β subunit. OSM is well known for its function in inflammation, cell proliferation, and hematopoiesis. Furthermore, OSM induces potent growth-inhibitory and morphogenic responses in several different tumor cell types [T. M. Rose, A. G. Bruce, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 8641; T. J. Brown et al., *J. Immunol.* **1991**, *147*, 2175; N. Underhill-Day, J. K. Heath, *Cancer Res.* **2006**, *66*, 10891].

On-resin monitoring, \rightarrow preview analysis, \rightarrow Kaiser test.

OPA, 2-phthaldialdehyde.

Ophthalmic acid, H- γ -Glu-Abu-Gly-OH, an acidic 3-peptide found in animal lens and in the brain of cattle and rabbits. Ophthalmic acid inhibits the γ -glutamylcysteine synthetase (\rightarrow glutathione) and the glyoxalase I. Ophthalmic acid occurs also together with norophthalmic acid (H- γ -Glu-Ala-Gly-OH). Recently, it has been reported that ophthalmic acid acts as a oxidative stress biomarker indicating hepatic glutathione consumption [S. G. Waley, *Biochem. J.* **1958**, *68*, 189; S. Tsuboi et al., *Anal. Biochem.* **1984**, *126*, 520; T. Soga et al., *J. Biol. Chem.* **2006**, *281*, 16768].

Opioid peptides, \rightarrow endogenous opioid peptides.

Opioid receptors, \rightarrow endogenous opioid peptides.

Opiorphin, H-Gln-Arg-Phe-Ser-Arg-OH, a human 5-peptide acting as a natural antinociceptive modulator of opioid dependent pathways. Opiorphin is secreted into human saliva and shows dual-inhibitory

potency on the enkephalin inactivating human neutral ecto-endopeptidase (hNEP; EC 3.4.24.11) and the human ecto-aminopeptidase (hAP-N; EC 3.4.11.2) and inhibits chemically and mechanically evoked pain behavior. Its pain-suppressive potency is as effective as morphine in the behavioral rat model of acute mechanical pain (pin-pain test), and may have therapeutic implications [A. Wisner et al., *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17979].

Orbiculamide A, → keramamide.

ORD, optical rotatory dispersion.

Orcokinin, NFDEIDRSGF¹⁰GFN, a myotropic 13-peptide from the abdominal nerve cords of the crayfish (*Orconectes limosus*). It acts as a highly potent stimulator of hindgut contractions. More members of the orcockinin neuropeptide family have been isolated from several crustacean species [J. Stangier et al., *Peptides* **1992**, *13*, 859; D. Bungart et al., *Peptides* **1995**, *16*, 199; L. Li et al., *J. Comp. Neurol.* **2002**, *444*, 227].

Orexins, also known as → hypocretins.

ORL1 receptor, acronym of orphan opioid receptor-like receptor (→ nociceptin).

Orn, ornithine (2,5-diaminopentanoic acid).

Ornithorhynchus venom C-type natriuretic peptide B (OvCNP_a), a biologically active peptide found in platypus venom. OvCNP_a and its D-amino-acid-containing isomer (D-Leu²), OvCNP_b, cause rat uterine smooth muscle relaxation, edema and mast cell histamine release [G. M. de Plater et al., *Toxicol. Endocrinol.* **1998**, *120*, 99; *Toxicon* **1998**, *36*, 847; A. M. Torres et al., *Toxicon* **2002**, *40*, 711; *FEBS Lett.* **2002**, *524*, 172].

Orphanin FQ, → nociceptin.

Orthogonal protecting groups, completely different classes of protecting groups (temporary, semipermanent) characterized by the ability to be cleaved independently one from another. Therefore, although the chemical cleavage mechanisms should be different for an optimum degree of orthogonality, in most cases strict orthogonality cannot be achieved easily and the protecting schemes rely on differences in cleavage kinetics [F. Albericio, *Biopolymers* **2000**, *55*, 123].

Orpotrin, H-His-Gly-Gly-Tyr-Lys-Pro-Thr-Asp-Lys-OH, a 9-peptide isolated from the venom of the Brazilian stingray *Potamotrygon gr. orbignyi*, exhibiting a strong vasoconstriction in the microcirculatory environment [K. Conceicao et al., *Peptides* **2006**, *27*, 3039].

Osteocalcin, also termed *bone Gla protein*, **BGP**, a 49 aa Ca-binding protein ($M_r \sim 5.9$ kDa) comprising 10–20% of bone protein. Beside the → matrix Gla protein, osteocalcin is the second most abundant Gla-containing protein in bone. It was found in bone organic matrix, dentin, and in other mineralized tissues. Osteocalcin from various vertebrates has Gla residues at positions 17, 21, and 24, and contains a disulfide bond (C²³–C²⁹). Osteocalcin has α -helical domains forming a tightly packed charged (pI = 4.0) molecule that coordinates Ca²⁺ at the surface of the hydroxyapatite-like lattice of bone mineral crystals, so that all Gla residues are located on the same side of the α -helix at a distance of 5.4 Å. This distance corresponds nearly to the spacing between adjacent calcium atoms in hydroxyapatite crystals. The osteocalcin protein sequence is highly conserved within the central area of the molecule that contains the Gla residues and Ca²⁺ binding sites, whereas the N-terminal region displays considerable variations. Osteocalcin

is presumed to play a role in the mineralization of bone, and appears to function as a highly specific osteoblastic marker formed during bone formation. Recently, osteocalcin protein sequences of fossil hominids, from two Neanderthals dating to $\approx 75\,000$ years old from Shanidar Cave in Iraq have been described [J. W. Poser et al., *J. Biol. Chem.* **1980**, 255, 8685; P. V. Hauschka et al., *Physiol. Rev.* **1989**, 69, 990; Q. Q. Hoang et al., *Nature* **2003**, 425, 977; C. M. Nielsen-Marsh et al., *Proc. Natl. Acad. Sci. USA* **2005**, 102, 4409].

Osteogenic growth peptide (OGP), ALKRQGR¹⁰LY¹⁰GF¹⁰GG, a 14-peptide with regenerating bone marrow activity. OGP is identical to the C-terminal sequence of histone H4. It has been found in human as well as in animal serum. Synthetic OGP stimulates the proliferation and alkaline phosphatase activity of osteoblastic cells *in vitro*. From the experimental data obtained it has been concluded that OGP is a key factor in the mechanism of the systemic osteogenic reaction to marrow injury. OGP and its C-terminal 5-peptide have been attracted clinical interest as bone anabolic agents and hematopoietic stimulators [I. Bab, *Clin. Orthop.* **1995**, 313, 64; I. Bab et al., *EMBO J.* **1992**, 11, 1867; Z. Greenberg et al., *J. Cell Biochem.* **1997**, 65, 359; I. Bab, M. Chorev, *Biopolymers* **2002**, 66, 33].

Osteonectin (ON), an acidic bone-specific phosphorylated glycoprotein ($M_r \sim 32$ kDa) localized to mineralized bone trabeculae and occurring at higher levels in the matrix than in the bone cells. It binds, as implied by its name, selectively to the organic (\rightarrow collagen) and inorganic (hydroxyapatite) phases of the bone. Furthermore, ON binds Ca^{2+} and represents about 25% of the non-collagenous proteins of fetal bovine bone. ON isolated from adult bovine bone was shown to inhibit hydroxyapatite

crystal formation more strongly than \rightarrow osteocalcin [J. D. Termine et al., *Cell* **1981**, 26, 99].

Osteopontin (OPN), a multifunctional phosphorylated glycoprotein containing an integrin-binding RGD sequence (\rightarrow RGD peptides). OPN was first isolated from the mineralized matrix of bovine bone. It is a member of the small integrin-binding ligand, N-linked glycoprotein (SIBLING) family of glycoposphoproteins expressed in bone and/or teeth. OPN is an important regulator of bone remodeling, and regulates \rightarrow cytokine production, migration and activation of macrophages [J. Sodek et al., *Crit. Rev. Oral Biol. Med.* **2000**, 15, 279; B. Christensen et al., *Biochem. J.* **2005**, 390, 285].

OT, oxytocin (also OXT).

Ovalbumin, a member of the \rightarrow albumins. Ovalbumin is a glycoprotein (hen ovalbumin: $M_r \sim 44.5$ kDa; 385 aa) characterized by four sites of post-translational modifications. Beside the acetylated N-terminus, the carbohydrate moiety is located at Asn²⁹², and the two phosphorylated serines at residues 68 and 344. Ovalbumin is a non-inhibitory member of the serine protease inhibitor family of the \rightarrow serpins. It has been classified as ovalbumin A₁–A₃, depending on the number of phosphorylated serine residues. Ovalbumin comprises $\sim 60\%$ of the total protein amount of egg-white [A. D. Nisbet et al., *Eur. J. Biochem.* **1981**, 115, 335; J. A. Huntington, P. E. Stein, *J. Chromatogr. B* **2001**, 756, 189].

Ovarian jelly-peptides (OJP), a family of regulatory peptides discovered in the cephalopod *Sepia officinalis*. Three members of this family are released by full-grown oocytes (FGO) in the genital coelom and in the lumen of the oviduct in the

cuttlefish *Sepia officinalis*. The first OJP, H-Asp-Gln-Val-Lys-Ile-Val-Leu-OH, was identified by monitoring a purified fraction using a myotropic bioassay. Two additional water-borne OJP, H-Asp-Asn-Val-Lys-Ile-Val-Leu-OH, and H-Asp-Glu-Val-Lys-Ile-Val-Leu-Asp-OH have been identified. These peptides modulate the whole female genital tract and the main nidamental gland contractions [B. Bernay et al., *Peptides* **2006**, 27, 1259].

Ovokinin, H-Phe-Arg-Ala-Asp-His-Pro-Phe-Leu-OH, a vasorelaxing 8-peptide corresponding to → ovalbumin-(358–365). It shows relaxing activity for canine mesenteric artery, which is specifically blocked by the bradykinin B₁ antagonist [desArg⁹, Leu⁸]bradykinin [H. Fujita et al., *Peptides* **1995**, 16, 785].

5(4H)-oxazolone formation, → 2-alkoxy-5(4H)-oxazolones.

Oxime resin, → Kaiser oxime resin.

Oxyntomodulin, → glicentin.

Oxytocin (OT), H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gln-NH₂ (disulfide bond: Cys¹–Cys⁶), a member of the neurohypophyseal peptide hormones. The name has been derived from Greek: *oxys* (*oksys* = fast), and *tokos* (= give birth). OT is synthesized in hypothalamic cells which project either to the neurohypophysis or to sites within the CNS. Synthesis occurs in the hypothalamus together with the precursor protein → neurophysin I, and OT is transported via the tractus paraventriculo-hypophyseus to the posterior lobe. It is released proteolytically from the precursor in this storage site in response of an appropriate biological stimulation, and secreted into the bloodstream. The neurohypophyseal OT release has long been associated with uterine smooth muscle contraction during la-

bor and milk ejection during lactation. Cholesterol and Mg²⁺ probably function as allosteric modulators. OT also plays an important role in many other reproduction-related functions, e.g., control of the estrous cycle length, ovarian steroidogenesis, and follicle luteinization in the ovary. Furthermore, in the male OT is a stimulator of spontaneous erections in rats and is involved in ejaculation. However, the function of intracerebral OT remains unclear. It has been suggested that brain OT influences the formation of social bonds and bonding behaviors, and is involved in the modulation of the neuroendocrine reflexes. The human OT receptor (388 aa) is a typical class I G protein-coupled receptor primarily coupled via G_q proteins to phospholipase C-β. Its structure and expression was described in 1992. Due to the structural similarities to → vasopressin, OT shows some vasopressin activity. During the course of structure–activity studies, a large number of analogues with prolonged or dissociated biological effects, as well as those with antagonistic properties, have been synthesized. Preterm birth affects about 10% of all births, and is the major cause of perinatal morbidity and death. Because OT is likely to be involved causally in preterm labor, the design of synthetic peptide and non-peptide OT antagonists as potential tocolytic agents for the prevention of preterm births is an area of intensive research. Of the many OT antagonists described to date, only one, the combined vasopressin V_{1a} and OT receptor antagonist → atosiban, has been approved for the treatment of preterm labor. However, atosiban is far from being an ideal OT antagonist with the consequence of a pressing need for OT antagonists with superior potency, and selectivity than atosiban. In 1953, the heterodetic cyclic 9-peptide amide was structurally elucidated and one

year later chemically synthesized as the first peptide hormone by the Nobel laureate Vincent → du Vigneaud [V. du Vigneaud et al., *J. Am. Chem. Soc.* **1953**, 75, 4879; V. J. Hruby, *Topics Mol. Pharmacol.* **1981**, 1, 99; T. Kimura et al., *Nature* **1992**, 356, 526; G. Gimpl, F. Fahrenholz, *Physiol. Rev.* **2001**, 81, 629; T. M. Reinheimer et al., *J. Clin. Endocrinol. Metab.* **2005**, 90, 2275; M. Manning et al., *J. Peptide Sci.* **2005**, 11, 593].

P

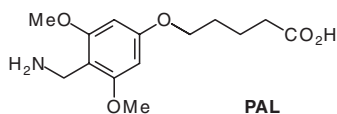
P149, → growth inhibitory peptide.

Pac, phenacyl, PhCOCH_2 (Pac has been also used for PhCH_2CO).

PACAP, pituitary adenylate cyclase activating polypeptides.

PAGE, polyacrylamide gel electrophoresis.

PAL handle, 5-(4-aminomethyl-3,5-dimethoxyphenoxy)valeric acid, a commercially available handle for the Fmoc/ Bu^t SPPS of peptide amides [F. Albericio, G. Barany, *Int. J. Pept. Protein Res.* **1987**, 30, 206].



PAMP, proadrenomedullin N-terminal 20-peptide, → adrenomedullin [T. Ishimitsu et al., *Biochem. Biophys. Res. Commun.* **1994**, 203, 631].

PAM resin, 4-(hydroxymethyl)phenylacetamidomethyl resin, an alternative to the → Merrifield resin used for the synthesis of C-terminal peptide acids. The PAM resin is fully compatible with the Boc/Bzl protection scheme and is cleaved with strong acids such as liquid HF, TFMSA, or HBr/TFA [A. R. Mitchell et al., *J. Am. Chem. Soc.* **1976**, 98, 7357; *J. Org. Chem.* **1978**, 43, 2845].

Pancreastatin (PST), GESRSEALAV¹⁰DG AGKPGAEE²⁰AQDPEGKGEQ³⁰EHSQQK EEEE⁴⁰EMAVVPQGLF⁵⁰RGa (hPST), a 52-peptide derived from the sequence of the precursor human chromogranin A

(→ chromogranins). Fragments of the precursor and hPST itself were isolated from human carcinoid liver metastases and from the liver metastases of a patient with insulinoma. Porcine PST isolated from the porcine pancreas consists of 49 residues. PST strongly inhibits glucose-induced and gastric inhibitory peptide-induced insulin secretion from rat pancreas. The inhibitory effect is restricted to the C-terminal part of PST [K. Tatemoto et al., *Nature* **1986**, 324, 476; W. E. Schmidt, W. Creuzfeldt, *Acta Oncol.* **1991**, 30, 441; V. Sanchez-Margalet et al., *Adv. Exp. Med. Biol.* **2000**, 482, 247].

Pancreatic polypeptide (PP), APLEPVY PGD¹⁰NATPEQMAQY²⁰AADLRRYINM³⁰LTRPRYa (hPP), a 36-peptide amide belonging to the → neuropeptide Y family (→ PP-fold family). The PP among different higher mammals differ only by 1–4 amino acids. PP is formed in the PP cells of the pancreas, and the pulsatory release is coupled to an insulin pulse. In general, the plasma level of PP is increased by electric stimulation of the vagus, food intake and several other stimulating factors. PP inhibits exocrine secretion from the pancreas, which is stimulated, e.g., by → secretin, → cerulein, and → cholecystokinin. The three-dimensional structures of different PP as determined by X-ray analysis and NMR comprise an N-terminal polyproline II helix and a C-terminal amphiphilic α -helix, connected by a β II-turn, an overall supersecondary structure that is known as the PP-fold. There is evidence that the active sequence of PP is located in the C-terminal region, the C-terminal

hexapeptide, and especially the C-terminal tyrosine amide being essential for the biological activity. The C-terminal hexapeptide is capable of stimulating the inhibition of PP on the exocrine pancreas secretion. It has been reported that PP causes a sustained decrease in both appetite and food intake [J. R. Kimmel et al., *J. Biol. Chem.* **1975**, *250*, 9369; R. L. Batterham et al., *J. Clin. Endocrinol. Metab.* **2003**, *88*, 3989].

Pancreozymin, → cholecystokinin.

Papain, EC 3.4.22.2, the archetype of → cysteine peptidases. It was isolated from the latex of the tropical papaya fruit (*Carica papaya*). Papain is a single-chain protein (212 aa; $M_r \sim 23$ kDa) containing three disulfide bonds and a known three-dimensional structure with 1.65 Å resolution. The catalytic amino acid residues have been identified as Cys²⁵, His¹⁵⁹ and Asn¹⁷⁵, whereas Gln¹⁹ helps to stabilize the oxyanion hole. Papain has a fairly broad specificity [J. R. Kimmel, E. L. Smith, *J. Biol. Chem.* **1954**, *207*, 515; A. C. Storer, R. Menard, *Methods Enzymol.* **1994**, *244*, 486].

PAPS, 3'-phosphoadenosine-5'-phosphosulfate.

Papuamides, a family of cyclodepsipeptides (→ depsipeptides) isolated from the sponges *Theonella mirabilis* and *Theonella swinhoei* collected near Papua New Guinea. The papuamides A–D are 22-membered macrocycles containing a number of unusual amino acids, such as 3,4-dimethylglutamine, β-methoxytyrosine, 3-methoxyalanine, 2,3-diaminobutanoic acid, 2-amino-2-butenic acid, 3-hydroxyleucine, homoproline, and 2,3-dihydroxy-2,6,8-trimethyldeca-(4Z,6E)-dienic acid. Papuamides are structurally quite similar to → callipeltins. Papuamides A and B exhibit both strong antiviral and

anticancer activity [P. W. Ford et al., *J. Am. Chem. Soc.* **1999**, *121*, 5899].

PAQR proteins, a membrane receptor family characterized by an ancient 7-transmembrane pass motif [Y. T. Tang et al., *J. Mol. Evol.* **2005**, *61*, 372].

Paracrine hormones, also termed local mediators, peptide hormones involved in biochemical communications which are directed to surrounding cells by diffusion.

Parallel synthesis, *multiple synthesis*, an approach to → combinatorial peptide synthesis characterized by targeted simultaneous multiple synthesis (SMPS).

Paramyosin, a major structural component of thick filaments. It occurs exclusively in invertebrate organisms, where it is widely distributed. Paramyosin is found in varying quantities in different muscles types ranging from smooth to cross-striated muscles. It interacts with the core proteins within the thick myofilaments as well as with the surrounding myosin components, thus stabilizing the thick myofilaments. It is not a component of the cytoskeleton [L. Winkelman, *Comp. Biochem. Physiol. B* **1976**, *55*, 391; P. R. Deitiker, H. F. Epstein, *J. Cell Biol.* **1993**, *123*, 303].

Paraproteins, "*pathological proteins*", abnormal proteins occurring in blood, urine and tissues. The first report of an abnormal protein dates from 1847, but the term paraproteins was coined in 1940 to describe the abnormal proteins that are produced by myeloma cells. They are the earliest described tumor markers. Paraproteins are classically detected by various electrophoresis procedures. Paraproteins are abnormal → immunoglobulins synthesized by atypical cells of the reticuloendothelial system. Paraproteins occur in increased quantities in various hematological disturbances

(paraproteinemias). Well-known members are \rightarrow Bence Jones proteins and amyloid proteins. Depending on the origin of the cells from a common stem cell, immunoglobulins of the classes A, G, M, D, or E and one of the light chains of the Type κ and λ can occur as paraproteins, whereas the isolated occurrence of chains of the L- or H-type is very seldom [H. Bence Jones, *Lancet* **1847**, 2, 88; K. Apitz, *Virchows Arch. Pathol. Anat.* **1940**, 306, 630; X. Bossuyt et al., *Clin. Chem.* **1998**, 44, 760; A. Maniatis, *Renal Fail.* **1998**, 20, 821].

Parathormone, \rightarrow parathyroid hormone.

Parathyroid hormone (PTH), *parathormone*, *parathyrin*, SVSEIQLMHN¹⁰LGKHLNSMER²⁰VEWLRKKLQD³⁰VHNFVALGAP⁴⁰LAPRDAGSQR⁵⁰PRKKEDNVLV⁶⁰ESHEKSLGEA⁷⁰DKADVNVLT⁸⁰AKSQ (hPTH), an endocrine 84-peptide hormone regulating the metabolism of calcium and phosphate in the body. The regulation caused by PTH is effected through actions on kidney, intestine, and bone cell receptors. PTH is secreted in the parathyroid gland in response to subnormal serum calcium levels. It is expressed as a 115-peptide precursor (prepro-PTH) and secreted as an 84-peptide, but the major functions are associated with the N-terminal 34-residue sequence part. Because of the diverse actions of PTH in multiple target tissues, it was initially thought that several different receptors would be found. However, it was somewhat surprising that only a single G protein-coupled receptor, now referred to as the common PTH/PTHrP receptor, or PTHR1. PTHR1 belongs to a distinct family of G protein-coupled receptors. In humans, the gene encoding the PTHR1 is located on chromosome 3. PTH acts in the kidney to increase the synthesis of 1,25 (OH)₂D and thus indirectly to increase intestinal Ca²⁺ absorption. PTH regulates

renal Ca²⁺ and phosphate transport. Especially, the latter action is important for supporting the overall homeostatic role of the hormone. In case of calcium-deficient diets or vitamin D insufficiency, the required calcium is mobilized from bone by increased PTH concentration. Furthermore, PTH promotes phosphate excretion by blocking its reabsorption. PTH also acts at distal tubular sites of the kidney in order to reduce the amount of urinary calcium excreted. PTH affects a wide variety of specialized bone cells, such as osteoblasts and stromal cells. PTH shows a variety of actions via the abundant receptors on osteoblasts which are directly involved in promoting bone formation. Physiologically, the most important role is its stimulation of osteoclast differentiation and development of, and ultimate increase in, bone resorption. The latter action has been traditionally associated with PTH. At present, beside the recombinant native hormone (rhPTH-(1–84) [PreosTM], two very interesting fragments/analogues (rhPTH-1–34) [ForteoTM] and [Leu²⁷]cyclo(Glu²²-Lys²⁶)hPTH-(1–31)NH₂ [Ostabolin-CTM] are available. The PTH analogs treat osteoporosis by strongly stimulating bone formation and strengthening bone microarchitecture in humans, rodents, and monkeys, with few or no side effects. ForteoTM, from Eli Lilly, has been available commercially for more than 3 years, while PreosTM from NPS Pharmaceutical has recently completed Phase III clinical trials and should be available shortly. The analogue Ostabolin-CTM, from Zelos Therapeutics, is currently in Phase II clinical trials. These peptides are versatile drug candidates. For example, studies have been started using these compounds in cancer patients as a novel tool to treat bone marrow depletion caused by chemotherapeutic drugs and ionizing radiation [J. B. Collip,

J. Biol. Chem. **1925**, 63, 395; G. N. Hendy et al., *Proc. Natl. Acad. Sci. USA* **1981**, 78, 7365; T. Kimura et al., *Biochem. Biophys. Res. Commun.* **1983**, 114, 493; P. Morley et al., *Curr. Medicinal Chem.* **1999**, 6, 1095; J. F. Whitfield, *Growing Bone*, Landes Bioscience, Eureka.com, Georgetown, Texas, **2005**; J. F. Whitfield et al., *Cancer Lett.* **2003**, 200, 107; J. F. Whitfield, *Exp. Opin. Invest. Drugs* **2005**, 14, 251; J. P. Potts, *J. Endocrinol.* **2005**, 187, 311; P. M. Guerreiro et al., *Am. J. Physiol. R.* **2007**, 292, R679].

Parathyroid hormone-related peptides (PTHrP), a family of protein hormones produced by almost all tissues in the body. PTHrP was originally discovered as a peptide thought to be responsible for tumor-associated hypercalcemia. PTHrP acts as a paracrine regulator in several tissues, and plays a central role in the physiological regulation of bone formation by promoting the recruitment and survival of osteoblasts. Only the human gene of the autocrine/paracrine PTHrP is expressed to three PTHrH isoforms of 139, 141, and 173 aa. In analogy to the \rightarrow parathyroid hormone (PTH), most of the known biological functions are exerted by the N-terminal PTHrP-(1–34), AVSEHQLLHD¹⁰KGKSIQDKRR²⁰RFFLHHLIAE³⁰IHTA, with 60% sequence similarity to PTH-(1–34). The C-terminal part PTHrP-(107–139) was found to be a potent inhibitor of osteoclastic bone reabsorption. The PTH/PTHrP receptor, or PTHR1, binds both PTHrP and PTH, which activates by coupling to multiple G proteins both adenylate cyclase/protein kinase A- and phospholipase C/protein kinase C-dependent signaling cascades. PTHrP should not be regarded as a hormone at all in its normal function. Although it promotes the transfer of Ca^{2+} across the placenta from mother to fetus, and during late pregnancy and lactation, in

which its action is still not fully defined, the physiological function in postnatal mammals appears to be better characterized as a paracrine effector. PTHrP analogues which strongly inhibit PTHrP adenylate cyclase stimulation seem to be useful for the treatment of malignancy-associated hypercalcemia in animal trials, but failed in human tests [L. J. Suva et al., *Science* **1987**, 237, 893; J. M. Mosely et al., *Proc. Natl. Acad. Sci. USA* **1987**, 84, 5048; H. Juppner et al., *Science* **1991**, 254, 1024; W. M. Philbrick et al., *Physiol. Rev.* **1996**, 76, 127; T. J. Martin et al., *J. Endocrinol.* **1997**, 154(Suppl.), S23; P. Morley et al., *Curr. Medicinal Chem.* **1999**, 6, 1095; G. J. Strewler, *N. Engl. J. Med.* **2000**, 342, 177; T. J. Martin, *J. Clin. Invest.* **2005**, 115, 2322].

Pareptide, \rightarrow melanostatin.

Parvalbumins, water-soluble, monomeric proteins ($M_r \sim 12$ kDa) with high-affinity sites for Ca^{2+} , predominantly found in the skeletal muscle of vertebrates. The parvalbumins also bind Mg^{2+} competitively. They occur not only in skeletal muscle of fish and amphibia, but also in mammalian muscle. Parvalbumins are related in structure and function to \rightarrow calmodulin and \rightarrow troponin C. They contain six α -helical regions (A to F), and the binding sites for two Ca^{2+} are formed by helix-loop-helix motifs (EF hands) between helices C/D and E/F. Human alpha and beta parvalbumins belong to the EF-hand type proteins [C. H. Heizmann, *Experientia* **1984**, 40, 910; U. G. Föhr et al., *Eur. J. Biochem.* **1993**, 215, 719].

Parvulins, enzymes termed Par10 according to the very small, 10 kDa prototype from *E. coli*. In comparison to other small enzymes it is already enzymatically active in its monomeric state. In terms of catalytic activity and substrate specificity, Par10 resembles the prototypic cyclophilin Cyp18

(→ cyclophilins). The secondary structure of Par10 consists of four helical regions and a four-stranded antiparallel β -sheet. The three-dimensional structure of Par10 is mirrored in the catalytic domains of human parvulins, the Pin1 and Par14. The substrate specificity of Pin1 is specially adapted to isomerize-pSer(pThr)-Pro peptide bonds. This activity functionally links the enzyme to the action of protein phosphatases in the cell. Human Pin1 consists of two domains, the parvulin-like catalytic domain that follows a group IV WW domain, whereas in plant parvulins the WW domain is lacking. Both domains may act in a concerted manner to improve substrate specificity of Pin1 in mammals. Unlike cyclophilins and → FKBP, parvulins have not yet been recognized as a potent reversible inhibitor from a natural source [Z. Y. He et al., *Plant. Physiol.* **2004**, *134*, 1248; E. S. Yeh, A. R. Means, *Nature Rev.* **2007**, *7*, 381].

Pauling, Linus, (1901–1994), American chemist and winner of both the Nobel Prize for Chemistry in 1954 for his research in chemical bonding, and the Nobel Prize in Peace in 1962 for his efforts to halt nuclear testing. His fundamental work on the structure of proteins is well documented. In 1925, he was awarded his Ph.D. (*summa cum laude*) in chemistry and was appointed to the staff of the California Institute of Technology as elected Research Associate. He had chairs at both Caltech and Stanford University. Pauling was the first recipient of the American Chemical Society Award in Pure Chemistry (Langmuir Prize) in 1931, and a member of numerous societies in the USA as well as in other countries worldwide. To Linus Pauling came many honors. In 1973, he founded the “Linus Pauling Institute of Science and Medicine” in Palo Alto (California).

PCR, polymerase chain reaction.

PDGF, platelet-derived growth factor.

PDI, protein disulfide-isomerase.

PD-MS, plasma desorption mass spectrometry.

Pediocin-like antimicrobial peptides, *class IIa bacteriocins*, cationic membrane-permeabilizing → antimicrobial peptides with 37 to 48 residues produced by a group of lactic acid bacteria. Members of this class include, for example, leucocin A, pediocin PA-1, sakacin P, curvacin A, and mesentericin Y105 [G. Fimland et al., *J. Peptide Sci.* **2005**, *11*, 688].

PEG, polyethylene glycol.

Pelvetin, pGlu-Gln-Ala-OH, a naturally occurring pyroglutamyl peptide isolated from algae.

Pen, penicillamine (β -mercaptovaline, β,β -dimethylcysteine).

Penetratin, → cell-penetrating peptides.

Pentafluorophenylester (OPfp), one of the most common → active esters.

Pentagastrin, Boc- β -Ala-Trp-Met-Asp-Phe-NH₂, a synthetic 5-peptide derivative with the most potent sequence region of → gastrin. It shows gastrin-like effects when given parenterally. Pentagastrin is used as diagnostic aid for the evaluation of gastric acid secretory function [O. Brawman-Mintzer et al., *Am. J. Psychiatry* **1997**, *154*, 700].

Pep-1, Ac-KETWWETWWT¹⁰EWSQPKK KRK²⁰V-cysteamine, an artificial → cell-penetrating peptide forming physical assemblies with a great variety of proteins and other macromolecules which allows translocation in various cell lines. It has been reported that pep-1 translocates

across membranes by a physical process mediated by transmembrane potential in free form or when complexed with the cargo molecule [M. C. Morris et al., *Nat. Biotechnol.* **2001**, *19*, 1143; S. T. Henriques et al., *FEBS Lett.* **2005**, *579*, 4498; *Biochemistry* **2005**, *44*, 10189].

Pep-13, VWNQPVRGFK¹³VYE, a plant defense-inducing pathogen-associated pattern from *Phytophthora* transglutaminases. P-13 was first described as a peptide elicitor of defense responses in parsley. Later it was reported that P-13 constitutes a surface-exposed fragment within the Ca²⁺-dependent cell wall transglutaminase from *Phytophthora sojae*. Transglutaminases with a highly conserved P-13 motif were discovered in all *Phytophthora* species under investigation [F. Brunner et al., *EMBO J.* **2002**, *21*, 6681].

Pep5, a member of the Type-A family of → lantibiotics. Pep5 (34 aa; M_r 3488 Da) consists of three rings from which A is a single ring, whereas rings B and C form a bicycle. It is extremely basic, and the N-terminus is modified with a 2-oxobutyryl moiety. Pep5 is produced by strains of the bacterial species *Staphylococcus epidermidis*, and kills bacteria – as do other Type-A lantibiotics – by the formation of discrete, voltage-dependent channels (or pores) [R. W. Jack, G. Bierbaum, H.-G. Sahl, *Lantibiotics and Related Peptides*, Springer, Berlin, Heidelberg, New York, **1998**].

Pepstatin, isovaleryl-Val-Val-*Sta*-Ala-*Sta*-OH, a low-molecular-weight inhibitor of acidic proteases (e.g., → renin, pepsin, cathepsin D, bacterial aspartic proteases and → HIV protease) isolated from the culture fluid of *Actinomyces*. Pepstatin contains two building blocks of → statine (*Sta*). Pepstatin has proved to be a lead in the search for inhibitors of renin [H. Umezawa

et al., *J. Antibiot.* **1970**, *23*, 259; K. Arima et al., *Phytochemistry* **2000**, *54*, 559].

Peptaibiome, → peptaibiomics.

Peptaibiomics, a technical term proposed to define the analytical methodology for the structural characterization of the *peptaibiome*, e.g., the complete expression of → peptaibiotics by fungal multienzyme complexes [C. Krause et al., *Amino Acids* **2006**, *30*, 435].

Peptaibiotics, a sub-group of the → peptaibols. They are *N*-acylated linear peptide antibiotics (M_r ~500–2200 Da) containing a high content of α-aminoisobutyric acid (Aib) exerting antibiotic or other bioactivities [H. Brückner et al., *Amino Acids* **1991**, *1*, 251; T. Degenkolb et al., *J. Peptide Sci.* **2003**, *9*, 666; *Chem. Divers.* **2006**, *3*, 593; C. Krause et al., *Amino Acids* **2006**, *30*, 435].

Peptaibolin, Ac-Leu-Aib-Leu-Aib-Pheol, an unusual short-sequence representative of the → peptaibols. It exhibits moderate antimicrobial activity against Gram-positive bacteria and yeasts. The total synthesis, 3-D structure, and membrane-modifying properties of peptaibolin and selected analogues were described in 2001 [H. Hülsmann et al., *J. Antibiot.* **1998**, *51*, 1055; M. Crisma et al., *Tetrahedron* **2001**, *57*, 2813].

Peptaibols, amphiphilic, membrane-active peptides produced by soil fungi and molds comprising 5 to 20 amino acid residues. Peptaibols are fungal secondary metabolites produced by a widespread group of filamentous fungi comprising soil and aquatic species, wood-decaying, plant pathogenic, fungicolous and coprophilous species. They exhibit antibiotic activity against bacteria and fungi and hence belong to the → peptaibiotics. Peptaibols are synthesized non-ribosomally and contain α-aminoisobutyric acid (Aib,

C $^{\alpha,\alpha}$ -dimethylglycine) and other C $^{\alpha}$ -tetrasubstituted α -amino acids such as isovaline (Iva, α -ethylalanine, C $^{\alpha}$ -methyl-C $^{\alpha}$ -ethylglycine) or in a single case α -ethylnorvaline that support helix formation (α -helices and 3_{10} -helices). Furthermore, they are characterized by the presence of other non-proteinogenic amino acids or lipoamino acids, and a reduced C-terminus such as L-phenylalaninol (Pheol), valinol (Valol) or leucinol (Leuol). An unusually short member of the peptaibols is \rightarrow peptaibolin. The longest members of the class, e.g., \rightarrow alamethicin, are N-acetylated at the N-terminus, whereas the N-terminus of the shortest members (seven building blocks) is acylated with a fatty acid of eight or ten carbon atoms. *Lipopeptaibols* are very lipophilic peptaibols with an N-terminus acylated by octanoic, decanoic, or (Z)-dec-4-enoic acid. The amphipathic nature of peptaibols allows them to self-associate into oligomeric ion-channel assemblies which span the lipid bilayer membranes. The substitutions at the C $^{\alpha}$ -atoms, together with those of the terminal amino acid residues, cause a lack of local flexibility of the peptide chain and promote the formation of stable secondary structure domains (α - and 3_{10} -helices, respectively, and β -turns). Peptaibols induce leakage of the cytoplasmic material which may lead to cell death. Long-sequence peptaibols form potential-dependent ion-conducting pores in liquid membranes. According to the carpet-like mechanism, short-sequence (lipo)peptaibols tend to float on the lipid bilayer. The peptaibols exert bacteriostatic, fungicidal, cytostatic, and hemolytic effects. In 1995, a stepwise automated SPPS of naturally occurring peptaibols, such as alamethicin F30 and F50, saturnisporin SA III, and trichotoxin A50-J, was described. Recently, the first total synthesis of the peptaibol hypo-

murocin A1 in solution phase using the \rightarrow azirine/oxazolone method was reported. More than 300 peptaibols have been reported. A sequence and structure resource for peptaibols is provided by the *Peptaibol Database*, which can be freely accessed at <http://www.cryst.bbk.ac.uk/peptaibol> [E. Benedetti et al., *Proc. Natl. Acad. Sci. USA* **1982**, 79, 7951; R. F. Epand et al., *Eur. J. Biochem.* **1999**, 266, 1021; H. Wenschuh et al., *J. Org. Chem.* **1995**, 60, 405; C. Toniolo et al., *Cell Mol. Life Sci.* **2001**, 58, 1179; L. Whitmore, B. A. Wallace, *Nucleic Acids Res.* **2004**, 32, D593; N. Pradeille et al., *Chem. Divers.* **2005**, 2, 1127].

PeptiCLECs, crosslinked enzyme crystals, **CLECs**, of proteases used as catalysts in peptide synthesis. CLECs are microcrystals grown from aqueous solution and crosslinked with a bifunctional agent. They are highly stable against autolysis and exogenous protease degradation, and are used as catalysts in environments that are normally incompatible with enzyme activity, such as aqueous-organic solvent mixtures, near-anhydrous organic solvents, and increased temperature. CLECs offer the advantages of high product purity and the potential for enzyme recycling. Thermolysin-CLEC (T-CLEC), also termed PeptiCLEC-TR, and subtilisin-CLEC have been successfully used for peptide synthesis, especially for the preparation of dipeptides [R. A. Persichetti et al., *J. Am. Chem. Soc.* **1995**, 117, 2732; Y.-F. Wang et al., *J. Org. Chem.* **1997**, 62, 3488; S. J. Faulconbridge et al., *Organ. Process Res. Dev.* **2000**, 4, 563].

Peptidases, *proteolytic enzymes, peptide-cleaving enzymes, proteases*, enzymes catalyzing the hydrolysis of peptide bonds. More than 500 members are known and, in a general sense, they all catalyze the same reaction. In the past,

there has been widespread uncertainty about the exact meaning of the terms. The NC-IUBMB recommends the term *peptidase* as the general term for all peptide bond-hydrolyzing enzymes. The EC List can be found in its revised version on the World Wide Web (WWW) at <http://www.chem.qmw.ac.uk/iubmb/enzyme/index.html>. An enzyme is said to be an *endopeptidase* when the susceptible peptide bond is located internally in a peptide or protein. In contrast, an enzyme is termed an *exopeptidase* when the susceptible peptide linkage is at the carboxyl terminus or at the amino terminus of the substrate. In the EC List there are also terms for subtypes of exopeptidases and endopeptidases. Exopeptidases acting at the free *N*-terminus liberate a single amino acid residue (*aminopeptidases*) or a dipeptide or a tripeptide (*dipeptidyl-peptidases* and *tripeptidyl-peptidases*), whereas those acting at the free *C*-terminus liberate a single residue (*carboxypeptidases*) or a dipeptide (*peptidyl-dipeptidases*). Peptidases differ in the specificities that they display in hydrolysis reactions. It is somewhat simplistic to designate a peptidase on the basis of single amino acid residue at the active site. The binding site for a peptide substrate in the active site of a peptidase is envisioned as a series of subsites *S* which interact with the amino acid building blocks *P* of the peptide or protein substrate. The sites are numbered from the catalytic site, $S_1 \dots S_n$ towards the *N*-terminus of the peptide substrate, and $S'_1 \dots S'_n$ towards the *C*-terminus. In analogy, the residues which they accommodate are numbered $P_1 \dots P_n$, and $P'_1 \dots P'_n$, respectively. The site of enzymatic cleavage of the substrate occurs between the residues P_1 – P'_1 . Proteolysis is functionally irreversible, since energy is liberated in the hydrolysis of peptide bonds. From the overall change in energy it

follows that the ionized hydrolysis products are thermodynamically more stable. The overall process of peptide bond scission is identical in all classes of peptidases, and differences between the catalytic mechanism are rather subtle. The attack on the carbonyl group of the peptide bond requires some nucleophilic agents, either oxygen or sulfur, in order to approach the slightly electrophilic carbonyl carbon atom. To remove a proton from the attacking nucleophile, general base catalysis will assist this process. Furthermore, some type of electrophilic action on the carbonyl oxygen increases the polarization of the C–O-bond. Generally, the four classes of peptidases differ in the groups that perform nucleophilic attack, general base catalysis, and electrophilic assistance (\rightarrow serine peptidases, \rightarrow cysteine peptidases, \rightarrow aspartic peptidases, \rightarrow metallopeptidases) [A. J. Barrett, N. J. Rawlings, J. F. Woessner (Eds.) *Handbook of Proteolytic Enzymes*, Academic Press, San Diego, 1998].

Peptide 6A, H-Ala-Arg-Pro-Ala-Lys-OH, a 5-peptide with permeability-increasing properties originally derived from plasmin-degraded human \rightarrow fibrinogen. Furthermore, it acts as a potent coronary vasodilator and effective pulmonary ACE inhibitor *in vitro* and *in vivo* [T. Saldeen et al., *Thromb. Res.* **1981**, 23, 465; R. Moalli et al., *J. Pharmacol. Exp. Ther.* **1987**, 243, 897].

Peptide 19 (PEP 19), a peptide ($M_r \sim 7.6$ kDa) first discovered in the developing rat cerebellum. Later, PEP 19-immunoreactivity was investigated in the rat vagal and glossopharyngeal sensory ganglia. PEP 19 binds to \rightarrow calmodulin and inhibits Ca^{2+} -calmodulin signaling [L. Sangameswaran et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 5651; H. Ichikawa, T. Sugimoto, *Brain Res.* **2005**, 1038, 107].

Peptide 46, human cellular tumor antigen p53 (361–382), GSRAHSSHLK¹⁰SKK GQSTSRH²⁰KK, a lysine-rich 22-peptide derived from the C-terminal domain of p53. Peptide 46 is capable of restoring the growth suppressor function of mutant p53 in human tumor cells. Later, it was shown that peptide 46 binds mutant p53 within the core and C-terminal domains of p53. These results may facilitate the design of p53-reacting drugs for cancer therapy [G. Selivanova et al., *Mol. Cell. Biol.* **1999**, 19, 3395].

Peptide 74, TMRKPRCGNP¹⁰DVAN, a synthetic 14-peptide derived from a prosegment of the 72-kDa type IV collagenase. It inhibits tumor cell invasion of both A2058 fibrosarcoma and HT1080 melanoma cells. Peptide 74 could be a potential antimetastatic agent due to lacking cytotoxic effects [A. Melchiori et al., *Cancer Res.* **1992**, 52, 2353].

Peptide 810, H-Gln-Asp-Leu-Thr-Met-Lys-Tyr-Gln-Ile-Phe¹⁰-OH, a 10-peptide encoded by a gene fragment from human melanoma M14. It contains the antigenic epitope -Lys-Tyr-Gln-Ile-recognized by the human mAb L92. Peptide 810 is the first peptide recognized by cytotoxic T lymphocytes in melanoma patients, and should be interesting as a melanoma vaccine replacing whole cells [N. Morioka et al., *J. Immunol.* **1994**, 153, 5650].

Peptide aldehydes, peptide derivatives bearing a functional aldehyde moiety. They are highly reactive compounds characterized by chemical and optical instability. Epimerization of peptide aldehydes is a permanent danger during synthesis and purification. A good indicator of possible epimerization is the aldehyde signal in ¹H NMR. The functionalization of peptides and proteins has been developed to a subject of intensive research. Peptide

aldehydes are of great importance as enzyme inhibitors and are used as starting materials for further carbonyl chemistry, e.g., peptide backbone modification or ligation reactions (→ chemical ligation). The aldehyde function allows the generation of transition-state analogues and reacts easily with naturally occurring amino acids, e.g., cysteine (thiazolidine formation) or serine and threonine (oxazolidine formation). For the synthesis of peptide aldehydes, two main strategies have been developed. The first strategy consists of prior synthesis of the peptide, followed by the introduction of the aldehyde function. The second procedure uses protected α -amino aldehydes as starting materials. After peptide elongation, the masked aldehyde function is deprotected, yielding the peptide aldehyde [F. Guillaumie et al., *Tetrahedron Lett.* **2000**, 41, 6131; T. Groth, M. Meldal, *J. Comb. Chem.* **2001**, 3, 45; A. Moulin et al., *J. Peptide Sci.* **2007**, 13, 1 (Review)].

Peptide alkaloids, a group of linear and cyclic peptides belonging to the major class of alkaloids. Cyclic peptide alkaloids have been isolated from the leaves, stem bark, root bark, and seeds of a huge variety of plant species, for example, of the Rhamnaceae and Sterculiaceae families, all over the world. They are characterized by their structural similarity, and possess a 13-, 14-, or 15-membered cycle containing an aromatic ring system. To date, over 200 cyclic peptide alkaloids have been described. These have been used historically for the treatment of a variety of diseases. Their biological activities comprise sedative, antibacterial, antifungal, and antiparasitic effects. Frangulofoline, amphibine H, rugosanines A and B, and nummularines B, K, R, and S are members of the peptide alkaloid family, the antifungal properties of which include significant growth inhibition

activity against *Aspergillus niger* but not *Candida albicans*. Interestingly, franguloline is known to bind to \rightarrow calmodulin. According to the classical definition, alkaloids are of plant origin; however, with the celenamides A and B linear peptide alkaloids have been isolated from the sponge *Cliona celata*. The synthesis of cyclopeptide alkaloids is of great interest due to their restricted natural availability (0.0002–1% of dried plants). Several synthetic strategies have been developed, starting with the initial approach to macrolactamization of a pentafluorophenyl ester reported by the research group of U. Schmidt. Further strategies have been developed for the key macrocyclization step, e.g., based on an intramolecular S_NAr reaction or an intramolecular copper(I)-mediated vinylation for installing the 13-membered macrocyclic enamide, as has been recently demonstrated in the first total synthesis of the sedative paliurine F [E. W. Warnhoff, *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 162; U. Schmidt et al., in: *The Alkaloids*, Volume 26, Academic Press, **1985**, 299; R. J. Stonand, R. J. Andersen, *J. Org. Chem.* **1980**, *45*, 3687; D. Gournelis et al., *Nat. Prod. Rep.* **1997**, *14*, 75; N. H. Tan, J. Zhou, *Chem. Rev.* **2006**, *106*, 840; M. Toumi et al., *Angew. Chem. Int. Ed.* **2007**, *46*, 572].

Peptide antibiotics, a chemically heterogeneous group of peptides produced by microorganisms (bacteria and fungi) that kill or inhibit the growth of other microorganisms (\rightarrow antimicrobial peptides). Initially, peptide antibiotics were classified according to their chemical structure into linear and cyclic compounds, which can be further subdivided into homomeric peptide antibiotics composed exclusively of amino acids, and heteromeric antibiotics that additionally contain non-amino acid-derived building blocks. Furthermore, homodetic

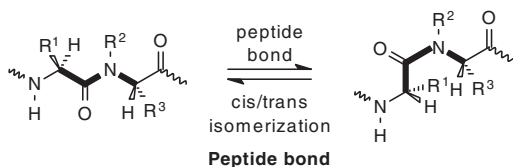
and heterodetic peptide antibiotics can be distinguished based on the character of the covalent bond. For example \rightarrow tyrocidins, gramicidin S (\rightarrow gramicidins), \rightarrow bacitracins, \rightarrow cyclosporins, \rightarrow viomycin, and \rightarrow capreomycin belong to the homomeric, homodetic cyclic peptide antibiotics. Linear peptides, such as \rightarrow gramicidins A-C, bleomycin, and peplomycin are found in the family of heteromeric peptide antibiotics. The representatives of cyclic peptide antibiotics can be either homodetic (\rightarrow polymyxins, colistines etc.) or heterodetic (\rightarrow vancomycin, dactinomycin, ristocetin A, etc.). Furthermore, according to their mode of biosynthesis, the hundreds of known peptide antibiotics can be classified into non-ribosomally synthesized peptide antibiotics (e.g., bacitracins, polymyxins, gramicidins) and ribosomally synthesized compounds (e.g., \rightarrow lantibiotics and related peptides). Ribosomally synthesized peptide antibiotics play a major role in natural host defenses. Generally, these peptides do not exceed 50 amino acid residues. They are rich in positively charged building blocks, and are distinctly amphiphilic. Characteristic features are β -structures stabilized by disulfide bonds, amphipathic α -helices, extended structures, and loops. These structurally heterogeneous peptides have been classified into five different groups. The \rightarrow cecropins and the \rightarrow magainins are prototypes of linear, preferentially helical peptides lacking cysteine. Linear proline- and arginine-rich peptides form an extremely heterogeneous group which are found, for example, in bovine neutrophils, pig intestine, honeybee, *Drosophila*, and other insects, e.g. \rightarrow battenecin 5, \rightarrow indolicidin, and \rightarrow apidaecin Ia. Peptides with more than one disulfide bridge and β -sheet structure comprise a large group, including the families of animal and insect \rightarrow defensins. Finally, peptides which

originate from non-antibiotic proteins form the fifth group of the classification, that includes GIP-(7–42) and DBI-(32–86), these being proteolytic fragments of → gastric inhibitory polypeptide (GIP) and the diazepam-binding inhibitor (DBI), respectively. Although the existence of the first member of the → lantibiotics, → nisin has been known since 1928, while → subtilin, another member of the group was discovered in 1944, the complete structure of these early two antibiotics was elucidated relatively late in time. Non-ribosomally synthesized peptide antibiotics are very often drastically modified, and are largely produced by bacteria. In 1962, the occurrence of antimicrobial and hemolytic peptides in the skin secretions of *Bombina variegata* was described for the first time, and this led to the discovery of → bombinin. Peptide antibiotics have found application in various fields, ranging from the classical → β -lactam antibiotics, although clearly not peptide antibiotics, to immunosuppressors such as → cyclosporins to teichoplanin or → daptomycin, for example. The natural glycopeptide antibiotics → vancomycin and teicoplanin play a significant role in the therapy of Gram-positive bacterial infections [R. E. W. Hancock, *Lancet* **1997**, 349, 418; H. Kleinkauf, H. von Döhren, *Biochemistry of Peptide Antibiotics*, de Gruyter, Berlin, **1990**; R. E. W. Hancock, D. S. Chapple, *Antimicrob. Agents Chemother.* **1999**, 43, 1317].

Peptide aptamers, *paptamers*, *thioredoxin-inserted proteins (TIPs)*, *perturbagens*, artificial proteins selected from combinatorial libraries that display conformationally constrained variable regions. Peptide aptamers are selected from randomized expression libraries based on their *in-vivo* binding capacity to the appropriate target

protein. Inserted peptides are expressed as part of the primary sequence of a structurally stable protein, termed as “scaffold”. This is achieved by the insertion of oligonucleotides encoding the peptide into existing or engineered restriction sites in the open reading frame encoding the scaffold. An ideal scaffold should not interact with any cellular molecule or organelle and should not show enzymatic activity. Peptide aptamers are capable of disrupting specific protein interactions. Peptide aptamer technology has the advantage over existing techniques that the reagents identified are designed for expression in eukaryotic cells. Analogous to intracellular antibodies, peptide aptamers are capable of binding specifically to a given target protein, both *in vitro* and *in vivo*, with the potential to block selectively the function of their target protein. They are powerful new tools for molecular medicine. Blocking the intracellular function of a target protein by peptide aptamers allows the investigation of distinct physiological and pathological processes within living cells. Furthermore, peptide aptamers meet the requirements for the development of novel diagnostic and therapeutic strategies with potential importance for a broad variety of various disease entities such as metabolic disorders, infections, and cancer. They represent a stride forwards in the evolution of modular, molecular tool kits for cell biology and for drug target validation [P. Colas et al., *Nature* **1996**, 380, 548; F. Hoppe-Seyler, K. Butz, *J. Mol. Med.* **2000**, 78, 426; M. Crawford et al., *Brief. Funct. Gen. Proteom.* **2003**, 2, 72; F. Hoppe-Seyler et al., *Curr. Mol. Med.* **2004**, 4, 529].

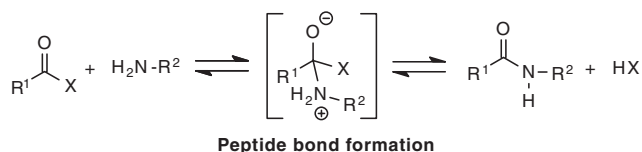
Peptide bond, *amide bond*, the covalent bond between the carboxy group of one amino acid and the amino group of the following amino acid in peptides and proteins. The free rotation about the C–N



amide bond is drastically restricted due to the amide resonance which is based on the ability of the nitrogen atom to delocalize its lone pair over the whole functional group. The resulting partial double-bond character of the C–N bond causes restrictions for the number of energy minima in amide bond torsion (dihedral angle ω). The free energy dependence of the peptide bond *cis/trans* isomerization in a chain fragment indicates two minimum-energy structures. Consequently, two rotamers of the peptide bond exist: the *trans*-configured peptide bond ($\omega \approx 180^\circ$); and the *cis*-configured peptide bond ($\omega \approx 0^\circ$). Both geometric isomers are separated by the rotational barrier corresponding to the perpendicular high-energy state of $\omega \approx 90^\circ$. The distinction between the *cis* and *trans* isomers of the peptide bond originates from a geometry-based classification of organic molecules. The peptide bond exists preferentially in *trans* conformation as the *cis* conformation (\rightarrow *cis* peptide bond) is thermodynamically unfavored with respect to the *trans* form by about 2 kcal mol⁻¹. *Cis*-type arrangements in proteins mainly involve proline amino acids in -Xaa-Pro- sequences (\rightarrow peptidyl prolyl *cis/trans* isomerases), whereas non-proline *cis* peptide bonds ([http://www.imb-jena.](http://www.imb-jena.de/ImgLibDoc/cispep/non-proline/IMAGE_CISPEP2.html)

[de/ImgLibDoc/cispep/non-proline/IMAGE_CISPEP2.html](http://www.imb-jena.de/ImgLibDoc/cispep/non-proline/IMAGE_CISPEP2.html)) are extremely rare in peptides and proteins (<0.03%, usually occurring in β -turns) [A. Jabs et al., *J. Mol. Biol.* **1999**, 286, 291; C. Dugave, L. Demange, *Chem. Rev.* **2003**, 103, 2475; R. Poteau, G. Trinquier, *J. Am. Chem. Soc.* **2005**, 127, 13875].

Peptide bond formation, a nucleophilic substitution reaction of an amino group (nucleophile) at a carboxy group involving a tetrahedral zwitterionic intermediate. In order to perform peptide bond formation under mild conditions, it is an important prerequisite to activate the carboxy function of the carboxy component R¹-CO-XR² by the introduction of electron-accepting moieties, thereby increasing its electrophilicity. Groups which exert either an inductive (-I) effect or mesomeric (-M) effect decrease the electron density at the C=O group. The amino component R³-NH₂ attacks with its nitrogen lone pair the electrophilic position of the carboxy group to give the tetrahedral zwitterionic intermediate. Peptide bond formation is then completed by dissociation of the leaving group (nucleofuge R²X⁻) from the tetrahedral intermediate. The leaving group capacity (nucleofugicity) is another factor influencing the reaction



rate. The variation of the leaving group XR^2 provides a broad spectrum of methods for peptide bond formation (\rightarrow coupling reagents) [M. Goodman et al. (Eds.), *Synthesis of Peptides and Peptidomimetics*, in: *Houben-Weyl, Methoden der organischen Chemie*, Volume E22a, K. H. Büchel (Ed.), Thieme, Stuttgart, **2002**; N. Sewald, H.-D. Jakubke, *Peptides: Chemistry and Biology*, Wiley-VCH, Weinheim, **2002**; N. L. Benoiton, *Chemistry of Peptide Synthesis*, CRC Press, Boca, Raton, **2006**].

Peptide catalysts, peptides that catalyze chemical reactions such as aldol, retro-aldol, and Michael reactions. In contrast to enzymes or catalytic antibodies (\rightarrow abzymes), small peptides often display limited catalytic activity and substrate specificity. Combinatorial methods combined with reaction-based or catalysis-based high-throughput selection approaches are suited for catalyst optimization [F. Tanaka, *Chem. Record* **2005**, 5, 276].

Peptide cleavage, partial hydrolysis of peptides and proteins by chemical (\rightarrow end group analysis) or enzymatic methods (\rightarrow proteolysis) for \rightarrow sequence analysis. Limited peptide cleavage (limited proteolysis) is important for various metabolic processes.

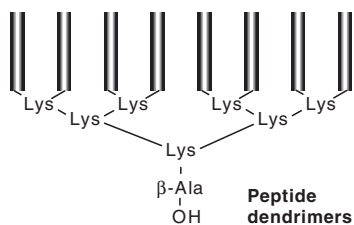
Peptide chronomics, the quantitative description of molecular mechanisms involved in chronobiological phenomena related to peptides and their biological activity. Chronobiology examines periodic (cyclic) phenomena in living organisms. While the classical concept of homeostasis postulates that physiological processes remain largely constant within a certain range in the healthy state, and change over to deviation from such "normal values" in a pathologic state, it becomes evident that living organisms undergo rhythmic and chaotic variations ("biological clock").

Endogenous peptides, e.g., hormones, may undergo periodic modulations over time of their concentration *in vivo* or their efficacy towards the corresponding receptor binding; a similar situation applies to peptide drugs. For instance, \rightarrow endothelin-1 (ET-1), \rightarrow substance P (SP), and \rightarrow neuropeptide Y undergo an about 8 hour (circaoctohoran) rather than a circadian variation in clinical health, whereas vasoactive intestinal peptide (VIP) is circadian (24 h) rhythmic. Maps of circadian and extra-circadian patterns are expected to support screening and diagnosis in order eventually to lead to an improved knowledge on disease mechanisms [A. Löckinger et al., *Peptides* **2004**, 25, 533].

Peptide deformylase (PDF), EC 3.5.1.17, an enzyme catalyzing the subsequent removal of the \rightarrow formyl group at the *N*-terminus of nascent polypeptide chains from the majority of bacterial proteins. Peptide deformylase represents a subfamily of metalloproteases of various bacteria sharing 28–65% sequence identity, but have no resemblance to other known enzymes [J. M. Adams, *J. Mol. Biol.* **1968**, 33, 571; M. K. Chan et al., *Biochemistry* **1997**, 36, 13904; A. Becker et al., *J. Biol. Chem.* **1998**, 273, 11413].

Peptide dendrimers, highly ordered and highly branched compounds with peptide moieties attached. Dendrimers are formed by successive reactions of polyfunctional monomers around a core, and consequently have many terminal groups. Peptide dendrimers may be applied as multivalent antigens and immunogens, for sero-diagnosis and drug delivery. They may be synthesized either by a divergent or by a convergent strategy. While the divergent strategy employs a stepwise assembly of the multivalent target, starting from an initiator core to the periphery, the convergent strategy uses preformed fragments

that are attached to the central core. The core should be an oligofunctional compound, such as a carbohydrate molecule, or alternatively a branched oligolysine derivative. A low resin loading is required throughout the synthesis to minimize interactions between the peptide chains that may be detrimental for the coupling efficiency in the divergent approach. In the convergent synthesis, classical fragment condensation in solution using fully protected peptides may be employed. This approach, however, often suffers from low yield and slow coupling reactions as well as poor solubility and sometimes problems of racemization. Alternatively, chemical ligation protocols with unprotected peptides have been successfully employed [P. Vepřek, J. Ježek, *J. Peptide Sci.* **1999**, 5, 5; P. Vepřek, J. Ježek, *J. Peptide Sci.* **1999**, 5, 203].



Peptide drugs, pharmacologically active peptides that are used for therapeutic purposes. Peptides have, in principle, the potential of being interesting lead compounds for drug development or even drugs by themselves. Many peptides address specifically one receptor or one family of receptors exerting a well-defined spectrum of biological answers upon binding. However, most peptides are usually regarded not to be useful as drugs because they lack metabolic stability *in vivo* and are not orally available. Moreover, many body barriers cannot be crossed by peptidic compounds. Often, peptides are

more expensive to produce and hence need to be more potent than other alternatives. However, the past decade has witnessed a renaissance of peptides to be applied as drug molecules. This coincides with advancements in chemical modification of peptides, administration, and formulation. Most peptides still have to be administered by injection, although recently different delivery methods have been developed and some have already reached the market. These include transdermal patches, inhalation, transdermal electrophoresis and sometimes even oral formulations. The half-life of a peptide *in vivo* can also be prolonged by chemical modifications such as glycosylation or conjugation to polyethylene glycol (PEG). The resistance towards proteolytic degradation is improved upon cyclization and/or D-amino acid incorporation. One class of peptide drugs is formed by peptide hormones that have been used traditionally for the treatment of several diseases. In particular, \rightarrow insulin should be mentioned in this context. Today, insulin is produced by recombinant technology and, in addition to the native sequence of human insulin, both fast-acting and slowly-acting insulin derivatives have been obtained by amino acid replacements. While insulin is used in diabetic patients to lower the blood glucose level, its antagonist \rightarrow glucagon increases blood glucose. Exenatide (\rightarrow exendins) is a synthetic peptide that enhances glucose-dependent insulin secretion by the pancreatic β -cell and suppresses inappropriately elevated glucagon secretion. Pramlintide, a synthetic analogue of human \rightarrow amylin, is used by injection for antihyperglycemic therapy of diabetic patients treated with insulin. \rightarrow Oxytocin and its analogues, when applied either intranasally or by injection, cause uterine contractions and are used to induce labor, to control bleeding after childbirth, and to

support milk secretion during breastfeeding. The oxytocin analogue atosiban acts as an oxytocin receptor antagonist and is used clinically to suppress premature labor between weeks 24 and 33 of gestation. → Vasopressin and its analogues, e.g., desmopressin, when administered by injection support the kidneys in reabsorbing water in the body. They also raise the blood pressure by constricting the blood vessels. Human → secretin is used, by intravenous injection, to stimulate pancreatic and gastric secretion. The → calcitonins are administered nasally or by injection to treat osteoporosis and high blood calcium levels. → GnRH agonists are used for the treatment of prostate cancer, while antagonists are being tested as contraceptive agents. Recombinant human → parathyroid hormone (1–34) [PTH(1–34)] is employed as a subcutaneous injection for the treatment of osteoporosis. The human → brain natriuretic peptide (hBNP) has been approved as a vasodilatory cardiovascular drug for intravenous administration. → Somatostatin analogues, e.g. → octreotide, are applied as an injection for the treatment of severe diarrhea caused by certain types of cancer. It is sometimes also used to treat acromegaly. Besides the above-mentioned hormones, several other peptide drugs are currently on the market. The → conotoxin-derived analgesic → ziconotide must be administered intrathecally, but displays an 800-fold increased analgesic activity compared to morphine. The orally available cyclosporin A is an immunosuppressant indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. → T20 is a synthetic 36-peptide used by injection as a fusion inhibitor for the treatment of HIV/AIDS. Human protein C concentrate is employed for therapy of patients with life-threatening blood clotting complications. Eptifibatide

(integrilin) is a cyclic peptide containing an RGD-sequence that is applied for inhibition of blood platelet aggregation. → Daptomycin is a novel lipopeptide antibiotic used in the treatment of certain infections caused by Gram-positive organisms. Glycopeptide antibiotics inhibiting peptidoglycan biosynthesis, with → vancomycin as one representative, are indicated for serious infections where other antibiotics are not effective. The glycopeptide antibiotic bleomycin inhibits DNA synthesis and is used as an injection in cancer chemotherapy. Besides these derivatives, many other peptides are under clinical investigation. Therapeutic cancer targeting peptides have been developed and shown clinical promise because they can be conjugated with cytotoxic agents and hence be delivered to tumor tissues. Monoclonal antibodies or peptides recognizing cell-surface receptors that are up-regulated on tumor cells can be used as homing devices for tumor-targeting strategies [D. J. Ward, *Peptide Pharmaceuticals: approaches to the design of novel drugs*, Open University Press, Philadelphia, **1991**; V. Marx, *Chem. Eng. News* **2005**, 83, 17; L. Gentilucci et al., *Curr. Med. Chem.* **2006**, 13, 2449].

Peptide E, bovine adrenal medulla peptide 3200 BAM-3200, YGGFMRRVGR¹⁰PE WWMDYQKR²⁰YGGFL, a proenkephalin A-processing product ($M_r \sim 3.2$ kDa; 25 aa) originally isolated from the bovine adrenal medulla. It contains both a Met-enkephalin sequence at the N-terminus and a Leu-enkephalin sequence at the C-terminus (→ enkephalins). Peptide E shows κ -opioid receptor agonistic activity, and is a good substrate for the ECE-2 (→ endothelin-converting enzymes) [D. L. Kilpatrick et al., *Proc. Natl. Acad. Sci. USA*

1981, 78, 3265; N. Mzhavia et al., *J. Biol. Chem.* **2003**, 278, 14704].

Peptide histidine isoleucine amide (PHI), peptide with N-terminal histidine and C-terminal isoleucine amide, HAGGVF TSDF¹⁰SRLGQLSAK²⁰KYLESLIa, a 27-peptide amide from porcine intestine belonging to the → secretin family. It shares the same peptide precursor with the → vasoactive intestinal peptide (VIP), and is found together with VIP, for example, in the neurons of the central nervous system, in the digestive tract, urogenital tract, lungs, and wall of the gallbladder. The biological activities are similar to those of VIP and → secretin. PHI may be involved in the regulation of food intake [K. Tatemoto, V. Mutt, *Proc. Natl. Acad. Sci. USA* **1981**, 78, 6603; M. Bodner et al., *Proc. Natl. Acad. Sci. USA* **1985**, 82, 3548; P. K. Olszewski et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2003**, 284, R1445].

Peptide hydrolysis, complete hydrolysis of peptides and proteins for → amino acid analysis or the production of individual amino acids from the peptide or protein hydrolysate. For this purpose, numerous chemical and enzymatic protocols are known, but none of these procedures alone is fully satisfactory. Besides hydrolysis with 6 M hydrochloric acid at 120 °C for 12 h, or with dilute alkali (2–4 M NaOH) at 100 °C for 4–8 h, mixtures of → peptidases can also be used for complete peptide hydrolysis. Restricted or limited peptide hydrolysis (→ peptide cleavage) is important for → sequence analysis and peptide mapping.

Peptide leucine arginine (PLR), LVRG CWTKSY¹⁰PPKPCFVR (disulfide bond: C⁵–C¹⁵), an immunomodulatory peptide isolated from the skin of the Northern Leopard frog (*Rana pipiens*). The name PLR reflects the N- and C-terminal residues.

PLR elicits rapid, non-cytolytic histamine release with a two-fold greater potency compared with → mellitin. PLR is capable of permeabilizing negatively charged unilamellar lipid vesicles, but not neutral vesicles – a result that is consistent with its non-hemolytic action. It inhibits the early development of granulocyte macrophage colonies from bone marrow stem cells [A. L. Salmon et al., *J. Biol. Chem.* **2001**, 276, 10145].

Peptide library, a collection of different peptides e.g., to be subjected to biological testing. Peptide libraries can be obtained following the methodology of combinatorial peptide synthesis. The peptide library is either present as a mixture of many different peptides or as a collection of spatially resolved single compounds. In the latter case, the single members of the peptide library are present either, e.g., in the wells of microtiter plates (products of → parallel synthesis), bound to resin beads (one bead, one compound library), or present in any other containment that might be applicable for the biological test system. A peptide library can also be attached to planar surfaces, as obtained by → light-directed spatially addressable parallel synthesis or by → spot synthesis on cellulose membranes. Peptide libraries may be designed to contain between <10² and >10⁶ compounds. → High-throughput screening methodology enables thousands of compounds to be tested per day in a protein-based biological assay. The complexity of a peptide library depends on the state of knowledge about the target structure to be addressed. If very little is known about the target, as many compounds as possible with a structural diversity as wide as possible should be present in the library. When a lead compound has been identified, the libraries may be much more

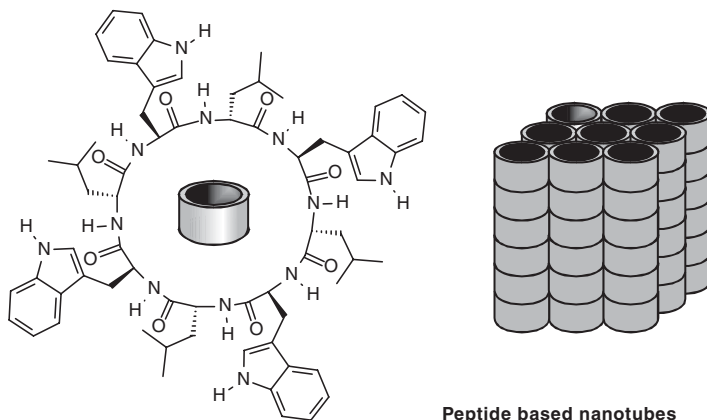
focused and contain only a relatively small number of different members. If compound mixtures are to be obtained during library synthesis, then chemical encoding can be used in the split-and-combine method to identify the peptide sequence present on a single bead. Alternatively, for larger beads whose core contains a micro-electronic transponder, radiofrequency tagging is viable. When working with compound mixture libraries, deconvolution is an important issue once the biological results concerning the activity of the library have been obtained. Peptide libraries of biological origin may be present in the form of a phage display library. In this case, the geno- and the phenotype are connected and, e.g., the bacteria that present a certain bioactive peptide sequence encoded by the DNA-sequence of the phage can be selected and amplified [G. Jung (Ed.), *Combinatorial Peptide and Nonpeptide Libraries: A Handbook*, Wiley-VCH, 1996; S. Cabilly (Ed.), *Combinatorial Peptide Library Protocols*, Humana Press, Totowa, N.J., 1998].

Peptide ligation, methodologies for coupling peptide fragments through the formation of natural backbone amides. Such strategies have enormous potential for the preparation of protein pharmaceutical lead compounds containing novel peptide or protein domains. Furthermore, such approaches allow the facile site-specific introduction of unnatural structures, for example, fluorescent labels into the protein molecule, not possible by recombinant-DNA-based methods. These methods include \rightarrow chemical ligation (native chemical ligation, NCL; extended native chemical ligation, ENCL, solid-phase chemical ligation; "one-pot" synthesis approach), and \rightarrow biochemical protein ligation (expressed protein ligation, EPL/intein-mediated protein ligation, IPL), beside

mixed approaches (ligation combined with bioconjugation) and enzyme-assisted methods (\rightarrow expressed enzymatic ligation).

Peptide M, DTNLA^{SSTII}¹⁰KEGIDKTV, an 18-peptide corresponding to a sequence region 303–320 of the retinal S-antigen. It produces experimental autoimmune uveitis (EAU), similar to that produced by native S-antigen, in several vertebrates species including non-human primates [L. A. Donose et al., *Arch. Ophthalmol.* 1987, 105, 838; S. Nityanand et al., *J. Clin. Immunol.* 1993, 13, 352].

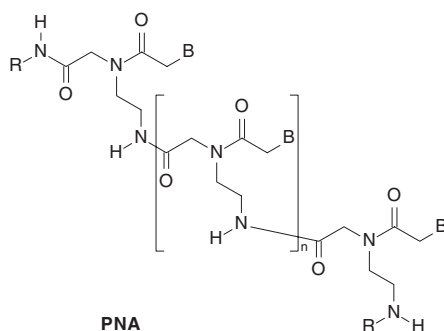
Peptide-based nanotubes, well-ordered supramolecular nanoparticles formed from linear or cyclic oligopeptides by self assembly. The latter process can be defined as the spontaneous organization of individual components into an ordered structure favored by complementarity in shape among the individual components and weak, non-covalent interactions. Besides nanotubes, various types of self-assembly peptide systems such as vesicles, tapes, sheets, and nanowires are known. Peptide-based nanotubes can be formed by the self assembly of flat, ring-shaped peptide subunits built up of alternating D- and L-amino acids, giving rise to extended tubular β -sheet-like structures. This process is directed by the formation of an extensive network of intersubunit hydrogen bonds. In crystal structures, nanotubes are stabilized by hydrophobic interactions. Peptide-based nanotubes are valuable for the construction of biotechnology-related devices such as biosensors and biomolecular filters. *Nanobiotics* constitute a new class of antibacterial agents based on self-assembling peptide nanotube architecture. Stacks of ring-shaped peptides undergo self assembly into three-dimensional tubular structures selectively within bacterial membranes. These structures



cause increased membrane permeability, collapse of transmembrane ion potentials, and rapid cell death. Generally, channel structures are important in biological systems, and their potential application in nanotechnology and biomedicine have maintained an active area of investigations [H. S. Kim et al., *J. Am. Chem. Soc.* **1998**, 120, 4417; S. Y. Fung et al., in: *Handbook of Nanostructured Biomaterials and Their Applications in Nanobiotechnology*, H. S. Nalwa (Ed.), American Scientific Publishers, Stevenson Ranch, **2005**, pp. 1–66].

Peptide nucleic acids (PNA), DNA-mimicking peptides containing neutral amide backbone linkages. In PNA, the normal phosphodiester backbone of a DNA is replaced by *N*-(2-aminoethyl)glycine units. The standard nucleotide bases are connected by a methylene carbonyl linker to this backbone at the amino nitrogens. This PNA type binds in a sequence-specific manner to a complementary strand of DNA, RNA, or PNA oligomer with Watson–Crick or Hoogsteen base pairing. PNA hybridizes better in the antiparallel orientation than in the parallel orientation, with the amino terminus equivalent to the 3' DNA end and the carboxy terminus equivalent to the 5'

DNA end. A slightly different type of PNA consists of amino acids with nucleobases in their side chains. PNA bind strongly to complementary DNA and RNA sequences. The high metabolic stability renders PNA interesting for *in-vivo* applications. However, further modifications are required in order to make it suitable for treatment in eukaryotic cells because of a lacking diffusion across lipid membranes. PNA may be used in diagnostic techniques for the detection of specific DNA, as well as for site-specific labeling and hybridization of functional molecules to both DNA and RNA [T. Koch et al., *Nucleosides Nucleotides* **1997**, 16, 1771; D. R. Corey, *Trends Biotechnol.* **1997**, 15, 224; E. Uhlmann, *Biol. Chem.* **1998**, 379,



1045; P. E. Nielsen, *Curr. Opin. Biotechnol.* **1999**, *10*, 71; S. Karkare, *Appl. Microbiol. Biotechnol.* **2006**, *71*, 575].

Peptide polymers, peptide-derived compounds of high molecular weight that do not represent proteins. Peptide polymers are either homopolymers of only one amino acid or protein-like compounds composed of repeating peptide sequences or peptide drugs that are chemically conjugated to polymer particles. Homopolymers of only one type of amino acid, the polycondensation products of this amino acid, can be obtained from *N*-carboxy anhydrides. Polycationic compounds such as polylysine or polyarginine are able to cross the membrane of cells and can consequently be used to transport biopolymers across the membrane. As polylysine interacts electrostatically with the negatively charged phosphate backbone of DNA, it can be used for gene transfer. Peptide polymers containing repetitive patches of peptide sequences can be obtained either by chemical or recombinant synthesis. This does not limit the polypeptides to be obtained to one amino acid species, as for the homopolymers. The third type of peptide polymers, the conjugates of peptide drugs to polymer particles, may be used for formulation strategies in order to increase the lifetime of a drug *in vivo*. Such polymeric material must be biocompatible and display the necessary mechanical properties. Poly(2-hydroxyethyl-methacrylate), which is probably one of the most extensively studied biocompatible, hydrogel-forming polymers, and poly(hydroxypropylmethacrylamide) or polyethylene glycol may be used in this approach.

Peptide production, → large-scale peptide synthesis.

Peptide production plant, production facility for manufacturing of peptides as bulk pharmaceuticals. The equipments used should fulfill the standard of "Current Good Manufacturing Practice" (cGMP) according to the Federal Regulations of the Food and Drug Administration. The product structure to be synthesized became more complex and, at present, proteins more than 100 aa are amenable to chemical synthesis under cGMP conditions (→ large-scale peptide synthesis). The reactors used in peptide production plants include steel reaction vessels, systems for heating and cooling, and a heterogeneous group of units for filtration, concentration under reduced pressure, and hydrogenation. Intermediates isolated during the course of production should be obtained as solids rather than as oils, and the method of choice for this is either precipitation (crystallization if possible) or chromatography. Due to the high risk of explosion it is necessary to eliminate, for example, diethyl ether as a precipitation agent. Furthermore, the ozone-destroying dichloromethane must be substituted by other solvents. Corrosive cleavage agents such as trifluoroacetic acid and HF, or the toxic hydrazoic acid HN₃ which occurs as the byproduct of azide coupling (→ acyl azide method), are highly hazardous and must be avoided. The coupling agent → BOP should be substituted, as the byproduct hexamethylphosphoramide (HMPA), which is formed in coupling reactions, is known to be carcinogenic. By contrast, the highly efficient (but also expensive) coupling additive (→ carbodiimide method) → HOAt is normally substituted by the less expensive → HOBt, for commercial and economic reasons. The simplicity of the SPPS and the speed represent the advantages of this alternative strategy and a growing body of improvements in protecting group

schemes and coupling-chemistry has further facilitated the application in peptide production plants. For this purpose, various companies have constructed special equipments which differ significantly from the commercially available laboratory-scale synthesizer. In general, the SPPS process is far more robust and faster, and, therefore, easier to transfer. However, highly skilled chemists are required if problems occur during the synthesis. Savings during the development of the process should be carefully compared to the increased efforts necessary to establish an effective purification program based on expensive chromatographic equipment. Shorter peptides needed in larger quantities should be produced in a solution-phase procedure. Solid-phase chemistry may have advantages for the production of more complex structures, especially, when time is limited [L. Andersson et al., *Biopolymers* **2000**, 55, 227; T. Vorherr et al., *Chimia* **2005**, 59, 25].

Peptide S, NPS or PEPS, a 20-peptide identified in the brain and in periphery via a strategy using an orphan G protein-coupled receptor as target. NPS injection in the brain of mice causes wakefulness, locomotion and arousal, and produces anxiolytic-like paradigms. Recently, it has been reported that NPS is a potent inhibitor of voluntary and fast-induced food intake in rats [B. Beck et al., *Biochem. Biophys. Res. Commun.* **2005**, 332, 859].

Peptide synthesis, a multi-step chemical process for controlled linking of amino acids to form peptides. Peptide synthesis serves: (i) to confirm the primary structure of peptides and proteins determined by sequence analysis; (ii) to determine the structures responsible for the biological activity of a natural peptide by comparison of synthetic analogues with native peptides; (iii) for the chemical alteration of a natural

peptide in order to change its pharmacological effects; (iv) for industrial production (\rightarrow large-scale peptide synthesis, \rightarrow peptide production plant) of biologically active peptides and their analogues; and (v) for the synthesis of model peptides for physical-chemical studies, determination of antigenicity, and as artificial substrates in enzymology. Peptide synthesis can be achieved under mild reaction conditions (\rightarrow peptide bond formation) yielding a defined final product only if all functional groups not involved in the peptide bond forming step are temporarily blocked by suitable protecting groups (\rightarrow protection schemes). Although methodologies for peptide synthesis have been developed since the beginnings of organic chemistry, in recent years the design and synthesis of innovative \rightarrow coupling reagents has been an area of intensive investigation. The development of onium-type coupling reagents has facilitated the incorporation of non-coded or sterically hindered amino acids, including *N*-methylated and α -alkylated amino acids, smoothly into the corresponding peptides. The avoidance of \rightarrow racemization is completely possible only in \rightarrow enzymatic peptide synthesis, but this approach has not yet found wide application. Problems based on \rightarrow difficult sequences represent the main difficulties to be overcome in the near future. The most widely used approach to the synthesis of peptides in a scale up to 50–100 amino acid residues is \rightarrow solid-phase peptide synthesis (SPPS). This procedure allows the synthesis of every kind of peptide and modified peptide sequence. However, the high costs of instrumentation and reagents have restricted SPPS to synthesis on a small scale (from a few milligrams to grams), although in some cases the procedure has been scaled up to multi-tonne preparations. The best choice

for industrial-scale synthesis of short to medium peptides is the traditional solution-phase approach (\rightarrow large-scale peptide synthesis). Recombinant DNA technology can provide large quantities of long-chain peptides and proteins from inexpensive starting materials by fermentation. Unfortunately, however, unnatural residues cannot be easily introduced. New bioactive peptides can be discovered by generating libraries with a high possible number of different sequences by \rightarrow combinatorial peptide synthesis [P. Lloyd, F. Albericio, E. Giralt, *Chemical Approaches to the Synthesis of Peptides and Proteins*, CRC Press, Boca Raton, **1997**; J. Howl (Ed.), *Peptide Synthesis and Applications*, Humana Press, Totowa, N.J., **2005**; J. W. Bode, *Curr. Opin. Drug Discov. Develop.* **2006**, 9, 765].

Peptide synthesizer, an automatic device for polymer-supported peptide synthesis. In 1966, the first semiautomated peptide synthesizer consisting of a reactor unit and a controlling unit was developed by Merrifield for batch-wise peptide synthesis. This first-generation, solid-phase synthesizer is now displayed in the Smithsonian Museum. Later, semiautomatic continuous-flow peptide synthesizers were developed. Continuous-flow mode devices need columns filled with pressure-stable resin material. In some instances the continuous-flow mode has proven to be superior to the batch-wise synthesizer. The major advantages lie in the reduced reagent and solvent consumption, and in the very short coupling cycles, for example, 1–2 min for TentaGel polymers of size 8 μm . The reaction progress may be monitored on a real-time basis by recording the conductivity of the solution. Nowadays, different types of highly sophisticated synthesizers are commercially available. Beside such laboratory-scale synthesizers, large-scale solid-phase

reactors are known which fulfill the standards of cGMP (\rightarrow peptide production plant) [R. B. Merrifield, *Angew. Chem. Int. Ed.* **1985**, 24, 799; E. Atherton, R. E. Sheppard, *Solid Phase Peptide Synthesis: A Practical Approach*, IRL Press, Oxford, **1989**].

Peptide synthetases, *non-ribosomal peptide synthetases* (NRPS), large multifunctional enzymes catalyzing template-directed \rightarrow non-ribosomal peptide synthesis.

Peptide T, H-Ala-Ser-Thr-Thr-Thr-Asn-Tyr-Thr-OH, an 8-peptide corresponding to the partial sequence 185–192 of gp120, the coat protein of HIV. The synthetic peptide, named peptide T according to its high Thr content, was shown to inhibit the binding of both isolated gp120 and HIV-1 to the CD4 receptor. Later, it was reported that the invasion of healthy cells by HIV-1 requires the sequential interaction of the gp120 envelope protein not only with the CD4 primary receptor, but also with a co-receptor which belongs to the chemokine receptor family of seven-helix transmembrane receptors. It has been suggested that CD4 binding triggers a conformational transition of gp120, moving the regions V2, which contains the sequence of peptide T still closer to the co-receptor. Furthermore, peptide T shows potent chemotactic activity on human monocytes, which is correlated with the inhibition of CD4 binding. Peptide T is potentially useful as antiviral agent in AIDS therapy. The minimum sequence of peptide T that retains most of the biological activity is the C-terminal 5-peptide (-Thr-Thr-Asn-Tyr-Thr-OH) that is probably representative for a widespread recognition motif [C. B. Pert et al., *Proc. Natl. Acad. Sci. USA* **1986**, 83, 9254; D. Picone et al., *J. Peptide Sci.* **2001**, 7, 197].

Peptide toxins, toxic peptides and proteins used by various species for defense against

predators, or are employed in the struggle for limited nutrient resources. The peptide toxins are mostly low-molecular-weight, single-chain compounds developed during evolution and produced, for example, by snakes and invertebrates, as well as by virulent strains of bacteria and some plants. The isolation of toxic peptides from venoms of various snakes was first attempted during the late 1960s. After elucidation of the amino acid sequence of a neurotoxin from the cobra *Naja nigricollis*, the primary structure of α -bungarotoxin was described in 1971. The neurotoxic 71-peptide α -cobratoxin from the venom of the Thai cobra *Naja naja siamensis* shows similar activity, and binds specifically to the acetylcholine receptor, thereby inhibiting its opening. Peptide neurotoxins of the venom of the fish-hunting sea snail (genus *Conus*) are the \rightarrow conotoxins. More than 750 scorpion species produce venoms, of which about 40% are capable of damaging mammals, including human beings. The primary neurotoxic components of scorpion venoms are basic peptides ($M_r \sim 8$ kDa). Toxin II from *Androctonus australis Hector*, and toxin V from *Leiurus quinquestriatus quinquestriatus*, for example, are both 64-peptides containing four intrachain disulfide bridges and cause membrane potential-dependent slackening of Na^+ channel activation. Spider peptide toxins paralyze insects by blocking the neuromuscular transmission mediated via glutamate receptors. Argiotoxin from *Argiope lobata* was the first spider venom to be structurally elucidated. The curtatocins from the venom of *Hololena curta* are cysteine-rich peptide amides with 36–38 aa. The toxic effect of these peptides results from an irreversible presynaptic neuromuscular blockade. Sea anemone toxins are divided into type I and type II toxins that cause neurotoxicity by binding

non-neural and muscular Na^+ channels, respectively. For example, toxin Sh-I, a 48-peptide from *Stichodactyla helianthus*, is a type II toxin, whereas \rightarrow anthopleurin A belongs to the type I toxins. Bee venoms contain neurotoxic and cytolytic peptides in addition to enzymes, such as hyaluronidase and phospholipase A2. Members of those peptides are, for example, \rightarrow mellitin, \rightarrow mastoporan, \rightarrow mast cell-degranulating peptide, \rightarrow apamin, and bombolitin from bumblebee venom, which show mellitin-like effects on cell membranes. Amphibian skin is a rich source of various bioactive compounds, including those involved in defense against predators or microorganisms. Furthermore, neuroexcitatory peptides are \rightarrow achatin and \rightarrow fulicin. In contrast to the peptide toxins mentioned above, the poisonous constituents of the notorious toadstool *Amanita phalloides* are rather complex cyclic peptides. Both in Europe and in the United States, *A. phalloides* is responsible for 95% of casualties after ingestion of poisonous fungus. Doubtless, most fatal intoxications by mushrooms occur after ingestion of the *Amanita* species (\rightarrow amatoxins, \rightarrow phallotoxins) [T. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer-Verlag, New York, 1986; A. T. Tu (Ed.) *Handbook of Natural Toxins*, Volumes 1–5, Dekker, New York, 1983–1991; J. E. Alouf, J. H. Freer (Eds.) *Sourcebook of Bacterial Protein Toxins*, Academic Press, London, 1991; A. L. Harvey (Ed.) Snake toxins, in: *International Encyclopedia of Pharmacology and Therapeutics*, Pergamon Press, New York, 1991].

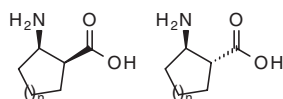
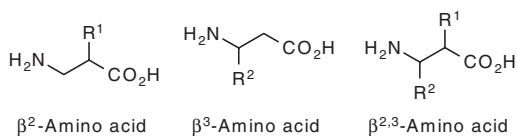
Peptide WE-14, WSKMDQLAKE¹⁰LTAE, a 14-peptide possessing N-terminal W and C-terminal E amino acid residues derived from chromogranin A (\rightarrow chromogranins) and isolated from a human ileal

carcinoid tumor. Human and bovine WE-14 are identical, while porcine and mouse analogues show 93% sequence homology [W. J. Curry et al., *FEBS Lett.* **1992**, 301, 319].

Peptide YY (PYY), *peptide tyrosine tyrosine amide*, *peptide with N-terminal tyrosine and C-terminal tyrosine amide*, YPAKP EAPGE¹⁰DASPEELSR²⁰YASLRHYLNL³⁰ VTRQRYa (porcine PYY), a 36-peptide amide which belongs to the → neuropeptide Y family/ → PP-fold family. Beside → pancreatic polypeptide, → glucagon-like peptide-1, → cholecystokinin, as well as → oxyntomodulin, PYY and its other endogenous form PYY₃₋₃₆ are known as short-term regulators of food intake, in contrast to the long-term satiety regulators → leptin and → insulin. The gut-derived PYY is released postprandially by the L cells of the lower intestine, and inhibits gastric acid and motility through neural pathways. In the dog and pig it is formed primarily in the mucous membranes of the ileum and colon. PYY is involved in the regulation of energy homeostasis in obese children [K. Tatemoto, *Proc. Natl. Acad. Sci. USA* **1982**, 79, 5485; D. Grandt et al., *Regul. Pept.* **1994**, 51, 151; R. L. Batterham et al., *Nature* **2002**, 418, 650; C. L. Roth et al., *J. Clin. Endocrinol. Metab.* **2005**, 90, 6386].

Peptide-based vaccines, peptides used in immunotherapeutic strategies for vaccination against tumors (e.g., adenocarcinoma, glioma, melanoma, etc.), Alzheimer's disease, pathogenic microorganisms (e.g., *Pseudomonas aeruginosa*), and malaria. Peptide vaccines may be designed based on the subunit of a pathogen, either with naturally occurring immunogenic peptides or synthetic peptides corresponding to highly conserved regions required for the pathogen's function. The aim of this

strategy is vaccination with a minimal structure that consists of a well-defined antigen and elicits effectively a specific immune response, without potentially hazardous risks. During the past few years, tremendous progress has been made in the development of fully synthetic vaccines. Synthetic peptides may even take into account the immunological diversity of cytotoxic T lymphocyte responses among patients in the frame of a personalized therapy. Tumors express many different antigens that distinguish them from normal healthy tissue. The microenvironment of the tumor tissue supports tolerance and limits T-cell immunity. Tumor vaccines aim at reversing tumor-induced immunosuppression by eliciting high-avidity T cells against subdominant tumor antigen epitopes. In the case of vaccines against Alzheimer's disease, circulating antibodies are directed towards the CNS and prevent β -amyloid formation or even dissolve the aggregates. Peptides even with post-translational modifications (glycosylation, lipidation) can be obtained synthetically. Modified peptides resist proteolytic cleavage and display improved metabolic stability *in vivo*. Knowledge on the antigenicity of peptides has improved significantly during the past few years as a result of X-ray crystallographic analyses of complexes between peptides and monoclonal antibodies. However, this has not yet been achieved for immunogenicity. The development of a peptide-based vaccine requires the induced antibodies not only to recognize but also to neutralize the infectious agent. However, there are no chemical rules for designing peptide immunogens that elicit neutralizing antibodies. For immunization purposes, peptides are required to exceed a certain molecular mass, and hence they are either conjugated to a protein, or single peptide antigens are

Cyclic $\beta^{2,3}$ -amino acids **β -Peptides**

incorporated into an antigenic \rightarrow peptide dendrimer, also called a multiple antigen peptide, MAP (M_r : 3–100 kDa). This approach has been reported to increase the immunogenicity of weakly immunogenic monomeric peptides, presumably because of the multivalency and improved half-life *in vivo* [K.-H. Wiesmüller et al., *Biol. Chem. Hoppe-Seyler* **2001**, 382, 571; M. H. V. Van Regenmortel, *Biologicals* **2001**, 29, 209; R. Sundaram et al., *Biopolymers (Pept. Sci.)* **2002**, 66, 200; P. J. Cachia, R. S. Hodges, *Biopolymers (Pept. Sci.)* **2003**, 71, 141].

β -Peptides, oligomers of β -amino acids, where the amino group is attached to C^β instead of C^α . The side chains of β -amino acids may be attached either to C^α (β^2 -amino acid) or to C^β (β^3 -amino acid), or to both of them. β^3 -Homoamino acids are homologated by one C_1 unit which is inserted between the carboxy group and C^α of an α -amino acid. Many β -peptides form surprisingly stable helical structures even in aqueous solution. β -Peptides contain more degrees of freedom than α -peptides because of the additional carbon atom per backbone unit, and because the number of secondary structures potentially accessible by the peptide is increased. However, there is only a small number of discrete

conformations that are inherently more stable than all the others and even more stable than the equivalent structures of the corresponding α -peptides. For instance, the β^3 -peptide 3_{14} -helix was shown to exist in solution even for oligomers as short as hexapeptides, while the corresponding α -helix of the equivalent α -hexapeptide is not stable in solution. Interestingly, the helix chirality is also inverted when comparing α -peptides and β -peptides. The macrodipole of the helices is also inverted, because of the different hydrogen bond pattern. β -Peptides have been shown to be completely stable towards proteolytic enzymes of any type. They are not metabolized *in vivo*, and are excreted only slowly via the kidney [D. Seebach et al., *Chem. Biodiv.* **2004**, 1, 1111].

γ -Peptides, oligomers of γ -amino acids. The amino acid building blocks of γ -peptides formally represent doubly homologated analogues of α -amino acids. Depending on the position of the side chain (2,3,4), γ^2 -, γ^3 -, γ^4 -amino acids can be distinguished. A stable solution structure has been found for a γ^4 -hexapeptide that adopts a 2.6_{14} -helix. The same helix has been found for $\gamma^{2,4}$ and $\gamma^{2,3,4}$ -peptides. γ -Peptides containing between 2 and 15 residues have been shown to be completely

stable towards common proteases, without inhibiting their normal activity [J. Frackenhöhl et al., *ChemBioChem* **2001**, *2*, 445; D. Seebach et al., *Chem. Eur. J.* **2002**, *8*, 573].

Peptidome, all peptides expressed in a cell, tissue, body fluid, organ or organism. A term derived by analogy with → proteome.

Peptidomics, an approach to comprehensive analysis of the whole → peptidome. This comprises all expressed peptides with their post-translational modifications. Comparison of peptides in samples of diseased tissue, for example, with those in normal tissue allows the identification of differential expression patterns that may in turn lead to the identification of novel biomarkers. The peptidomics technology is aimed at the simultaneous visualization and identification of small endogenous peptides in the molecular-mass range 1 to 20 kDa. Peptidomics covers the gap between → proteomics and metabolomics. This approach is generally based on separating complex endogenous peptide mixtures, usually by nanoscale capillary reversed-phase liquid chromatography, multistep chromatographic approaches, or gel- or liquid-based isoelectric focusing combined with MS techniques to identify peptides. The technological approach for detailed analysis of endogenous peptides from the brain is termed *neuropeptidomics*. This detection system must accomplish several tasks simultaneously, such as to detect and quantify peptide patterns in the sample, compare and select peptides that differ in abundance more than normal biological variation, and identify and further characterize the selected peptides. This qualitative and quantitative approach has been termed *differential peptide display*. The MS procedure, with either electrospray ionization (ESI) or MALDI, permits the simulta-

neous detection of peptide changes in complex mixtures of hundreds of different peptides [P. Schulz-Knappe et al., *Comb. Chem. High Throughput Screen.* **2001**, *4*, 207; P. Verhaert et al., *Proteomics* **2001**, *1*, 118; G. Baggerman et al., *J. Chromatogr. B* **2004**, *803*, 3; L. D. Fricker et al., *Mass Spectrom. Rev.* **2006**, *25*, 327; M. Svensson et al., *Anal. Chem.* **2007**, *79*, 14].

Peptidomimetics, non-peptidic compounds usually designed as drug candidates that imitate the structural features of a peptide in its conformation and – in the case of agonists – also the biological mode of action on the receptor level. Three different types of peptidomimetics have often been distinguished: (i) *type I peptidomimetics* are usually designed to closely match the peptide backbone, including amide bond isosteres and secondary structure mimetics; (ii) *type II peptidomimetics* are functional mimetics binding to a receptor or enzyme. However, despite being often presumed to serve as structural analogues of native peptide ligands, these non-peptidic compounds often bind to a different receptor subsite and, hence, do not necessarily mimic the parent peptide; (iii) *type III peptidomimetics* are non-peptidic compounds containing the functional groups necessary for the interaction of the native peptide with the corresponding protein (pharmacophoric groups) grafted onto a rigid scaffold. Members of type III may be regarded as ideal mimetics. The design of all three types of peptidomimetics may be assisted by X-ray crystallographic or NMR data, computational *de-novo* design ("in-silico screening"), and combinatorial chemistry. Morphine is a classical example of a natural peptidomimetic that was found to be a mimetic of endogenous peptides (→ endorphins) [A. S. Ripka, D. N. Rich, *Curr. Opin. Chem. Biol.* **1998**, *2*, 441;

R. E. Babine, S. L. Bender, *Chem. Rev.* **1997**, 97, 1359; R. S. Bohacek, C. McMartin, *Curr. Opin. Chem. Biol.* **1997**, 1, 157; K. S. Lam et al., *Chem. Rev.* **1997**, 97, 411].

Peptidyl, an acyl group derived from a C-terminal carboxyl function of a peptide.

Peptidyl dipeptidase, *peptidyl-dipeptide hydrolase*, a term initially used to denote enzymes cleaving C-terminal dipeptides from longer peptide substrates. In 1972, this entry was referred by the IUB to \rightarrow angiotensin-converting enzyme (ACE).

Peptidyl prolyl *cis/trans* isomerases (PPIases), EC 5.2.1.8, ubiquitous and abundant enzymes ($M_r \sim 10$ –150 kDa) catalyzing the isomerization of \rightarrow peptide bonds preceding the proline residue (prolyl bond). The human genome contains 40 different PPIases, as a minimum. Subfamilies of this enzyme class comprise the \rightarrow cyclophilins (Cyp), the \rightarrow FK506-binding proteins (FKBPs), the \rightarrow parvulins and the \rightarrow protein phosphatase 2A phosphatase activator (PTPA) proteins. Cytosolic cyclophilins and FKBPs are high-affinity receptors for the immunosuppressants \rightarrow cyclosporin A and FK506, respectively. Host cell cyclophilins were found to play an essential role in propagating viral infections such as HIV-1 and hepatitis C. Usually, PPIases are enzymatically active in their native fold. However, the human FKBP38 is inactive by its own and requires prior binding to Ca^{2+} /calmodulin for activation. In the only ribosome-bound PPIase, the prokaryotic trigger factor belongs to the FKBP family and has been used in co-transfection experiments to increase the yield of recombinantly expressed proteins. According to the substrate specificity, the human parvulin Pin1 seems to be linked to conformational interconversions of

side-chain-phosphorylated Ser(Thr)-Pro-moieties produced by the action of proline-directed protein kinases. The 18 kDa enzyme Pin 1 has emerged as a switch-like regulatory protein, the deregulation of which plays an important role in a growing number of pathophysiological conditions such as cancer, \rightarrow Alzheimer's disease, asthma, ageing, and viral infections. Generally, PPIases are composed of a catalytic core, which is also found as a single domain in the prototypic PPIases human Cyp 18, human FKBP12 and *E. coli* Par 10, and a different number of additional domains or short motifs covering other functional properties. In contrast to the classical mechanism of the action of \rightarrow molecular chaperones, PPIases catalyze a distinct chemical reaction, namely the rotation about prolyl peptide bonds. Besides their putative function in accelerating slow folding steps, compartmentalized PPIases are likely to have pleiotropic effects within cells. The first member of the PPIases was discovered by Gunter Fischer et al. in pig kidney in 1984 [G. Fischer et al., *Biomed. Biochim. Acta* **1984**, 43, 1101; G. Fischer, A. Aumuller, *Rev. Physiol. Biochem. Pharmacol.* **2004**, 148, 105; L. Min et al., *Front. Biosci.* **2005**, 10, 385].

Peptidyl transferase center (PTC), a ribosomal complex catalyzing peptide bond formation. The ribosomal PTC resides in the large ribosomal subunit and catalyzes both peptide bond formation and peptide release. The peptidyl transferase reaction involves aminolysis by the deprotonated α -amino function of the A-site aminoacyl-tRNA of the ester bond linking the nascent peptide to the 3' hydroxyl of the 3' terminal ribose of the P-site tRNA. The formed short-lived tetrahedral reaction intermediate decomposes by donation a proton back to the leaving oxygen, yielding

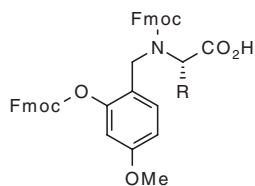
deacylated tRNA at the P-site and one residue-elongated peptidyl-tRNA at the A-site. The ribosome-catalyzed reaction occurs with a speed of ~ 15 –50 peptide bonds per second. From the results of biochemical and crystallographic studies it follows that the PTC is composed entirely of 23S rRNA, and consequently, catalysis of peptide bond formation is based on a ribozyme mechanism. However, the molecular details of the ribozyme mechanism have yet to be revealed [P. Nissen et al., *Science* **2000**, 289, 920; V. I. Katunin et al., *Mol. Cell* **2002**, 10, 339; N. Polacek, A. S. Mankin, *Crit. Rev. Biochem. Mol.* **2005**, 40, 285; M. D. Erlacher et al., *J. Am. Chem. Soc.* **2006**, 128, 4453].

Peptidyl-glycyl-leucine-carboxamide (PG La), GMASKAGAIA¹⁰GKIAKVALKA²⁰La, a cationic, highly potent antimicrobial 21-peptide amide from the skin of the South African frog *Xenopus laevis* belonging to the \rightarrow magainin peptide family. PGLa kills bacteria by permeabilizing membranes [D. Andreu et al., *Eur. J. Biochem.* **1985**, 149, 531; A. Latal et al., *Eur. J. Biochem.* **1997**, 248, 938; O. Konovalov et al., *Eur. Biophys. J.* **2002**, 31, 428].

Peptoid methodology, a method of Fmoc-based SPPS for the synthesis of \rightarrow difficult sequences free of \rightarrow aspartimide and related products. This approach utilizes the well-established concept of \rightarrow backbone amide protection with benzyl-type

protecting groups (Dmb, Hmb, etc.). Such N^α -benzyl-protected amino acid derivatives can be regarded as peptoid monomers. While usually amino acids being protected at N^α with both Fmoc and, e.g., Hmb are employed as building blocks, the sub-monomer strategy of \rightarrow peptoid synthesis can be used to assemble Asx-Gly fragments without any aspartimide formation. The *N*-terminus of a resin-bound peptide is acylated with bromoacetate, and subsequently the bromide is displaced by, e.g., 2,4-dimethoxybenzylamine to give the Dmb-glycyl-derivatized peptide that can be further reacted with a carboxy-activated Asp or Asn residue [S. Zahariev et al., *Tetrahedron Lett.* **2006**, 47, 4121].

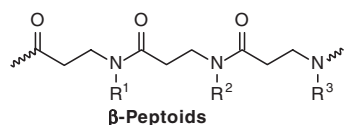
Peptoids, oligomers of *N*-substituted glycine building blocks. The side chain of each amino acid is formally shifted by one position from C^α to the amino group nitrogen when converting peptides into peptoids. Comparison of the peptide chain with a peptoid chain shows that, consequently, the direction of the peptide bond and of the peptide sequence should be reversed (retro-sequence) in order to provide the same relative arrangement of side-chain functional groups and amide bonds. Peptoids have an achiral backbone, but may have chirality present in the side chains attached to the nitrogen. α -Peptoids as short as pentamers, with chiral aromatic side chains, are assumed to adopt regular chiral secondary structure because of intense chain-length-dependent CD. The solid-phase synthesis of peptoids follows two complementary approaches: Fmoc-protected *N*-substituted glycine may be employed for peptoid synthesis as a building block followed by Fmoc deprotection to provide the elongated peptide. Alternatively, in the sub-monomer approach a bromoacetate is used to acylate the *N*-terminus of a resin-anchored



Amino acid protected with
Fmoc and Hmb
Peptoid methodology

peptide. Subsequently, the bromide substituent is nucleophilically displaced by an amine, which results in the formation of resin-bound secondary amines with the peptoid side-chain substituents attached to the glycine nitrogen [R. J. Simon et al., *Proc. Natl. Acad. Sci. USA* **1992**, 89, 9367; R. N. Zuckermann et al., *J. Am. Chem. Soc.* **1992**, 114, 10646; H. Kessler, *Angew. Chem. Int. Ed.* **1993**, 32, 543].

β -Peptoids, oligomeric *N*-substituted β -aminopropionic acids. β -Peptoids are homologated analogues of α -peptoids. While the α -peptoid parents adopt regular chiral secondary structure when chiral residues [(*R*)- or (*S*)-1-(phenylethyl)amino groups] are present in the *N*-alkyl side chain, it is still a controversial issue as to whether the analogous β -peptoids do the same. It has been shown that the α - and β -peptoid structures form helical structures with both *trans* and *cis* peptide bonds, although missing hydrogen bond-forming capability [B. C. Hamper et al., *J. Org. Chem.* **1998**, 63, 708; A. S. Norgren et al., *Org. Lett.* **2006**, 4533; C. Baldauf et al., *Phys. Biol.* **2006**, 3, S1].



Peptolides, \rightarrow desipeptides.

Perforin, *cytolysine*, a pore-forming protein ($M_r \sim 70$ kDa) found within intracellular granules of natural killer cells and cytotoxic T cells. It is a cytolytic mediator produced by killer lymphocytes, and is stored and released by cytoplasmic granules. At the point of contact, the released perforin lyses these target cells by aggregation and forming pores in the plasma membranes. The formation of lytic pores (5–16 nm) is performed by Ca^{2+} -dependent polymerization

of perforin in the membrane, analogously to the complement system. Perforin consists of two Cys-rich domains and an amphiphilic α -helix-forming region typically for cell-lysing molecules [B. B. Herberman et al., *Annu. Rev. Immunol.* **1986**, 4, 651; C. C. Liu et al., *Immunol. Today* **1995**, 16, 194].

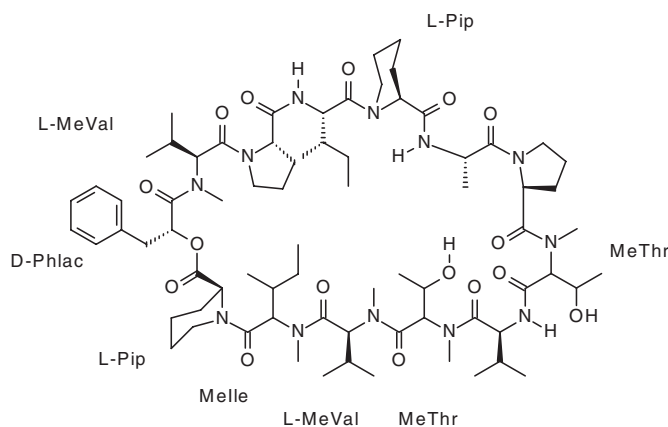
Perisulfakinin, EQFDDY^SGHMR¹⁰Fa, a sulfated 11-peptide amide [$\text{Y}^{\text{S}} = \text{Tyr}(\text{SO}_3\text{H})$], originally isolated from the corpora cardiaca of the American cockroach (*Periplaneta Americana*). Perisulfakinin shows sequence similarity to \rightarrow cholecystokinin and \rightarrow gastrin. It stimulates hind gut contractions [J. A. Veenstra, *Neuropeptides* **1989**, 14, 145].

Peroxinectin, a cell adhesion protein ($M_r \sim 76$ kDa) isolated from the blood cells of the fish *Pacifastacus leniusculus*. Peroxinectin seems to be the first cell adhesion protein in the blood of invertebrates. It shows also peroxidase activity because of a high degree of sequence similarity to myeloperoxidase [M. W. Johansson et al., *Biochem. Biophys. Res. Commun.* **1995**, 216, 1079; K. Sritunyalucksana et al., *Dev. Comp. Immunol.* **2001**, 25, 353].

Perutz, Max Ferdinand, (1914–2002), Austrian-born British biochemist and winner of the Nobel Prize in Chemistry 1962, shared with \rightarrow Kendrew, for studies of the structure of globular proteins. Already in 1959, Perutz had shown that \rightarrow hemoglobin had a tetrameric structure with four heme groups near the molecule's surface, and discovered the molecular mechanism of oxygen transport and release by hemoglobin. In 1940, he received his Ph.D at the University of Cambridge. Along with Kendrew, he founded the Medical Research Council Unit for Molecular Biology at Cambridge in 1947. Perutz was director from its inception until 1962. He was appointed a

Commander of the British Empire in 1963 and received the Order of Merit in 1989.

Petriellin A, a 13-cyclodepsipeptide from the coprophilous (dung-colonizing) fungus *Petriella sordida* (UAMH 7493). This only second natural product from the genus *Petriella* contains 13 building blocks, including the β -phenyllactic acid and two equivalents of pipecolic acid. It is heavily *N*-methylated, and contains a lactone backbone linkage similar to \rightarrow cyclosporin A. Petriellin A shows activity against other coprophilous fungi, *Ascobolus furfuraceus* and *Sordaria fimicola*, but not against *Candida albicans*. It also shows activity against human fibroblast MRC5 cells, but the diacetate of petriellin proved to be much more potent against the same cell line. Recently, the solution structure by NMR has been described [K. K. Lee et al., *J. Org. Chem.* **1995**, *60*, 5384; J. Dang et al., *Org. Biomol. Chem.* **2006**, *4*, 3802].



Petriellin A

PG, protecting group.

PGLa, GMASKAGAIA¹⁰GKIAKVAlKA²⁰La, a cationic, highly potent \rightarrow antimicrobial peptide from the skin of the South African frog *Xenopus laevis* [D. Andreu et al., *Eur. J. Biochem.* **1985**, *149*, 531; A. Latal et al., *Eur. J. Biochem.* **1997**, *248*, 938].

pGlu, pyroglutamic acid.

Ph, phenyl.

Phac, phenylacetyl.

Phacm, phenylacetamidomethyl.

Phage display, a technology which links the phenotype of a peptide displayed on the surface of a bacteriophage with the genotype encoding for this peptide. This molecular biology technique permits the generation of a peptide library by site-directed mutagenesis. Some 10^7 – 10^9 different oligopeptide sequences can be generated and expressed

Pfg, pentafluorophenyl.

PfPyU, O-(pentafluorophenyl)-1,1,3,3-bis-(tetramethylene)uronium hexafluorophosphate.

on the surface of phages, whilst subsequent screening using affinity-based techniques allows the selection of phage that present high-affinity peptides on the surface and which may subsequently be amplified [B. K.

Kay, J. Winter, J. McCafferty, *Phage Display of Peptides and Proteins: a Laboratory Manual*, Academic Press, San Diego, 1996].

Phakellistatins, a family of naturally occurring cyclic peptides in the marine sponges of the genus *Phakellia*. One of the latest structurally elucidated member has been phakellistatin 14, cyclo-(-Phe-Asp(OMe)-Ala-Met(SO)-Ala-Ile-Pro-), isolated from the Western Pacific marine sponge *Phakellia* sp. It shows cancer cell growth inhibitory activity (ED_{50} $5 \mu\text{g mL}^{-1}$) against the murine lymphocytic leukemia P388 cell line [G. R. Petit, R. Tan, *J. Nat. Prod.* **2005**, 68, 60; A. Napolitano et al., *Tetrahedron* **2005**, 61, 6808].

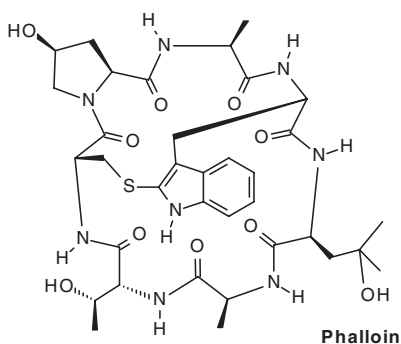
Phallotoxins, heterodetic bicyclic 7-peptides from *Amanita phalloides* that form, together with the \rightarrow amatoxins, the main toxic components of these mushrooms. The toxic effect of phallotoxins is most probably related to their capability to bind tightly to F-actin in the parenchymal cells of the liver, resulting in hemorrhagic shock and death within 2 to 5 h. The phallotoxins cause death in experimental animals after intraperitoneal or intravenous injection, but not perorally. In general, the lethal doses are higher than those of the amatoxins; e.g., the LD_{50} values are about 2 mg kg^{-1} in white mice. All phallotoxins are derived from the same cyclic

peptide backbone, and consist of seven amino acids, crosslinked by tryptathionine between residues 3 and 6. The naturally occurring phallotoxins differ mostly in their number of hydroxyl groups in the side chain of L-leucine. The structure of *Phalloin* is shown as a member of this peptide group. Interestingly, \rightarrow antamanide (0.5 mg kg^{-1} , injected not more than 1 h before or simultaneously with 5 mg of the toxic peptide per kg) provides full protection of mice against death by phalloidin [Th. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer Series in Molecular Biology, Springer, Berlin, New York, 1986; H. Faulstich et al., *Biochemistry* **1980**, 19, 3334].

Phase-change synthesis, *hybrid approach*, a combined solid-phase and solution approach used in lipophilic segment coupling. Although not yet used widely, phase-change synthesis shows great promise in the production of large peptides on a commercial scale [M. K. Lawless et al., *Biochemistry* **1996**, 35, 13697; K. Barlos, D. Gatos, *Biopolymers* **1999**, 51, 266; L. Andersson et al., *Biopolymers* **2000**, 55, 227].

Phenylalanine (Phe, F), α -amino- β -phenylpropionic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{-CH}(\text{NH}_2)\text{-CO-OH}$, $\text{C}_9\text{H}_{11}\text{NO}_2$, M_r 165.19 Da, a proteinogenic amino acid.

Phenacyl ester (OPac), an important orthogonal protecting group for carboxyl functions in peptide synthesis. Phenacyl esters are generally solids which are easily prepared, purified and handled. The phenacyl group is stable in 50% TFA in methylene chloride and to HF (0°C , 1 h). It is easily cleaved by various nucleophiles, including sodium thiopentoxide, KCN/18-crown-6, hydrazine, and tetrabutylammonium fluoride. Furthermore, it can be removed by hydrogenolysis with



H₂/Pd-C, by reduction with zinc or magnesium in acetic acid, and by photolysis [T. W. Greene et al., in *Protective Groups in Organic Synthesis*, 3rd edn., J. Wiley & Sons, New York, **1999**, p. 393; S. Kokinaki et al., *Org. Lett.* **2005**, 7, 1723].

2-[Phenyl(methyl)sulfonio]ethoxycarbonyl tetrafluoroborate group (Pms), [Ph-S⁺(Me)-CH₂-CH₂-O-CO-]⁺BF₄⁻, a water-soluble N-protecting group suitable for SPPS in water. The Pms group can be introduced onto amino acids by 2-[phenyl(methyl)sulfonio]ethyl-4-nitrophenyl carbonate, and is cleavable by β -elimination under basic conditions [K. Hojo et al., *Tetrahedron* **2004**, 60, 1875].

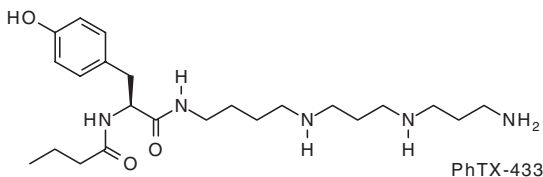
(2-Phenyl-2-trimethylsilyl)ethyl ester (OPT MSE), a carboxy protecting group cleavable under neutral conditions. PTMSE esters are stable under acidolytic cleavage of Boc groups, base-induced removal of Fmoc groups, palladium(0)-catalyzed removal of Alloc groups, and hydrogenolytic cleavage conditions. The PTMSE moiety is selectively cleaved by treatment with tetrabutylammonium fluoride (TBAF) trihydrate in dichloromethane under almost neutral conditions [M. Wagner, H. Kunz, *Z. Naturforsch.* **2002**, 57b, 928].

Phenylisothiocyanate, \rightarrow Edman degradation.

Pheromonotropin, KLSYDDKVFE¹⁰NVE FTPRLa, a pheromonotropic 18-neuropeptide amide originally isolated from head extracts of the armyworm larvae (*Pseudaletia separata*). It is also named *Pseudaletia* melanization and reddish coloration hormone (MRCH) because of its physiological function in lepidopteran insects. The hormone controls sex pheromone production in larvae [S. Matsumoto et al., *Biochem. Biophys. Res. Commun.* **1992**, 182, 534].

Phg, phenylglycine (2-aminophenylacetic acid).

Philanthotoxin-433 (PhTX-433), a polyamine toxin exerting a non-competitive antagonism on mammalian ligand-gated cation channels, including nicotinic acetylcholine receptors and ionotropic glutamate receptors. The natural PhTX-433 and synthetic philanthotoxin analogues are valuable probes in studies of receptor structure and function [M. Bixel et al., *Eur. J. Biochem.* **2000**, 267, 110; M. R. Jorgensen et al., *Synthesis* **2005**, 2687].

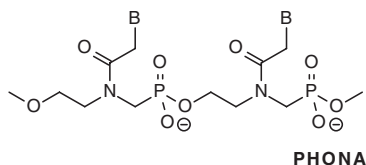


Philanthotoxin-433

Phlac, phenyllactic acid.

(2-Phenyl-2-trimethylsilyl)ethyl linker, a fluoride-sensitive linker for \rightarrow SPPS of protected peptides and glycopeptides using Fmoc chemistry [M. Wagner, H. Kunz, *Angew. Chem. Int. Ed.* **2002**, 41, 317].

PHONA, an analogue of \rightarrow peptide nucleic acids (PNA) in which the peptide bond is replaced by a phosphonic acid ester bridge [A. Peyman et al., *Angew. Chem. Int. Ed.* **1997**, 36, 2809].



Phosphonium reagents, phosphorus(III)-based coupling reagents for amide bond formation. Phosphonium reagents such as BroP [(Me₂N)₃P⁺-Br PF₆⁻] and PyBroP [(pyrrolidino)₃P⁺-Br PF₆⁻] directly activate carboxylic acids. Sterically hindered amino acids often can be coupled successfully using PyBroP. Halogenophosphonium reagents often give better results than other phosphonium-HOBT reagents when coupling *N*-methylated amino acids, but are prone to racemization/epimerization. Consequently, for most cases the HOBT or HOAt derived compounds → BOP, → Py-BOP, AOP, and PyAOP are preferred. They generate HOBT and HOAt active esters *in situ*; these highly reactive acylphosphonium species are immediately transformed into the HOBT ester in the presence of HOBT. The main disadvantage of BOP and AOP is that the highly toxic and carcinogenic HMPA is formed during the reaction course. PyBOP and its HOAt analogue PyAOP, where the dimethylamino groups of BOP are replaced by pyrrolidine groups, represent viable alternatives to BOP and AOP that do not produce the hazardous byproduct. The phosphonium reagents do not react with α -amino groups; therefore they may be added directly to a mixture of the amino and carboxy component to be coupled, which is a prerequisite for backbone cyclization. A tertiary amine is usually added in order to form the anion of the carboxy component. The use of BOP was successfully employed, e.g., in the ring closure of 12-membered tetrapeptides such as trapoxin B (→ histone deacetylase

inhibitors) [G. Jou et al., *J. Org. Chem.* **1997**, 62, 354; S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, 2447; C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, 10827].

Phosphopeptides, peptides preferentially bearing a phosphorous moiety at the side-chain hydroxyl function of serine, threonine, or tyrosine. Phosphopeptides are highly valuable tools for the investigation of protein phosphorylation and dephosphorylation, as well as the recognition of phosphorylated proteins. Furthermore, they have been used to determine sequence specificity of protein phosphatases. Phosphopeptide library approaches have been described. Two fundamentally different routes for the synthesis of phosphopeptides are known: (i) global phosphorylation; and (ii) a building block approach. Whilst the former method – which is also termed post-assembly phosphorylation – makes use of selectively side chain-deprotected serine, threonine or tyrosine residues that are being phosphorylated on completion of the synthesis, the building block approach utilizes phosphorylated amino acids. This, of course, imposes further problems with respect to protecting group strategy. Both solution-phase and solid-phase syntheses of phosphorylated peptides have been reported. Different types of protecting group have been used for the phosphate group, for example: allyl, methyl, benzyl, *tert*-butyl, and 2,2-dichloroethyl. Appropriate phosphoserine, phosphothreonine, or phosphotyrosine derivatives for the building block approach can be synthesized by two different methods. The first procedure involves phosphorylation with dialkyl- or diallylchlorophosphate under alkaline conditions, whereas the second method uses phosphorus(III) compounds, as they are used in oligonucleotide synthesis. The phosphopeptide → alaphosphin is a

modified dipeptide with antibiotic activity [H.-G. Chao et al., *J. Org. Chem.* **1995**, *60*, 7710; J. S. Murray et al., *Biopolymers (Pept. Sci.)* **2001**, *60*, 3].

Phosphotyrosyl phosphatase activator (PTPA), → protein phosphatase 2A phosphatase activator.

Photolabile protecting groups, protecting groups cleavable by photolysis. The first photolabile amino-protecting group of the urethane type, namely the → 6-nitroveratryloxycarbonyl group, was first described in 1970. Further amino-protecting groups that may be photolyzed include, the 3,5-dimethoxybenzyloxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, and the (2-nitrofluoren-9-yl)methoxycarbonyl groups. 4-Methoxyphenacyl ester is a carboxy-protecting group that can be cleaved by UV-photolysis at 20 °C. Beside the use of photolabile protecting groups in peptide synthesis, the α -carboxy-2-nitrobenzyl photolabile protecting group was successfully applied in such studies to cage different neurotransmitters, e.g., glutamate, serotonin, glycine, that activate different receptors. Recently, the photolabile protecting (caging) group 7-*N,N*-diethyl aminocoumarin was used to cage the γ -carboxyl group of glutamic acid, which can be photolyzed by visible light [P. J. Kocienski, *Protecting groups*, Georg Thieme Verlag, Stuttgart, **2003**; V. R. Shembekar et al., *Biochemistry* **2005**, *44*, 7107].

Phth, phthaloyl.

Phyllocerulein, pGlu-Glu-Tyr(SO₃H)-Thr-Gly-Trp-Met-Asp-Phe-NH₂, a 9-peptide amide originally isolated from the skin of the South American frog *Phyllomedusa sauvagei*. The pharmacological actions of phyllocerulein are quite similar to those of → cerulein.

Phyllolitorin family, a subfamily of the → bombesin-like family. *Phyllolitorin*, pGlu-Leu-Trp-Ala-Val-Gly-Ser-Phe-Met-NH₂, and [*Leu*⁸]phyllolitorin belong to this family. These peptides show similar activities as the members of the other subfamilies due to the related structure. In contrast to the other two subfamilies, mammalian homologues have not yet been found [V. Erspamer et al., *Peptides* **1985**, *6*, 7].

Phyllomedusin, pGlu-Asn-Pro-Asn-Arg-Phe-Ile-Gly-Leu-Met¹⁰-NH₂, a 10-peptide amide originally isolated from the skin of the South American frog *Phyllomedusa bicolor*. Phyllomedusin belongs to the → tachykinins and shows similar pharmacological actions as → physalaemin and → uperolein [A. Anastasi, V. Erspamer, *Experientia* **1970**, *26*, 866].

Phylloxin (PLX-S), GWMSKIASGI¹⁰GTF LSGVQQA, a 19-peptide amide from the skin secretion of the waxy monkey frog *Phyllomedusa sauvagei*. It is active against mollicutes (cell wall-less bacteria). PLX-S exhibits only a single site conservative amino acid substitution (Val for Met at position 17) when compared with phylloxin from *P. bicolor*. Phylloxin is a truly novel prototype peptide of → dermaseptins [T. N. Pierre et al., *Eur. J. Biochem.* **2000**, *267*, 370; T. Chen et al., *Regul. Pept.* **2005**, *129*, 103].

Physalaemin, <EADPNKFYGL¹⁰Ma, an 11-peptide amide originally isolated from the skin extracts of the South American frog *Physalaemus fuscumaculatus*. It belongs to the → tachykinins. Physalaemin exerts a potent hypotensive action and stimulates extravascular smooth muscle. It has been reported that the physalaemin effect on the short-circuit current in frog skin is mediated by its interaction with NK₁ receptors [V. Erspamer et al., *Experientia* **1964**,

20, 489; S. Lobasso et al., *Arch. Physiol. Biochem.* **1998**, 105, 329].

Phytosulfokines (PSK), mitogenic peptides produced and secreted by asparagus mesophyll cell cultures acting as plant growth regulators. *PSK- α* , H-Tyr(SO₃H)-Ile-Tyr(SO₃H)-Thr-Gln-OH, and *PSK- β* , the corresponding C-terminally truncated 4-peptide, from *Oryza sativa* and *Asparagus officinalis*, are necessary for cell proliferation. The synthesis of PSK requires both auxin and cytokinin in the culture medium. They are synthesized as prepro-phytosulfokines and, after release from the precursor and post-translational modification, the PSK interact with specific receptor proteins to mediate mitogenic activity. It has been suggested that PSK signaling affects the growth potential and longevity of plant cells [Y. Matsubayashi et al., *Planta* **1999**, 207, 559; A. Schaller, *Plant Mol. Biol.* **1999**, 40, 763].

Picolyl ester method, a soluble-handle approach using the acid-resistant picolyl ester moiety as a semipermanent blocking group for the C-terminal carboxy group and the Boc group for α -amino protection. The protonated picolyl handle increases the solubility of peptide intermediates in aqueous solution, and allows the isolation by passing the crude reaction mixture through an appropriate ion-exchange resin [R. Camble et al., *Nature* **1968**, 217, 247].

Pigment-dispersing hormones (PDH), a family of neuropeptides comprising closely related 18-peptides isolated from different species of crustaceans and insects. Translocation of retinal distal pigments and epithelial chromatophoral pigment dispersion are the physiological functions in crustaceans. The sequence of PDH from the CNS of *Drosophila melanogaster*, NSELINSLLS¹⁰LPKNMNDAA, differs from

that of the cockroach by only three amino acids. In fruitflies, PDH probably plays a role as a transmitter or modulator in the nervous system, especially in the visual system. Generally, PDH is involved as a mediator in neuronal pathways and rhythmic processes that are regulated on a circadian level [D. P. de Kleijn et al., *FEBS Lett.* **1993**, 321, 251; K. Rao et al., *Ann. N. Y. Acad. Sci.* **1993**, 680, 78; J. H. Park, J. C. Hall, *J. Biol. Rhythms* **1998**, 13, 219; J. V. Broeck, *Peptides* **2001**, 22, 241].

Pip, pipercolic acid (piperidine-2-carboxylic acid).

PITC, phenyl isothiocyanate.

Pituitary adenylate cyclase-activating polypeptide (PACAP), a peptide hormone occurring in two variants: a full-length 38-peptide, *PACAP-38*, and a truncated 27-peptide, *PACAP-27*, that is equivalent to the N-terminal of *PACAP-38*; h*PACAP-38*: HSDGIFTDSY¹⁰SRYRKQMAVK²⁰KYLAAVLGKR³⁰YKQVRVKNKa. *PACAP* is a neuropeptide that belongs to the \rightarrow secretin family. Originally isolated from ovine hypothalamus, *PACAP* has been found in virtually every tissue in the body. *PACAP* occurs in many species including humans, birds, fish, and rats. Furthermore, it is also found in an ancient protochordate, the tunicate (sea squirt, *Chelyosoma productum*). *PACAP* is very well conserved across species, e.g., there is 96% nucleotide identity between human and tunicate *PACAP* cDNA. *PACAP* is a multifunctional peptide hormone influencing diverse biological functions, e.g., smooth muscle and cardiac muscle relaxation, regulation of cell cycle, bone metabolism, and endocrine/paracrine function. The effects of *PACAP* on the immune system have also been partially elucidated. It both suppresses and activates inflammation by

regulating the → interleukins, IL-1 β , IL-6, and IL-10. With PAC1-R, VPAC1-R, and VPAC2-R, three distinct G protein-coupled receptors have been identified. PACAP shows considerable sequence homology to → vasoactive intestinal polypeptide (VIP), and stimulates adenylate cyclase more effectively than VIP. The distribution of PACAP-containing neuronal elements in the gut wall assumes their involvement in the regulation of both motor and secretory activities. PACAP-(6–38) acts as a selective antagonist. In lower vertebrates, especially fish, PACAP may function as a hypophysiotropic factor regulating pituitary hormone secretion. PACAP-27, but not PACAP-38, specifically stimulates intracellular calcium mobilization and ERK phosphorylation in human neutrophils. Moreover, it has been reported to be a functional ligand for the chemoattractant receptor, formyl peptide receptor-like-1 [A. Miyata et al., *Biochem. Biophys. Res. Commun.* **1990**, 170, 643; A. O. L. Wong et al., *Biochem. Cell Biol.* **2001**, 78, 329; H. Vaudry, A. Arimura (Eds.), *Pituitary Adenylate Cyclase Activating Polypeptides*, Kluwer, Dordrecht (NL), **2002**; O. Skott, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2003**, 284, R568; Y. Kim, *J. Immunol.* **2006**, 176, 2969].

Piv, pivaloyl.

Placenta lactogen, → chorionic mam-motropin.

Plantaricin A (PlnA), KSSAYSLQMG¹⁰AT AIKQVKKL²⁰FKKWGW, an antimicrobial 26-peptide pheromone produced by *Lactobacillus plantarum* C11. The cationic PlnA has antimicrobial membrane-permeabilizing activity, and is exported out of the cell by a bacteriocin-secretion machinery. It acts as a pheromone by interacting with membrane-associated histidine protein kinase of a three-component

regulatory system. Thereby, PlnA triggers the kinase to phosphorylate two response regulators, which then in turn activate the genes encoding the bacteriocin-like plantaricin E/F and J/K. Besides the full-length PlnA-26, two N-terminally truncated forms, PlnA-23 and PlnA-22, are identified, all of which are derived from a 48 aa precursor [D. B. Diep et al., *Appl. Environ. Microbiol.* **1994**, 60, 160; P. E. Kristiansen et al., *J. Biol. Chem.* **2005**, 280, 22945].

Plant defensins, antifungal peptides which are not related to mammalian or insect → defensins. The plant α -defensins are present in seeds or leaves and are characterized by complex structures. They contain disulfide-linked cysteines in a triple-stranded antiparallel β -sheet with only one α -helix, and are homologous to those produced in human and rabbit neutrophils. Plant α -defensins are not capable of forming ion-permeable pores in artificial membranes, but they may act through a receptor-mediated mechanism. They are considered PR proteins and are classified as members of the PR-12 group [K. Thevissen et al., *J. Biol. Chem.* **1996**, 271, 15018; A. J. De Lucca et al., *Can. J. Microbiol.* **2005**, 51, 1001].

Plant-derived antifungal peptides, peptides with antimicrobial activity against fungi. Although approximately 250 000–500 000 plant species exist, only a few of these have been investigated for antimicrobial activity. However, there is a increasing need for potent antifungals as fungi develop resistance to current antifungals in agriculture and medicine. Plant antifungal peptides include, for example, → thionins, → hevein and hevein-like peptides, → knottins, and → plant defensins [A. J. De Lucca et al., *Can. J. Microbiol.* **2005**, 51, 1001].

Plant peptides, peptides that contribute in plants to the regulation of intercellular

communication, growth, development, and defense, stress responses as well as self/non-self recognition. For instance, 4k-P is a 37-peptide which occurs in legumes, has similarities to peptide hormones, and regulates growth, differentiation and proliferation. AtPep1 is a 23-peptide that occurs in *Arabidopsis thaliana* leaves and is produced in response to defense-related stimuli such as wounding, methyl jasmonate, and ethylene. RALF (Rapid Alkalinization Factor) peptides have 49 to 52 amino acid residues and are MAP kinase-activating peptides that block a transmembrane proton pump. The 18-peptide \rightarrow systemin is a tomato defense response mediator active in femtomolar concentrations. Systemins activate defensive genes in response to herbivore or pathogen attack. \rightarrow Plant-derived antifungal peptides, \rightarrow defensins, host-defense effectors and regulators well-known for animals, also occur in plants (\rightarrow plant defensins) [H. Germain et al., *Can. J. Bot.* **2006**, 84, 1; A. Huffaker, *Proc. Natl. Acad. Sci. USA* **2007**, 104, 10732].

Plasma kinins, \rightarrow kinins.

Plasma proteins, \rightarrow globulins, \rightarrow albumins, \rightarrow fibrinogen.

Plasmin, *fibrinolysin*, a serine protease catalyzing Lys-Xaa and Arg-Xaa bond cleavage similar to that of \rightarrow trypsin. Plasmin is the key protease in blood clot lysis, and its major natural substrates are \rightarrow fibrinogen and \rightarrow fibrin. Human plasmin is derived from \rightarrow plasminogen, and is a two-chain protein consisting of the A or H chain ($M_r \sim 65$ kDa) and the B or L chain ($M_r \sim 27.7$ kDa). The active site is located in the B chain. The various molecular forms of plasmin are inactivated by protein inhibitors such as the Kunitz type, \rightarrow serpins, soybean and limabean trypsin inhibitors. The most important, fast-acting inhibitor of plasmin

in plasma is $\rightarrow \alpha_2$ -antiplasmin, whereas α_2 -macroglobulin forms stoichiometric complexes with plasmin, thereby inhibiting access to the active site of only large molecular mass substrates and inhibitors. Plasmin is readily prepared from plasminogen by \rightarrow urokinase-type plasminogen activator [F. J. Castellino, in: *Handbook of Proteolytic Enzymes*, A. J. Barret, N. D. Rawlings, J. F. Woessner (Eds.), p. 190, Academic Press, San Diego, **1998**].

Plasminogen activators, \rightarrow plasminogen, \rightarrow streptokinase, \rightarrow urokinase.

Plasminogen, the zymogen of \rightarrow plasmin. The mature molecule of human plasminogen consists of 791 residues in a single peptide chain. One of the major glycoforms of plasminogen contains only O-linked sialylated trisaccharide on Thr³⁴⁶, while the second glycoform possesses the same O-linked glycan and an Asn²⁸⁹-attached bisialylated oligosaccharide on the only N-linked consensus sequence in plasminogen. The two glycoforms can be separated by gradient elution of plasminogen. Plasminogen is synthesized in the liver and secreted into the plasma. The most intensively studied *in-vivo* plasminogen activators are the tissue-type activator, called *t-plasminogen activator* (tPA) and the urokinase-type, *u-plasminogen activator* (uPA). tPA converts plasminogen to plasmin by cleavage of a single Arg⁵⁶¹ \downarrow Val⁵⁶² bond, whereas uPA cleaves the sequence -Cys-Pro-Gly-Arg⁵⁶⁰ \uparrow Val⁵⁶¹-Val-Gly-Cys- that forms a small disulfide-bridged loop in plasminogen. Both plasminogen activators are used clinically for thrombolytic therapy. The *bacterial plasminogen activators* \rightarrow streptokinase and staphylokinase, acting in that capacity only via stoichiometric complexes with plasminogen or plasmin, are also important due to their *in-vivo* thrombolytic potential. They activate plasminogen in

solution bound to a variety of cell types, and when bound to \rightarrow fibrin [F. J. Castellino, J. R. Powel, *Methods Enzymol.* **1981**, 80, 365].

Platelet factor-4 related peptide, *hPF4*-(58–70): PLYKKIIKKL¹⁰LES, a 13-peptide corresponding to the C-terminal sequence of platelet factor 4. Like the intact platelet factor, this peptide is capable of alleviating immunosuppression in mice. It acts also as an inhibitor of angiogenesis in the chicken chorioallantoic membrane. Human [Gln¹⁸]-PF4-(15–22), termed CT-112, H-Thr-Thr-Ser-Gln-Val-Arg-Pro-Arg-OH, reduces the incidence of type II collagen-induced arthritis in mice and retards the disease progression [M. B. Zucker et al., *Proc. Natl. Acad. Sci. USA* **1989**, 86, 7571; T. E. Maione et al., *Science* **1990**, 247, 77].

Platelet-derived endothelial cell growth factor (PD-ECGF), an endothelial cell mitogen (482 aa; $M_r \sim 49$ kDa; pI = 4.0–4.8) initially isolated from human platelets that does not stimulate the proliferation of fibroblasts and does not bind to heparin. PD-ECGF is involved in angiogenesis. It is the most important mitogen for endothelial cells, and exerts chemotactic action on these cells [K. Miyazano et al., *J. Biol. Chem.* **1987**, 262, 4098; K. Usuki et al., *Cell Regulation* **1990**, 1, 577].

Platelet-derived growth factor (PDGF), a glycoprotein ($M_r \sim 30$ kDa) acting as a multifunctional growth factor. It consists of the two subunits A (125 aa) and B (160 aa) that can be composed as AA, AB, or BB. PDGF stimulates proliferation of connective tissue cells and neuroglial cells via specific receptors that belong to the family of single-pass transmembrane glycoproteins with tyrosine-specific protein kinase activity. PDGF also plays a role in wound healing [C. D. Stiles, *Cell* **1983**, 33, 653; R. Ross

et al., *Cell* **1986**, 46, 155; B. Westermark, *Acta Endocrinol.* **1990**, 123, 131].

Plectin, a protein ($M_r \sim 300$ kDa) forming a plexus-like structure. It binds to intermediate filaments of various cell types. Plectin and its isoforms ($M_r > 500$ kDa) are versatile cytoskeletal linker proteins which are expressed in a variety of mammalian cells and cell types [G. Wiche, *J. Cell Sci.* **1998**, 111, 2477].

Pleiotrophin, hPTN, *heparin-binding growth-associated molecule (HBGAM)*, a protein (136 aa; $M_r \sim 15.3$ kDa) with five intramolecular disulfide bonds. PTN belongs to the \rightarrow midkine family of developmentally regulated, secreted polypeptide growth factors expressed in a variety of established tumor cell lines, and exhibits 46% sequence homology to human \rightarrow midkine. It promotes cell growth of NIH3T3 and NRK fibroblasts, epithelial cells, osteoblasts, and endothelial cells. PTN induces neurite outgrowth from neuronal cells, and has been shown to exert angiogenic activity [Y.-S. Li et al., *Science* **1990**, 250, 1690; F. Czubayko et al., *Proc. Natl. Acad. Sci. USA* **1996**, 93, 14753; T. F. Deuel et al., *Arch. Biochem. Biophys.* **2002**, 397, 162].

Pleurocidin, GWGSFFKKAA¹⁰HVGKHH GKAA²⁰LTHYL, a cationic 25-peptide (\rightarrow antimicrobial peptides) from the skin mucous secretion of winter flounder (*Pseudopleuronectes americanus*). It has strong antibacterial activity against Gram-positive and Gram-negative bacteria. Pleurocidin is predicted to form an α -amphiphilic α -helix [A. Cole et al., *J. Biol. Chem.* **1997**, 272, 12008; R. T. Syvitski et al., *Biochemistry* **2005**, 44, 7282].

Pleurostrin, an antifungal 7 kDa peptide isolated from fresh fruiting bodies of the oyster mushroom, with inhibitory activity on

mycelial growth in special fungi [K. T. Chu, T. B. Ng, *Peptides* **2005**, 26, 2098].

Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl.

pMBzl, 4-methylbenzyl.

pNA, 4-nitroanilide.

PNA, peptide nucleic acid.

Pneumadin (PNM), human pneumadin, H-Ala-Gly-Glu-Pro-Lys-Leu-Asp-Ala-Gly-Val¹⁰-NH₂, and rat pneumadin, [Tyr¹] hPNM, 10-peptide amides occurring in significant concentrations in both normal mammalian and human fetal lungs. Natural and synthetic pneumadin exert antidiuretic effects by releasing → vasopressin from the neurohypophysis. It has been regarded as one of the factors responsible for SIAD (syndrome of inappropriate antidiuresis). In addition to lungs and hypothalamo-pituitary complex, the highest concentration of PNM-immunoreactivity was observed in the rat ventral prostate [V. K. Batra et al., *Regul. Pept.* **1990**, 30, 77; J. D. Watson et al., *Regul. Pept.* **1995**, 57, 105; B. Miskowiak et al., *Int. J. Mol. Med.* **2004**, 13, 801].

Poc, cyclopentylloxycarbonyl.

Polyamide resin, an alternative polymer support to polystyrene in SPPS. Polyamide resin is chemically more similar to the peptide chain itself. The polyamide resin and the peptide chain would then be well solvated in dipolar aprotic solvents. A very successful member of polyamide resins consists of crosslinked polydimethylacrylamide bearing sarcosine methyl ester side chains. These methyl ester moieties can then be modified by reaction with ethylene diamine. The resulting primary amino groups provide the points of attachment to the resin. In general, the properties of

polyamide resin are the reverse of those of polystyrene resin. Polyamide resins swell much less in dichloromethane, but swell up to ten times their dry volume in dimethylformamide, and even more in water. Polyamide gel resins embedded both within kieselguhr, known commercially as Pepsyn KTM, and within a highly crosslinked polystyrene, termed PolyhipeTM, show higher back pressures and reduced flow rates. Therefore they are much better suited for a continuous-flow → peptide synthesizer compared to standard resins [E. Atherton et al., *J. Chem. Soc. Chem. Commun.* **1981**, 1151; E. Atherton, R. C. Sheppard, *Solid Phase Peptide Synthesis. A Practical Approach*, IRL Press, Oxford, **1989**, 1; P. W. Small, D. C. Sherington, *J. Chem. Soc., Chem. Commun.* **1989**, 1589].

Polyarginine, a peptide homopolymer composed of arginine. Polyarginine and → polylysine are present under physiological conditions as polycations having an unique capability to cross the plasma membranes of cells. Consequently, they may be used to transport a variety of polymers and small molecules into cells [H. Ryser, R. Hancock, *Science* **1965**, 150, 501; D. J. Michell et al., *J. Peptide Res.* **2000**, 56, 318].

Polylysine, a peptide homopolymer composed of lysine. It shows similar properties to → polyarginine. Polylysine is synthesized by polymerization of the appropriate *N*-carboxy anhydride (→ *N*-carboxy anhydrides). However, the heterogeneity of commercially available polylysine in terms of degree of polymerization is a major obstacle in the preparation of reproducible, stable formulations [L. C. Smith et al., *Adv. Drug Deliv. Rev.* **1998**, 30, 115].

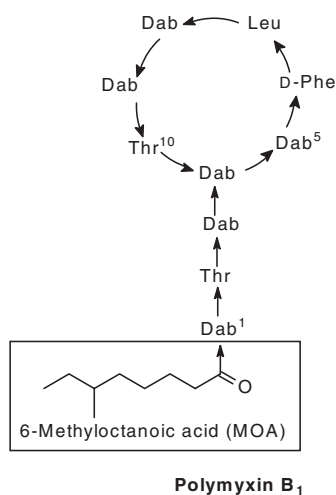
Polymer-supported coupling reagents, an approach to peptide synthesis in solution using polymer-bound coupling reagents.

The latter reacts with the amino component with liberation of the polymer and the protected peptide derivative, without formation of soluble byproducts. The polymer-bound reagents can be applied in excess, and the peptide formed may be separated – usually without difficulties [T. Wieland, C. Birr, *Angew. Chem. Int. Ed.* **1966**, 5, 310; E. Valeur, M. Bradley, *Chem. Commun.* **2005**, 1164].

Polymer therapeutics, *nanomedicine*, conjugates of drugs and polymers as well as other polymeric carrier systems comprising polymer–protein conjugates, drug–polymer conjugates, supramolecular drug-delivery systems, and other defined nanosized systems. The development of polymer therapeutics is an exciting field of research for improving the therapeutic potential of low-molecular-weight drugs and proteins. The anchoring of enzymes or biologically relevant proteins to polyethylene glycol, shortly called PEGylation, have led to numerous polymer–protein conjugates with improved stability and pharmacokinetic properties. Some such polymer–protein conjugates have received market approval. Anticancer drug–polymer conjugates and macromolecular prodrugs have been successfully studied in preclinical models, and several candidates have advanced into clinical studies. Furthermore, bio-nanotechnology has reached a new dimension due to the development of polymer therapeutics [R. Haag, F. Kratz, *Angew. Chem. Int. Ed.* **2006**, 45, 1198 (Review)].

Polymyxins, fatty acid-containing, branched cyclic peptides produced by *Bacillus polymyxa* possessing antibiotic activity against Gram-negative bacteria. The structure of *polymyxin B₁* is shown as a member of this peptide group. The basic sequence of polymyxins consists of

ten amino acids: Dab¹-Thr-Dab-Dab-Dab-D-Phe-Leu-Dab- Dab-Thr¹⁰, in which the cyclic heptapeptide part is achieved by coupling the C-terminal carboxy group of Thr to the γ -amino group of Dab (L- α,γ -diaminobutyric acid) in position 4. The N-terminal Dab residue is always acylated with 6-methyloctanoic acid or isooctanoic acid, which is responsible for the strong amphiphilic, detergent-like properties of the peptide. Some naturally occurring analogues contain either Ser⁵, Leu⁶, or Ile⁷. The activity of polymyxins is based on the high affinity of this rather basic peptide to the negatively charged core moiety of the lipopolysaccharide (LPS) in the outer leaflet of the Gram-negative bacterial outer membrane. Endotoxic shock is caused by the release of LPS, the structurally diverse component of Gram-negative bacterial outer membranes, and is responsible for 60% mortality in humans. Despite polymyxin B exerting severe side effects, such as nephrotoxicity and neurotoxicity, its efficient endotoxin-neutralizing capability offers possibilities for the design of non-toxic therapeutic agents for combating



endotoxycosis [A. L. Meyer, *Curr. Opin. Pharmacol.* **2005**, *5*, 490; V. M. Bhor et al., *Mol. Biosyst.* **2005**, *1*, 213].

Polyoxypeptins, cyclohexadepsipeptides (→ depsipeptides) isolated from the culture broth of *Streptomyces* sp. Both, polyoxypeptins A and B contain an array of amino acids, including (2*S*,3*R*)-3-hydroxy-3-methylproline. Both members are extremely toxic [K. Umezawa et al., *J. Org. Chem.* **1999**, *64*, 3034].

Polystyrene resin, frequently used resin material for → solid-phase peptide synthesis (SPPS). The polymeric support for SPPS must be chemically inert, mechanically stable, completely insoluble in the solvents used, and easily separated by filtration. For many applications a copolymer of polystyrene with 1% of divinyl benzene as crosslinker is used. The dry resin beads are able to swell up to the five- or sixfold volume in the different organic solvents mainly used for peptide synthesis (e.g., dichloromethane or dimethylformamide). For SPPS the resin material must be chemically functionalized in order to allow for attachment of a handle/like (e.g. → Wang resin), or the first amino acid (→ Merrifield resin). Hydrophilic tentacle polymers gels (TentaGel) are obtained by grafting polyethylene glycol (PEG) chains with an arbitrary degree of polymerization onto porous polystyrene beads.

POMC, proopiomelanocortin.

Porins, pore-forming proteins originally discovered in the outer membrane of Gram-negative bacteria. The porins consist of trimers of identical subunits, and each subunit forms a 16-stranded anti-parallel β -barrel containing a pore. They form aqueous channels used for the passive diffusion of water, ions and small molecules. Porins are found in bacterial cell walls, and also

in fungal, plants, mammalian and other vertebrate cell membranes. They are components of the mitochondrial outer membrane [T. Schirmer, J. P. Rosenbusch, *Curr. Opin. Struct. Biol.* **1991**, *1*, 539; S. W. Cowan et al., *Nature* **1992**, *358*, 727].

Porosome, a supramolecular structure at the cell plasma membrane acting as the universal secretory machinery in cells. Membrane-bound secretory vesicles dock at the porosome and fuse to release their content [L. L. Anderson, *J. Cell. Mol. Med.* **2006**, *10*, 126].

Positional scanning, a non-interactive method for → peptide library deconvolution. Positional scanning relies on the synthesis of partial compound libraries that represent first-order sub-libraries in which one position of the peptide sequence is kept invariant while all other positions are varied. Once biological activity has been detected in the complete library, all the sub-libraries are screened additionally in the same biological assay. Consequently, positional scanning reveals the optimum residue for every position in a peptide.

Postine, → poststatin.

Poststatin, H-Val-Val-Pos-D-Leu-Val-OH, a naturally occurring 5-peptide isolated from *Streptomyces viridochromogenes*. It acts as an inhibitor of prolyl endopeptidase. Pos is the abbreviation for (S)-3-amino-2-oxopentanoic acid, named L-postine. The α -keto-amide group seems to be necessary for the biological activity [M. Tsuda et al., *J. Antibiot. (Tokyo)* **1996**, *49*, 1022; H. H. Wassermann, A. K. Petersen, *Tetrahedron Lett.* **1997**, *38*, 953].

Post-translational modification, an essential prerequisite for mature polypeptides and proteins, and the most important

and fundamental process of proteomic complexity. Proteins can be modified post-translationally by covalent attachment of one or more of several classes of molecules, by the formation of intra- or intermolecular linkages, by proteolytic processing of a newly synthesized polypeptide chain, or by any combination of these events. Examples for covalent modifications include glycosylation, phosphorylation, lipidation (\rightarrow prenylation, acylation with fatty acids, and glycosylphosphatidylinositol groups), methylation, acetylation, hydroxylation, sulfatation, iodination, carboxylation, nucleotidylation, ADP-ribosylation, pyroglutamyl formation (\rightarrow pyroglutamyl peptides), and amino acid modification [C. T. Walsh, *Posttranslational Modification of Proteins: Expanding Nature's Inventory*, Englewood, Polo, Roberts and Co. Publ., 2006].

PP-2B, \rightarrow calcineurin.

PP-fold family, a member of the gastroenteropancreatic peptide families according to the classification proposed by Rehfeld. This family comprises \rightarrow pancreatic polypeptide (PP), \rightarrow peptide YY, and \rightarrow neuropeptide Y. The overall similarity in the primary structure varies between 45% and 70%. This similarity is connected to an almost identical and stable tertiary structure characterized by the PP-fold motif consisting of a polyproline-like helix (residues 1–8) and an amphiphilic α -helix (residues 15–30). Both helices are connected by a type I β -turn (residues 9–12), and the folded configuration is stabilized by hydrophobic interactions between the side chains of the α -helix residues and the N-terminal proline residues. Besides the term PP-fold family, the designation \rightarrow neuropeptide Y family is widely used in the literature [J. F. Rehfeld, *Physiol. Rev.* 1998, 78, 1087].

PPIase, peptidyl prolyl *cis/trans* isomerase.

PR-39, RRRPRPPYLP¹⁰RPRPPFFFP²⁰RLPPRIPPGF³⁰PPRFPPRFPa, an antimicrobial linear 39-peptide amide from porcine intestine with a high content of Pro and Arg residues. Like other \rightarrow antimicrobial animal peptides and Pro- and Arg-rich peptides (\rightarrow Bac5, \rightarrow Indolicidin), PR-39 is equally active against Gram-negative and Gram-positive bacteria. It has been assumed that they interact with membranes and disorganize them because of their basic nature. Furthermore, it has been reported that the macrophage-derived PR-39 can be used as potent inductor of angiogenesis [H. G. Boman et al., *Infect. Immun.* 1993, 61, 2978; J. Li et al., *Nat. Med.* 2000, 6, 49].

Prebiotic peptides, peptides formed before the origin of life. Most likely, amino acids were already present on primitive Earth. They are supposed to have been produced in the primitive atmosphere, in hydrothermal vents, or to have been imported in meteorites. α -Amino acids can undergo peptide formation by activation with carbon monoxide under hot aqueous conditions in the presence of freshly co-precipitated colloidal (Fe,Ni)S. Peptides may have been formed via \rightarrow N-carboxy anhydrides. A replicative synthesis involving aminoacyl-RNA intermediates has also been suggested. The question of whether a peptide/protein world preceded the RNA-driven template synthesis, or whether RNA and proteins should not be viewed as etiologically discrete entities in the origin of life, is still under debate [V. Borsenberger et al., *Chem. Biodivers.* 2004, 1, 203; C. Huber et al., *Science* 2003, 301, 938; A. Brack, *Chem. Biodivers.* 2007, 4, 665].

Preformed handles, bifunctional moieties to tailor reactivity, stability, and cleavage conditions of resin material in SPPS,

according to the requirements of the synthesis. Additional handles in the form of bi-functional linker moieties may be attached to the polymer matrix independent of the material used (e.g., polystyrene, polyacrylamides, controlled pore glass, chitin, cellulose, etc.). The peptide synthesis is then performed with attachment of the first amino acid to the handle. Many different linker systems available for solid-phase peptide synthesis and solid-phase organic synthesis have been developed. They allow for the simultaneous cleavage and conversion of C-terminal functional group into a carboxamide, thioester, amine, hydrazide, aldehyde, alcohol, etc. → Safety-catch linkers are also important in this context, as they require activation before cleavage. Handles often contain internal reference amino acids (IRAA) for improved monitoring of the reaction progress, exact yield determination, and control of integrity of the resin-bound peptide chain [I. W. James, *Tetrahedron* **1999**, 55, 4855; A. J. Wills, S. Balasubramanian, *Curr. Opin. Chem. Biol.* **2003**, 7, 346].

Preformed symmetric anhydrides, carboxy-activated derivatives of protected amino acids. These are formed when amino acid derivatives are reacted with strongly dehydrating agents such as carbodiimides. When no nucleophile (e.g., amine) is present during this reaction, → symmetric anhydrides are formed. These are stable, very often crystalline, and can be stored and employed in peptide couplings on request. The major disadvantage of the preformed symmetric anhydride method is that one half of the molecule consisting of a protected amino acid is wasted because it acts as the leaving group upon peptide formation.

Prenylation, a functionally important event of lipidation (→ post-translational

modification). The two different types of prenylation are S-farnesylation and S-geranylgeranylation. They are similar in their behavior, but they differ in specificity with regards to the C-terminal sequence of proteins. Prenylation can be performed via covalent attachment of either C₁₅ farnesyl or C₂₀ geranylgeranyl moiety to the cysteine residue of CAAX motif present in the protein to be modified (A: aliphatic amino acid, X: variable residue) [L. A. Beck et al., *Cell Biol.* **1988**, 107, 1307; F. L. Zhang, P. J. Casey, *Annu. Rev. Biochem.* **1996**, 65, 241; D. M. Leonard, *J. Med. Chem.* **1997**, 40, 2971].

Prepro-protein, a ribosomal synthesized protein bearing both the → presequence and the → prosequence.

Preprotein, a ribosomally synthesized protein bearing the → presequence.

Preptin, DVSTPPTVLP¹⁰DNFPRYPVGK²⁰FFQYDTWKQS²⁰TQRL (human) a 34-peptide hormone co-secreted with → insulin and → amylin from the pancreatic islet β cells. Its sequence corresponds to Asp⁶⁹-Leu¹⁰² of proinsulin-like growth factor II (proIGF-II). Synthetic preptin enhances insulin secretion from glucose-stimulated β TC6-F7 cells. It has been suggested that preptin is a physiological amplifier of glucose-mediated insulin secretion. Furthermore, it is anabolic to osteoblasts in cell and organ culture, but does not influence osteoclast activity [C. M. Buchanan et al., *Biochem. J.* **2001**, 360, 431; J. Cornish et al., *Am. J. Physiol. Endocrinol. Metab.* **2007**, 292, E117].

Presequence, *signal sequence*, an N-terminal 13 to 36 aa sequence consisting of a 7- to 13-aa hydrophobic core flanked by relatively hydrophilic residues that are essential for all secreted endoplasmic reticulum (ER) and lysosomal proteins, as well as

transmembrane proteins. According to the *signal hypothesis*, as established by the Nobel laureate Günter Blobel, the presequence of the growing polypeptide chain is specifically cleaved by a membrane-bound signal peptidase shortly after entering the lumen of the rough endoplasmic reticulum (RER).

Preview analysis, an on-resin monitoring of \rightarrow SPSS based on modified \rightarrow Edman degradation. For the analysis of peptide resins only very little sample is required as modern instruments are capable of analyzing 10 to 100 pmol quantities of amino acids [R. A. Laursen, *Eur. J. Biochem.* **1971**, *20*, 89; G. W. Tregear et al., *Biochemistry* **1977**, *16*, 2817].

Preview synthesis, a small-scale \rightarrow SPSS combined with appropriate analytical methods in order to identify potential weak points in the synthetic plan of longer peptides or peptides containing \rightarrow difficult sequences.

PRH, prolactin-releasing hormone.

Prⁱ, *i*-propyl.

Primary structure, the number and sequence of amino acids connected consecutively by peptide bonds within the peptide chain or cyclic peptide structure.

Prions, unprecedented infectious pathogens devoid of nucleic acids causing fatal neurodegenerative diseases in humans and animals. The majority (80%) of prion diseases or transmissible spongiform encephalopathies (TSE) arise sporadically, about one-fifth is genetically induced, and around 1% has been transmitted between mammals both by inoculation with and dietary exposure to infected tissues. Human TSE include Creutzfeldt–Jakob disease (CJD), fatal familial insomnia, the Gerstmann–Sträussler–Scheinker syndrome, and a new variant Creutzfeldt–Jakob

disease (nvCJD). The term *prion* is a short form derived from “proteinaceous infectious particle”, and was coined to describe the infectious agent that causes the neurodegenerative diseases. The *prion protein* (PrP) occurs in two physically and biologically distinct isoforms. The normal *cellular prion protein* (PrP^C) occurs as a constituent of the normal mammalian cells. It is a glycoprotein containing 209 residues, a disulfide bond (Cys¹⁷⁹–Cys²¹⁴), two N-linked glycosylation sites (Asn¹⁸¹-Ile-Thr/Asn¹⁹⁷-Phe-Thr) and a glycosylphosphatidylinositol (GPI) anchor linked to the C-terminal residue Ser²³¹. PrP^C is normally attached to the cell membrane via the GPI anchor containing a heterogeneous sialylated glycan. Although the biological functions of PrP^C are not yet clear, it might be involved in synaptic function, circadian rhythm, copper transport, and signal transduction. According to the “protein only” hypothesis, a modified form of PrP^C triggers human TSE, as well as animal prion diseases such as bovine spongiform encephalopathy (BSE) and scrapie in sheep. The conversion of PrP^C into the abnormal, disease-causing scrapie-like (“Sc”) or disease-causing isoform of the prion protein isoform, PrP^{Sc}, involves a significant conformational transition. The first fractions of PrP^{Sc} were isolated from the brain of Syrian hamsters with experimental scrapie. PrP^{Sc} is insoluble in detergents, contains an increased proportion of β -sheet and a protease-resistant core, whereas PrP^C is a soluble protein with a high content of α -helices and high susceptibility to proteolysis. Knowledge of the three-dimensional structure of PrP^C is essential for interpretation of the transition to PrP^{Sc}. Various molecular models for the region of PrP^C, corresponding to the protease-resistant core of PrP^{Sc} (residues 90–231) have been proposed based on

NMR structures. In 1996, the NMR structure of the mouse prion protein domain PrP(121–231) indicated that this domain contains two-stranded antiparallel β -sheets and three helices, leaving the last 14 amino acid residues without structure. Further NMR solution studies have been published for monomeric, cellular forms of PrP of the most widely used animals (mouse and Syrian hamster). Interestingly, in another report the C-terminal helix extends to residue 227, showing that only the last four residues are flexible. The NMR structure of the recombinant human prion protein hPrP(23–230), and the C-terminal fragments hPrP(90–230) and hPrP(121–230), indicates a globular domain (residues 125–228) containing three helices (144–154/173–194/200–228) and a short anti-parallel β -sheet (128–131/161–164). In 2001, the crystal structure of the human prion protein in dimeric form at 2 Å resolution was elucidated, and suggested a mechanism for oligomerization as an important step on the pathway of PrP^C \rightarrow PrP^{Sc} conversion. The protease-resistant core of PrP^{Sc}, PrP 27–30 (M_r ~27–30 kDa) is the designation for a protein that results from limited digestion of PrP^{Sc} with proteinase K by truncation of the N-terminus. The N-terminal sequence of PrP 27–30 led to molecular cloning of PrP cDNA and characterization of the chromosomal gene. Translation of PrP^C-mRNA provides the PrP^C precursor consisting of 254 amino acids that yields, after post-translational modification and proteolytic processing, PrP^C. Furthermore, antiserum of PrP 27–30 has enabled the examination of brains from humans and animals with putative prion diseases for the presence of this protein. The studies of prions have elucidated a previously unknown mechanism of disease in humans and animals. A normal genetically encoded protein is converted

to the disease-causing form PrP^{Sc} which differs significantly in the tertiary structure from PrP^C. In contrast to pathogens carrying a nucleic acid genome, prions appear to encipher strain-specific properties in the three-dimensional structure of PrP^{Sc}. From transgenic investigations it has been assumed that PrP^{Sc} functions as a template upon which PrP^C is refolded into a nascent PrP^{Sc} molecule via a process promoted by another protein (protein X), which might function as a molecular chaperone. The PrP^{Sc} molecules are then believed to cause lesions that damage the brain and give rise to transmissible spongiform encephalopathies. It has been postulated that prion strains are different conformational forms of the same protein, since, for example, some TSE strains cause disease more quickly than others. The protein-only hypothesis of TSEs was proposed by the 1997 Nobel laureate Stanley B. Prusiner during the 1980s. The prion biology of yeast and fungus supports the idea strongly. However, the direct proof of prion hypothesis in mammals, and particularly reconstitution of the disease-associated isoform of PrP^{Sc} *in vitro* and *in vivo* from non-infectious prion protein, seems to be difficult to achieve despite much effort being expended during the past few years [S. B. Prusiner et al., *Biochemistry* **1982**, 21, 6942; S. B. Prusiner, *Science* **1997**, 278, 245; S. B. Prusiner, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 13363; R. Zahn et al., *Proc. Natl. Acad. Sci. USA* **2000**, 97, 145; K. J. Knaus et al., *Nature Struct. Biol.* **2001**, 9, 770; P. M. Rudd et al., *Biochemistry* **2001**, 40, 3759; N. R. Deleault et al., *Proc. Natl. Acad. Sci. USA* **2007**, 104, 9741; J. Kheterpal, R. Wetzel (Eds.), in: *Methods in Enzymology*, Volume 412, *Amyloids, Prions, and Other Protein Aggregates*, Part B, Elsevier, Amsterdam, **2006**; I. V. Baskakov, *FEBS J.* **2007**, 274, 576].

PRL, prolactin.

Prⁿ, *n*-propyl.

Pro, proline.

Proadrenomedullin N-terminal 20-peptide,
→ adrenomedullin.

Proatherocytin, a protease ($M_r \sim 34$ kDa) from the venom of the East African viper, *Proatheris superciliaris*. This enzyme induced Src kinase-independent aggregation of both human and mouse platelets, and this activity is blocked by serine protease inhibitors. It has been suggested that proatherocytin is a selective protease-activated receptor-1 (PAR1) agonist [G. D. Laing et al., *Toxicon* **2005**, 46, 490].

Procholecystokinin, → cholecystokinin.

Proctolin, H-Arg-Tyr-Leu-Pro-Thr-OH, a bioactive neuropeptide modulating interneuronal and neuromuscular synaptic transmissions in a wide variety of arthropods. It was discovered as an excitatory neurotransmitter from the intestinal musculature of insects. Extremely low concentrations (10^{-9} mol L⁻¹) cause violent contraction of the end of the gut. For the first isolation of proctolin, 125,000 cockroaches (*Periplaneta americana*) were required. Although proctolin was the first insect neuropeptide to be discovered, it is now regarded as the main neuromuscular transmitter/modulator in the gut of most insect species. In 2003, a G protein-coupled receptor for proctolin in *Drosophila melanogaster* was identified and characterized [A. N. Staratt, B. E. Brown, *Life Sci.* **1975**, 17, 1253; D. Konopińska, G. Roziński, *J. Peptide Sci.* **1999**, 5, 533; E. J. Johnson et al., *Proc. Natl. Acad. Sci. USA* **2003**, 100, 6198].

Proglucagon, the precursor of → glucagon, → GRPP, → MPGF, the intervening peptides, → glicentin, and the → glucagon-like peptides.

Prolactin (PRL), lactogenic hormone, mam-motropin, luteotropic hormone, **LTH**, luteotropin, a single-chain proteohormone (198 aa, three disulfide bridges; $M_r \sim 22.5$ kDa) of the anterior pituitary that is responsible for lactation. It has been assumed that PRL is formed in the adenohypophysis under the control of → prolactoliberin and → prolactostatin. Later, it was reported that the → prolactin-releasing peptide (PrRP) fulfils the function to promote the release of PRL. PRL increases milk production in female mammals, and initiates maternal behavior. Analogous to → chorionic mam-motropin, PRL also has luteotropic properties and stimulates the synthesis of progesterone, but inhibits the synthesis of estradiol and testosterone. Measurement of prolactin is one of the most commonly undertaken hormonal investigations in evaluating patients with reproductive disorders. Receptors of PRL are found, for example, in the mammary gland, brain, liver, kidneys, prostate, testes, ovaries, and lymphocytes. PRL can be displaced from the receptors on lymphocytes by → cyclosporin. Prolactin receptors have recently been described in mammalian kidney; hence it might display renotropic activity in humans. In a similar way, PRL seems to play an important role in osmoregulation in sub-mammalian species [W. S. Oetting et al., *J. Biol. Chem.* **1986**, 261, 1649; M. E. Freeman et al., *Physiol. Rev.* **2000**, 80, 1523; M. J. Soares, *Trends Endocrinol. Metab.* **2007**, 18, 114].

Prolactin release-inhibiting hormone or factor, → prolactostatin.

Prolactin-releasing hormone or factor, → prolactoliberin.

Prolactin-releasing peptide (PrRP), *hPrRP* 31: SRTHRHSMEI¹⁰RTPDIQPAWY²⁰ASRGIRPVGR³⁰Fa, a 31-neuropeptide (and the N-terminally truncated sequence

(PrRP20)), derived from a 98-aa precursor was originally reported to function in the anterior lobe of the pituitary gland to stimulate → prolactin release. Later, based on a wide distribution of PrRP and its orphan seven-transmembrane-domain receptor, hGR3/GPR10, it was suggested that these have various functions not only in the pituitary gland but also in other tissues. The hypothesis of an alternative role for PrRP has been supported by numerous pharmacologic actions. For example, the inhibition of food intake and body weight, the stimulation of sympathetic tone, and the activation of stress hormone secretion in the central nervous system caused by PrRP underline an alternative role for this peptide. Recently, it was reported that PrRP acts as an endogenous regulator of cell growth. The bovine PrRP31 and PrRP20 were first isolated from hypothalamic extracts. With the help of the bovine PrRP31 sequence, the precursors of bovine, human and rat PrRP were cloned [S. Hinuma et al., *Nature* **1998**, 393, 272; J.-C. Meunier et al., *Nature* **1998**, 393, 211; B. L. Roland et al., *Endocrinology* **1999**, 140, 5736; R. Fujii et al., *Regul. Pept.* **1999**, 83, 1; C. B. Lawrence et al., *Nature Neurosci.* **2000**, 3, 645; W. K. Samson, M. M. Taylor, *Peptides* **2006**, 27, 1099].

Prolactoliberin, prolactin-releasing hormone (PRH), *prolactin-releasing factor (PRF)*, a hypothalamic substance (with for a long time an unknown structure) that stimulates the release of → prolactin in the adeno-hypophysis. Although the release of prolactin is stimulated by other peptides such as → thyroliberin (TRH), VIP, PACAP, oxytocin, and vasopressin, it has been assumed that the → prolactin-releasing peptide (PrRP) may function as prolactoliberin. Surprisingly, a dopamine-related stereospecific tetrahydroisoquinoline, termed *salsolinol*, 1-methyl-6,7-dihydroxy-1,2,3,4-

tetrahydroisoquinoline, produced by the neurointermediate lobe of the pituitary gland and by the hypothalamus, is capable of selectively releasing prolactin. Therefore, salsolinol has been considered to be the putative endogenous prolactoliberin [B. E. Toth et al., *J. Endocrinol.* **2001**, 13, 1042; I. Bodnar et al., *Ann. N. Y. Acad. Sci.* **2004**, 1018, 124].

Prolactostatin, *prolactin release-inhibiting hormone, PRIH* or *PIH, prolactin release-inhibiting factor, PRIF*, a hypothalamic substance of (until now) unknown structure that inhibits the release of → prolactin.

Prolamins, a group of storage proteins occurring in cereals. They are soluble in 50–90% ethanol and can be so separated from the alcohol-insoluble → glutelins. Prolamins are globular proteins ($M_r \sim 10\text{--}100$ kDa) with a high content of Glu (30–45%) and Pro (up to 15%). Members of the prolamins include → gliadin, → zeins, and the Lys-lacking hordein (barley).

Proline (Pro, P), pyrrolidine-2-carboxylic acid, $C_5H_9NO_2$, M_r 115.13 Da, a proteinogenic amino acid.

Pro-opiomelanocortin (POMC), *proopiomelanocortin*, a biosynthesis polypeptide (prepro-opiomelanocortin) that lacks the signal sequence and is formed in the distal and intermediary part of the hypophysis. POMC contains the sequences of → corticotropin (ACTH), → β -lipotropin, and γ -MSH (→ melanocortin peptides). The first two hormones are cleaved to smaller bioactive peptides in a tissue-specific manner. In the anterior lobe, POMC is proteolytically cleaved yielding the N-terminal fragment, ACTH, and β -lipotropin (β -LPH). However, in the intermediate lobe only, the latter polypeptide hormones are further cleaved to yield γ -MSH, α -MSH, corticotropin-like intermediate lobe peptide (CLIP), γ -LPH, and β -endorphin

[R. E. Mains, B. A. Eipper, *J. Biol. Chem.* **1979**, *254*, 7885; H. Gainer et al., *Neuroendocrinology* **1985**, *40*, 171; S. Solomon, *Ann. N. Y. Acad. Sci.* **1999**, *885*, 22].

Proprotein, an inactive protein precursor that is activated by removal of the propeptide.

Protamines, a group of strongly basic globular proteins ($M_r \sim 1\text{--}5$ kDa). They are characterized by a high content of Arg (80–85%). In particular, protamines occur in the sperm of fish, birds and mollusks, substituting there functionally the somatic histones. Members of the protamines include clupein (herring), salmin (salmon), sturin (sturgeon), and esocin (pike).

Proteases, a widely used term in literature for \rightarrow peptidases.

Protease-catalyzed peptide synthesis, an approach to \rightarrow enzymatic peptide synthesis using proteases (\rightarrow peptidases) as catalysts for \rightarrow peptide bond formation based on the reversal of \rightarrow proteolysis. The methods of protease-catalyzed peptide bond formation can be classified into two basic strategies according to the type of carboxyl component used. In the first approach, this component has a free carboxyl terminus, and formation of the peptide bond occurs with thermodynamic control as the reverse of peptide hydrolysis (\rightarrow equilibrium-controlled enzymatic synthesis). In the second approach, the carboxyl component is employed in a slightly activated form, mainly as an alkyl ester, and the synthesis occurs with kinetic control by competitive partitioning of a rapidly formed \rightarrow acyl enzyme intermediate between the nucleophilic amino component and water (\rightarrow kinetically controlled enzymatic synthesis). These two approaches are fundamentally different due to the energy required for

conversion of the substrates to the peptides products. The kinetic approach can be more efficiently manipulated than the thermodynamic approach, but is restricted to serine and cysteine proteases which form an acyl enzyme intermediate during catalysis. As all other proteases – including serine and cysteine proteases – are not perfect acyl transferases, undesired reactions may take place in parallel to acyl transfer. (Hydrolysis of the acyl enzyme, secondary hydrolysis of the formed peptide bond, and other undesired proteolytic cleavages of possible protease-labile bonds in educts and product). Manipulations to suppress competitive reactions are required, and these can be performed by medium engineering, enzyme engineering (\rightarrow subtiligase) and substrate engineering (\rightarrow substrate mimetic approach). Independently of the mechanism, one successful way to reverse the equilibrium towards synthesis is the formation of insoluble products. Besides this solubility-controlled process of precipitation, the biphasic approach product extraction represents a useful alternative, where the product is much more soluble in the organic phase and is thus continuously removed from the aqueous phase. In special cases, the formed peptide product may be removed from the equilibrium using molecular traps. However, it should be also mentioned that beyond organic solvents there are other approaches useful for manipulating enzyme properties. Although less popular (at least if the number of publications is considered the only criterion), these include studies in super-cooled and frozen media, in supercritical fluid extractions such as compressed carbon dioxide or propane, in solid-to-solid reaction systems (\rightarrow solid-to-solid conversion) and very recently even in ionic liquids (\rightarrow ionic liquid-mediated peptide synthesis). Bearing in mind that proteases have already

proven their value for organic synthesis, even up to the tonne scale, and including the fact that these enzymes are generally recognized as normal bench reagents for reactions based on their native hydrolytic activity, a general approach to the reverse enzymatic polypeptide synthesis remains to be formulated. However, by building on promising strategies, such as the substrate mimetic approach, site-specific chemically or ionic liquid-modified enzymes, significant improvements have been made, and more can be expected in the near future. The final breakthrough may be reached by using a combination of those strategies. Additional input can be expected from the combination of enzyme engineering with site-directed and, in particular, with directed evolution techniques that currently appear to be the most fertile approaches to the design of enzymes with tailored selectivities and synthetically relevant activities in essentially any suitable reaction medium [F. Bordusa, *Chem. Rev.* **2002**, *102*, 4817; N. Wehofskey et al., *Angew. Chem. Int. Ed.* **2003**, *42*, 677; N. Wehofskey et al., *J. Am. Chem. Soc.* **2003**, *125*, 6126; R. Günther et al., *Org. Biomol. Chem.* **2004**, *2*, 1442; F. Bordusa, *Enzymatic Formation of C-N Bonds*, in: *Bioorganic Chemistry Highlights II: From Chemistry to Biology*, C. Schmuck, H. Wennemers (Eds.), p. 389, Wiley-VCH, Weinheim, **2004**; F. Bordusa, *ChemFiles* **2005**, *6*, 13; C. Lombard et al., *Prot. Pept. Lett.* **2005**, *12*, 621].

Protease-catalyzed protein modification, a highly selective approach enabling irreversible and covalent *N*- and *C*-terminal modifications of proteins with functional synthetic moieties under native conditions. This technology is based on a designed trypsin variant containing four genetically mutated amino acid residues. The four mutations efficiently restrict the prote-

olytic activity of the protease towards the tripeptide sequence Tyr-Arg-His, which is highly unique in native proteins. The sequence is placed either at the *N*- or *C*-terminus of a given protein, followed by a very *N*- or *C*-terminal purification tag, respectively. This arrangement enables selective tag-cleavages by the biocatalyst, simultaneously providing a suitable precursor for site-specific modifications. For *N*-terminal modifications the process is mediated by the acceptance of substrate mimetics (\rightarrow substrate mimetic approach), whereas for *C*-terminal modifications synthetically modified short peptide building blocks fulfill the requirement. In both cases, functional synthetic moieties are covalently linked via stable carboxylic acid amide bond on either of the termini on the target protein by the enzyme. Interestingly, both tag-cleavage and subsequent modification reaction occurs not only in a highly efficient manner but also in a one-pot fashion, and are catalyzed by the same enzyme without any additional purification steps. The function of the approach has been demonstrated for a number of protein targets, including active enzymes such as the prolyl *cis/trans* isomerase cyclophilin 18 (\rightarrow cyclophilins) or the ribonuclease RNase A. The former was expressed recombinantly as a construct bearing the strep tag at the protein's *N*-terminus followed by the tripeptide recognition sequence Tyr-Arg-His and finally, the cyclophilin 18 itself. After one-step purification by using the strep tag-strep tactin system, the construct was incubated with the trypsin variant to allow for tag-cleavage which was completed after several minutes. Subsequently, the real modification reaction was initiated simply by adding the proper substrate mimetic, bearing a synthetic fluorescence moiety in that case, to the same reaction mixture. Analysis of the whole modification reaction

revealed a practical quantitative conversion of the expressed cyclophilin construct to the respective *N*-terminal-modified enzyme species bearing full enzymatic activity compared to the native wild-type protein. In a similar way, RNase A was modified specifically at the *C*-terminus. For this purpose, the biocatalyst's recognition sequence and the purification tag were placed downstream of the RNase A sequence; this led to a mirror imaged construct compared to cyclophilin 18, with the purification tag at the very *C*-terminus of the target protein and the recognition sequence in between. After purification, the RNase A construct was incubated with the biocatalyst and a synthetically modified tetrapeptide resulted in transamidation of the strep tag with the synthetic tetrapeptide, which finally led to the desired *C*-terminally modified RNase A species (F. Bordusa et al., DE04 019 237.9, EP1778839 and WO2006015879).

Protease inhibitors, artificial and natural compounds inhibiting the activity of proteolytic enzymes used, especially, to treat or prevent infection by viruses including → HIV and Hepatitis C. Such inhibitors are as diversified as the proteases themselves. Generally, they can be divided into main classes: (a) active site-specific, low-molecular-weight inhibitors; and (b) naturally occurring protein peptidase inhibitors. Examples of the first group are the serine peptidase inhibitors diisopropyl phosphofluoridate (DFP) and phenylmethanesulfonyl fluoride (PMSF). Both react with the active-site serine. Many of the naturally occurring peptidase inhibitors, isolated from animal, plant and bacterial organisms, behave as pseudo-substrates. They combine essentially irreversibly with the active site and are converted into a modified form in which a peptide bond, related to the primary substrate

specificity of the peptidase, is cleaved. Of special physiological interest are inhibitors which react with mammalian plasma serine peptidases, especially those involved in blood coagulation. In principle, such inhibitors have both protective and regulatory functions. Approximately 10% of the almost 200 proteins of blood serum are peptidase inhibitors. The α_1 -proteinase inhibitor secreted by the liver, for example, inhibits leukocyte elastase which is thought to be part of the inflammatory process. Furthermore, special variants of this inhibitor with reduced inhibiting power are associated with pulmonary emphysema. The latter is a degenerative disease of the lungs which results from the hydrolysis of its elastic fibers. Selected protease inhibitors include → aprotinin and other → serpins, → textilins, → eglin c, and → α_2 -macroglobulin. Interestingly, certain plants release peptidase inhibitors in response to insect bites in order to inactivate the digestive enzymes of the attacking insect [A. J. Barrett, G. Salvesen (Eds.), *Proteinase Inhibitors*, Elsevier, Amsterdam, 1986; R. C. Ogden, C. W. Flexner (Eds.), *Protease Inhibitors in AIDS Therapy*, Marcel Dekker, Inc., New York, 2001].

Proteasome, *prosome*, multimeric protease complex degrading preferentially ubiquitination-targeted intracellular proteins. The name "proteasome" was proposed to indicate its proteolytic and particulate nature. The ubiquitin-proteasome pathway is important for the regulated degradation of various proteins, since proteolysis and turnover of cellular proteins are essential processes in living cells. From 1989 on it became evident that the proteasome acts as the proteolytic core of a larger ATP-dependent complex. The 26S *proteasome complex* ($M_r \sim 1700$ kDa) is the key catalytic protease, and is composed of

the catalytic 20S proteasome and 19S cap regulatory complexes at each end of the core. The function of the cap complexes is to recognize substrate proteins, generally, after these have been ubiquitinated. The cap complexes present them in unfolded form to the 20S core in an ATP-dependent process. 20S proteasomes ($M_r \sim 700$ kDa) are found in the cytoplasm and nucleus of all known eukaryotes, and in the archaeobacterium *Thermoplasma acidophilum*. The multisubunit complex forms a hollow cylinder of approximately 15 nm length and 11 nm diameter, consisting of four stacked rings each containing seven low-molecular-weight subunits ($M_r \sim 20\text{--}35$ kDa). In eukaryotes, there exist 14 different (but homologous) subunits, which can be divided into two groups: α and β subunits. For example, in the crystal structure of the yeast proteasome, seven α subunits form the outer rings, while the seven β subunits form the inner rings of the complex. The proteolytic activity of the 20S proteasome can be specifically inhibited by \rightarrow lactacystin and \rightarrow salinosporamide A. In archaea, the proteasome contains only two different types of subunit that possess only one catalytic activity. The proteasome of bacteria consists of two rings with six subunits. Of the two different bacterial subunits, only one is related to the eukaryote and archaean subunits, whereas the other is an ATPase. Proteasomes are important in cellular regulation. They are, for example, responsible for the degradation of cyclins at key stages of the cell cycle, and for the removal of abnormal proteins during stress response. Furthermore, they degrade enzymes of intermediary metabolism and are involved in the immune response [A. P. Arrigo et al., *Nature* **1988**, 331, 192; J. Löwe et al., *Science* **1995**, 268, 533; A. Lupas et al., *Mol. Biol. Rep.* **1997**, 24, 125; R. J. Mayer, A. Ciechanover, M. Rechsteiner (Eds.), *Protein*

Degradation: The Ubiquitin-Proteasome System, Wiley-VCH, 2005].

Protecting groups, moieties for the protection of amino acid functionalities during the course of peptide synthesis. Most protecting groups currently used must be removable by mild methods such as hydrogenolysis and exposure to anhydrous acids or bases at room temperature. These three main approaches to deprotection afford the opportunity of orthogonal protection (\rightarrow orthogonal protecting groups), provided that particular protecting groups survive at least one type of deprotection procedure. Even when synthesizing the simplest peptide in a controlled manner, it is essential that certain functional groups are protected. Generally, it is of great importance to introduce – and, more importantly, to remove – all protecting groups under conditions that do not damage the integrity, and especially the stereochemical purity, of the peptide to be synthesized. A differentiation must be made between \rightarrow temporary protecting groups and \rightarrow semipermanent protecting groups of side-chain functionalities. The latter must be stable both during the repetitive cleavage reactions of the temporary protecting groups, and during the coupling reactions. The third category of protection applies to the C-terminus of the peptide. For *C $^\alpha$ -carboxy protection* esters of the methyl, ethyl, benzyl, *tert*-butyl, or aryl type are preferentially used. The protecting groups must be stable throughout the whole synthetic route but, on the other hand, C-terminal-protecting groups are sometimes required which can be removed in the presence of all other protecting groups. Especially, if a fully protected peptide segment is required to be coupled at its C-terminal amino acid residue. For most commonly used strategies in peptide synthesis, *N $^\alpha$ -protecting groups* are

nearly always a variety of urethane-type (alkoxycarbonyl-type) protecting groups such as \rightarrow *tert*-butoxycarbonyl group, \rightarrow 9-fluorenylmethoxycarbonyl group, \rightarrow benzyloxycarbonyl group, and the \rightarrow 4-nitrobenzyloxycarbonyl group. Furthermore, \rightarrow alkyl-type protecting groups, \rightarrow arene sulfonyl-type protecting groups, \rightarrow photolabile protecting groups, \rightarrow enzyme-labile protecting groups, and also \rightarrow amide-protecting groups and even \rightarrow backbone amide protecting groups fulfill the tactical requirements of protection in peptide synthesis. The protection of side-chain functionalities can be performed by a variety of specific semipermanent protecting groups, e.g., \rightarrow guanidino protection, \rightarrow indole protection, \rightarrow thioether protection, \rightarrow thiol protection, \rightarrow imidazole protection, \rightarrow hydroxy protection, \rightarrow ω -amino protection and \rightarrow ω -carboxy protection. The tactics of peptide synthesis comprise selection of the optimum combination of protecting groups (\rightarrow protection schemes) besides the most suitable coupling method for each synthesis concept [T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons Inc., 1999; P. Kocienski, *Protecting groups*, Georg Thieme Verlag, Stuttgart, 2003].

Protection schemes, combinations of \rightarrow protecting groups in peptide synthesis. Deliberate planning of both the order of peptide bond-forming steps and the choice of protecting group combinations is pivotal for successful peptide synthesis. A minimum protection tactics has been developed for reducing solubility problems and minimizing the number of synthesis steps. However, it is not possible in practice to omit side-chain protection completely. Especially the side-chain amino, thiol, and carboxy groups (Lys, Cys, Asp, Glu), require protection to avoid the for-

mation of side products. Consequently, the maximum protection approach seems to be the preferred tactical variant both in solution-phase synthesis and in solid-phase synthesis. This comprises global masking of all functional groups. The protection schemes Boc/Bzl (\rightarrow Merrifield tactics) and Fmoc/*t*Bu (\rightarrow Sheppard tactics) are preferably used. Merrifield tactics combines an acid-labile temporary N^α -protecting group (Boc) with less acid-labile linkers and semi-permanent benzyl type side-chain protection. Side-chain deprotection and detachment from the resin are performed in a single step under strongly acidic conditions, and the choice of scavengers is critical. Anhydrous HF or trifluoromethane sulfonic acid are the preferred agents for the final deprotection of benzyl-type protecting groups. Sheppard tactics utilizes the base-labile Fmoc group for N^α -protection, combined with acid-labile semi-permanent *tert*-butyl-type side chain-protecting groups. The chemistry of both procedures has different features and different problems. The maximum protection tactics (Boc/Bzl/Pac), termed \rightarrow Sakakibara tactics, is an extension of the Boc/Bzl tactics, which is especially suited for the synthesis of larger peptides and proteins. In special cases, e.g., if further orthogonality is required, photolabile, hydrazine-labile (Dde-type) or Pd $^\circ$ -labile (allyl type) protecting groups may be employed [K. Barlos, *Biopolymers* 1999, 51, 266; F. Albericio, *Biopolymers* 2000, 55, 123, S. Sakakibara, *Biopolymers* 1999, 51, 279].

Protegrins (PG), a family of Arg- and Cys-rich cationic peptides isolated from porcine leukocytes exhibiting a broad range of antimicrobial and antiviral activities. The protegrins are active against various Gram-positive and Gram-negative bacteria, and, furthermore, against HIV-1 and

mycobacteria. The protegrins consist of 16–18 residues, including four invariant Cys which form two disulfide bonds and stabilize a rigid structure of two antiparallel β -sheets and a β -turn segment. The protegrins show similarities to the \rightarrow tachyplesins. Five members of this family have been well characterized, and the sequence and numbering system of PG-1 from pig (*Sus scrofa*) is as follows: RGGRLCYCRR¹⁰RFCVCVGR (disulfide bonds: C⁶–C¹⁵/C⁸–C¹³) [V. N. Kokryakov et al., *FEBS Lett.* **1993**, 327, 231; R. L. Fahrner et al., *Chem. Biol.* **1996**, 3, 543].

Protein adducts, moieties covalently bound to a protein as a consequence of a reaction with an electrophilic agent [M. Törnqvist et al., *J. Chromatogr. B* **2002**, 778, 279].

Protein 7B2, an acidic protein ($M_r \sim 21$ kDa) first isolated from porcine adenohypophysis, and characterized via cDNA sequence in humans (185 aa) and *Xenopus*. 7B2 is widely distributed in neural and endocrine tissues. Its sequence shows high similarities among mammals. A most conserved sequence feature is characterized by its polyproline motif (-Pro-Pro-Asn-Pro-Cys-Pro-). In neuroendocrine cells, 7B2 acts as a specific chaperone for the proprotein convertase 2 [K. L. Hsi et al., *FEBS Lett.* **1982**, 147, 261; G. J. Martens, *FEBS Lett.* **1988**, 234, 160; M. Mbikay et al., *Biochem. J.* **2001**, 357, 329].

Protein C, vitamin K-dependent protein first purified from bovine plasma, and named protein C according to the third-eluted peak from an ion-exchange column. Human protein C precursor contains 461 residues. The mature protein C ($M_r \sim 62$ kDa) contains a light (L) chain (155 aa, $M_r \sim 21$ kDa) and a heavy (H) chain (262 aa; $M_r \sim 41$ kDa) linked together by a disulfide bond. The L chain consists of several separate do-

main, including a Gla-containing domain and two EGF-like domains, whereas the H chain forms the serine protease domain. The thrombin–thrombomodulin complex located on the surface of endothelial cells converts protein C to *activated protein C* (APC) by release of 12 residues from the N-terminus of the H chain. APC regulates the coagulation pathway by inhibiting the generation of thrombin via its selective proteolytic inactivation of coagulant cofactors Va and VIIIa [C. T. Esmon, K. Fukudome, *Semin. Cell Biol.* **1995**, 6, 259; B. Dahlbäck, *Thromb. Res.* **1995**, 77, 1; C. T. Esmon, *Chest.* **2003**, 124, 26S].

Protein disulfide isomerase (PDI), a homodimeric protein ($M_r \sim 110$ kDa) widely distributed across eukaryotic cells. PDI catalyzes the isomerization and rearrangement of disulfide bonds in the endoplasmic reticulum. Furthermore, S-denitrosation activity of PDI has been described. Recently, a direct, continuous, sensitive assay of PDI based on fluorescence self-quenching has been described [B. Wilkinson, H. F. Gilbert, *Biochim. Biophys. Acta* **2004**, 1699, 35; A. Raturi et al., *Biochem. J.* **2005**, 391, 351].

Protein domains, *tertiary structure elements*, globular clusters within protein molecules with more than ~ 200 amino acid residues. Generally, three classes of domains can be distinguished: (i) structures containing only α -helices; (ii) structures containing antiparallel β -pleated sheets; and (iii) structures containing α -helices and β -sheets.

Protein folding, a process in which a polypeptide chain folds into its characteristic three-dimensional structure. Protein folding can be subdivided into two major fields, the folding *in vitro* and *in vivo*. Protein folding (or renaturation) *in vitro* includes the regain of the functional

three-dimensional structure from a chemically synthesized polypeptide chain or from a denatured (or unfolded) protein that has been previously synthesized on the ribosome. Protein folding *in vivo* involves all folding processes with which a polypeptide chain can achieve its biologically active structure in the cell. It includes folding of the nascent polypeptide chain emerging from the ribosome. The folding process involves a huge number of intrinsically fast rotations of covalent bonds, also termed conformational interconversions. Disulfide bond formation is an exception because a covalent bond is formed during folding. Most rotational movements occur in a temporarily coupled manner, though a few of them uncouples forming slow phases in folding kinetics. The most abundant instance of the latter is the *cis/trans* isomerization of peptide bonds, especially the peptide bond preceding a proline residue (\rightarrow peptidyl prolyl *cis/trans* isomerases). This event is slow on the biological time scale, making it rate-limiting in the refolding of many proteins. The information of the three-dimensional structure of a protein is encoded in its amino acid sequence, but prediction of the structure from sequence information is still premature. The stabilization energy of the folded state relative to the unfolded chain of a protein is usually low, thus making it susceptible to minor changes in the chemical and physical environment. During the refolding reactions some proteins transiently form folding intermediates, such as the molten globule, whereas other proteins only populate the native and unfolded states. Aggregation-prone folding intermediates diminish the folding yield since the proteins precipitate adopting a biologically inactive state. The risk of forming precipitates was shown to be reduced in the cell by the presence of *folding helper*

proteins. Those folding helpers either do form a protected cavity in which the folding of a single guest polypeptide chain occurs, or enzymatically catalyzes the slow kinetic steps in the refolding reaction. The latter avoids the population of aggregation-prone intermediates. In other cases, the folding helper presents a template with a high affinity for unfolded and partially folded polypeptide chains, thus preventing the existence of aggregation-prone folding states free in solution (\rightarrow molecular chaperones). In many cases, folding helper proteins are induced by applying environmental stress such as heat, chemicals and altered physiological conditions. A multiplicity of findings exist which support the hypothesis that diverse human disorders are associated with proteins that misfold and aggregate under physiological conditions exhibiting toxic properties, decreased solubility, and diminished proteolytic degradation. The pathogenesis of spongiform encephalopathies (\rightarrow prions), for example, shows a link to prion protein misfolding [T. R. Jahn, S. E. Radford, *FEBS J.* **2005**, 272, 5962; J. Buchner, T. Kiefhaber (Eds.), *Handbook of Protein Folding*, Wiley-VCH, Weinheim, **2005**].

Protein modeling, the computational prediction of protein structure. Knowledge of three-dimensional protein structure is essential for a detailed understanding of its molecular function. An accurate description of protein structure is also required for an understanding of protein–ligand interactions. Computational studies on protein folding and protein interaction (structure prediction, fold recognition, homology modeling, and homology design) generally rely upon the postulate of a protein or a protein–ligand complex being in the state of lowest free energy under physiological conditions. The prediction of protein

structure, which relies basically on sequence and structure homology modeling, has become more precise, and this will lead to improved methods for protein–ligand docking and binding site analysis. However, the accurate prediction of binding free energies remains a central challenge in structure-based ligand design. Moreover, protein modeling is expected to contribute to the relationship of the three-dimensional structure of an individual protein and its role in complex biological systems involving many proteins. The spatial and temporal properties of large systems can now be simulated on molecular structures. Kinetic parameters can be included in the mathematical modeling of biochemical pathways based on protein structure information which is expected to provide information on regulation and manipulation of biochemical pathways by protein structure [H.-D. Höltje, W. Sippl, D. Rognan, G. Folkers, *Molecular Modelling: Basic Principles and Applications*, 2nd Ed., Wiley-VCH, Weinheim, 2003].

Protein nanocrystallography, a miniaturization process of protein crystallography's experimental methods. Nano-crystallogenesis is becoming a useful means of identifying crystallization conditions and producing seedlings for macroscopic crystals required for standard structure determination by X-ray crystallography. The major benefit is that it minimizes the amount of protein, while the automation required for nanocrystallogenesis additionally increases the throughput of experimentation [E. R. Bodestaff et al., *Acta Crystallogr.* 2002, D58, 1901].

Protein pharmaceuticals, proteins that are applied for therapeutic purposes. The developments in recombinant protein production brought about a therapeutic concept based on the pharmaceutical

application of endogenous proteins. Indications for pharmaceutical proteins are, e.g., cancer, infectious diseases, AIDS/related diseases, heart disease, respiratory diseases, autoimmune disorders, transplantations, skin disorders, diabetes, genetic disorders, digestive disorders, blood disorders, infertility, and growth disorders. Currently, more than 200 peptide and protein pharmaceuticals have been approved in the US by the FDA. Human serum → albumin maintains plasma colloid osmotic pressure and serves as a carrier of intermediate metabolites. It is applied for symptomatic relief and supportive treatment in the management of, e.g., shock, and burns. Recombinant human → erythropoietin is used in the treatment of anemia related to chronic renal failure, but has been heavily misused by athletes for the stimulation of red blood cell production. Patients with hemophilia require injections of Factor VIIa, Factor VIII, or Factor IX. Granulocyte → colony-stimulating factor (G-CSF) stimulates neutrophil production in the bone marrow and is given to cancer patients receiving chemotherapy or bone-marrow transplant. → Interferons are endogenous antitumor substances. Interferon- α is used to treat hairy cell leukemia, malignant melanoma, and AIDS-related Kaposi's sarcoma. Interferon- β is active against relapsing forms of multiple sclerosis. Interleukin 11 (→ interleukins) directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells in cancer patients during chemotherapy. Tissue plasminogen activator (tPA) is administered to lyse thrombi in the management of acute myocardial infarction. → Platelet-derived growth factor (PDGF) is used to treat skin ulcers of diabetic patients. Recombinant human deoxyribonuclease is administered by inhalation

for the treatment of cystic fibrosis. Human → growth hormone (somatotropin) is used for the treatment of dwarfism. FSH is indicated for induction of ovulation and to stimulate development of multiple follicles in ovulatory patients undergoing assisted reproductive therapy, and also for the induction of spermatogenesis in men. Likewise, menopins, an equal mixture of → follitropin (FSH) and → luteinizing hormone (LH) stimulates ovarian follicular growth in women. → Human chorionic gonadotropin (hCG) is a hormone applied by subcutaneous or intramuscular injection that supports the normal development of an egg in a woman's ovary, and is used to cause ovulation and to treat infertility. Recombinant human → parathyroid hormone (1-34) [PTH(1-34)] is employed as a subcutaneous injection for the treatment of osteoporosis. A combined hepatitis A/B vaccine comprises inactivated hepatitis A viruses and a recombinant hepatitis B surface protein (HBsAg). Whilst nowadays most therapeutic proteins are produced in recombinant form using bacteria, yeasts, plants, insect cells or mammalian cell lines, a high risk of HIV and hepatitis infection existed in the past, when the proteins had to be isolated from human sources. In general, the use of rodent mAb as therapeutic agents is hampered because the human organism recognizes them as foreign. Near-human clinical mAb, called "chimerized" or "humanized" antibodies have been created by fusing mouse variable domains to human constant domains in order to retain binding specificity while simultaneously reducing the portion of the mouse sequence. Transgenic mice technology allows for the generation of fully human therapeutic mAbs. Moreover, → monoclonal antibodies (mAb) are being increasingly used, as they mimic their natural function without inherent toxicity.

Seventeen therapeutic mAbs are already available commercially in the United States. The first example of an approved chimeric antibody was ReoPro (abciximab) from Centocor, an anticoagulant Fab fragment targeted against the thrombocyte integrin $\alpha_{IIb}\beta_3$. Simulect (basiliximab) and Zenapax (daclizumab) both target the IL-2 receptor on T cells and prevent transplant rejection. Humira (adalimumab) and Remicade (infliximab) block the interaction of TNF- α with receptors and modulate biological responses induced or regulated by TNF- α . They are used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. Herceptin (trastuzumab) is used for the treatment of patients with metastatic breast cancer. Campath (alemtuzumab) binds to CD52 and serves for the treatment of patients with chronic lymphocytic B-cell leukemia. Avastin (bevacizumab) binds to vascular endothelial growth factor and interferes with endothelial cell proliferation, thus being suitable for treatment of metastatic renal cell carcinoma. Similarly, Erbitux (cetuximab) binds to the EGF receptor and is administered against advanced squamous cell carcinoma of the head and neck. Rituxan (rituximab) is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen present on normal and malignant B lymphocytes, and is used against non-Hodgkin's lymphoma. Xolair (omalizumab) binds to human IgE, and limits the degree of release of mediators of the allergic response in severe persistent allergic asthma. Synagis (palivizumab), a neutralizing and fusion-inhibitory mAb against respiratory syncytial virus (RSV), inhibits RSV replication. Murine mAbs directed against CD20 that are conjugated with radioisotopes for tumor targeting have also reached the market: Zevalin (ibritumomab)/ ^{90}Y and Bexxar

(tositumomab)/¹³¹I. Progress has been made in nasal and intrapulmonary delivery, and also by chemical modification (protein pegylation or glycosylation to improve the pharmacodynamic properties). Nonetheless, the needle and syringe remain the primary means of protein delivery. Major hurdles remain in order to overcome the combined natural barriers of drug permeability, drug stability, pharmacokinetics and pharmacodynamics of protein therapeutics [A. K. Pavlou, J. M. Reichert; *Nature Biotechnol.* **2004**, *22*, 1513, J. M. Reichert et al., *Nature Biotechnol.* **2005**, *23*, 1073; S.-N. C. Liossis, G. C. Tsokos, *Curr. Rev. Allerg. Clin. Immunol.* **2005**, *116*, 721].

Protein phosphatase 2A phosphatase activator, also known as *Phosphotyrosyl phosphatase activator*, **PTPA**, a conserved protein from yeast to humans. Its enzymatic activity as a \rightarrow peptidyl prolyl *cis/trans* isomerase has recently been identified, making it the fourth family of the enzyme class EC 5.2.1.8. Its isomerase activity can be stimulated by Mg^{2+} /ATP. The three-dimensional structure of PTPA does not resemble those of other families of peptidyl prolyl *cis/trans* isomerases as an all-helical fold dominates the two-domain organization of the enzyme. In the enzyme-peptide substrate complex, the peptide binds at the interface of a peptide-induced PTPA dimer. Apparently, protein phosphatase 2A activation and peptidyl prolyl *cis/trans* isomerase activity of PTPA are functionally linked *in vitro* [N. Leulliot et al., *J. Mol. Cell* **2006**, *23*, 413].

Protein splicing, a form of post-translational processing characterized by an autocatalytic intramolecular rearrangement of a \rightarrow proprotein resulting in the extrusion of an internal protein domain, the intein,

followed by concomitant fusion of the two flanking protein regions (*N*- and *C*-exteins) via a native peptide bond. The splicing pathway consists of four nucleophilic displacements directed by the intein plus the first *C*-extein residue. Generally, standard inteins begin with Ser or Cys and end in Asn. The first residue in the *C*-extein is Ser, Thr or Cys acting often as nucleophiles. In the first step of the splicing mechanism, a linear (thio)ester intermediate is formed when Cys¹ (or Ser¹) undergoes *N*-S (or *N*-O) acyl rearrangement, converting the peptide bond at the *N*-terminal splice junction to a (thio)ester. In the second step, Cys + 1 (or Thr + 1, Ser + 1) cleaves the (thio)ester bond to form a branched (thio)ester intermediate. Cyclization of the *C*-terminal Asn resolves the branched intermediate in step 3. In step 4, the aminosuccinimide is slowly hydrolyzed to regenerate Asn or Iso-Asn, and another acyl shift rapidly forms the amide bond between the exteins. Protein splicing was first discovered in yeast in 1990. In protein *trans*-splicing, the intein domain is split into two protein fragments, Int^N and Int^C, which form a complex and fold into the active intein [P. M. Kane et al., *Science* **1990**, *250*, 651; H. Wu et al., *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9226; H. Paulus, *Annu. Rev. Biochem.* **2000**, *69*, 447; C. J. Noren et al., *Angew. Chem. Int. Ed.* **2000**, *39*, 450; F. B. Perler, *IUBMB Life* **2006**, *58*, 63; L. Saleh, F. B. Perler, *Chem. Rev.* **2006**, *106*, 183].

Protein transduction domains, \rightarrow cell-penetrating peptides.

Protein *trans*-splicing-mediated ligation, a \rightarrow biochemical protein ligation approach to the synthesis of *N*-terminally modified semisynthetic proteins based on protein *trans*-splicing (\rightarrow protein splicing). In contrast to native chemical ligation (\rightarrow

chemical ligation), this method requires neither an α -thioester at the synthetic peptide nor high reactant concentrations. Furthermore, the generation of an *N*-terminal cysteine at the recombinant protein is circumvented, and the amino acid left behind at the ligation junction is a serine, which should be better tolerated than a cysteine in the protein [C. Ludwig et al., *Angew. Chem. Int. Ed.* **2006**, 45, 5218].

Proteolysis, the action of \rightarrow peptidases in peptide and protein metabolism. Historically, enzymatic proteolysis has generally been associated with protein digestion. Digestive peptidases of the pancreatic and gastric secretions are among the best-characterized peptidases. Activation of the pancreatic digestive enzymes is initiated by \rightarrow enterokinase, an enzyme secreted by the mucous membrane of the stomach. It converts some trypsinogen into active trypsin, which then activates all the proenzymes, including more trypsinogen. The function of the digestive proteases is merely to breakdown all the proteins they encounter. Later, it became evident that peptidases play regulatory roles in a great variety of physiological processes. These include processing and molecular assembly of nascent polypeptide chains, and the processing of protein hormones, developing enzyme precursors to mature enzymes, fertilization, many other proteolytic processes important for cellular functions, and the regulation of programmed cell death (apoptosis). Besides various biochemical events involved in apoptosis, the most fundamental one is the participation of members of the \rightarrow caspase family in both the initiation and execution phases of cell death. Proteolytic processing occurs in many different ways, and is triggered by different proteases. *Limited proteolysis* is the key to this selectivity, which depends on the

accessibility of the scissile peptide bond to the acting peptidase and on its specificity. In this case, proteolysis is directed and limited to the cleavage of specific bonds in the target protein. A wide variety of prokaryotic and eukaryotic proteins are synthesized as larger pre- or prepro-forms. Some of these are biologically inactive and become activated upon limited proteolysis. Lysosomal enzymes, mitochondrial proteins, membrane proteins, secreted proteins, etc., undergo intracellular proteolytic maturation. Various viruses code for specialized peptidases which are essential for virus assembly. Some viral peptidases are interesting therapeutic targets. The \rightarrow aspartic peptidase HIV-1 protease (HIV-1 PR), more exactly named as human immunodeficiency virus 1 retropepsin (HIV-1 retropepsin; EC 3.4.23.16), has become the most thoroughly investigated system in the history of the peptidases. The great interest in HIV-1 retropepsin has been focused on the development of compounds that selectively inhibit the viral enzyme and not the related human aspartic peptidases. Secretory proteins are usually synthesized as precursors bearing an amino-terminal extension. The signal peptide is removed co-translationally by *signal peptidases* during translocation across the membrane. In the next step, precursors of protein hormones, growth factors and certain polycistronic precursor proteins are processed by specific enzymes. Generally, proteolytic processing induces the intramolecular rearrangements required for the expression of biological responses. As for blood coagulation, the complement system is triggered by a signal that activates several consecutive \rightarrow zymogen activation reactions. Complement takes part in the immune reaction directed against foreign organisms of tissues. Several components of the complement system are serine

peptidases. Peptidases as integral components of cells are only partly explored, e.g., lysosomal peptidases, granulocyte serine peptidases, membrane-bound peptidases, and enzymes of specialized tissues, such as the reproductive tract, skins, lens, muscle, pituitary, and adrenals. Various ATP-dependent peptidases have also been isolated. One large multifunctional protease complex that degrades intracellular proteins is the \rightarrow proteasome. Considerable attention has been paid to a group of intracellular serine peptidases associated with granulocytes as well as leukocytes and mast cells, as mentioned above. These peptidases are stored in granulae and released in response to inflammatory or allergic stimuli. Many of the peptidases are relevant to human health and disease, some as natural components of the human body, and others because they are important in species which provide us with food, or cause diseases. In order to understand proteolytic activity in biological processes, a knowledge of the contribution of the natural \rightarrow protease inhibitors to the regulation of the activity is essential. Proteolysis of proteins for \rightarrow sequence analysis and peptide mapping can be carried out according to different strategies. Last, but not least, it should be mentioned that some peptidases have industrial importance. In particular, some subtilisins have a broad substrate specificity and are highly stable at neutral and alkaline pH, and consequently are of considerable industrial interest as protein-degrading additives to detergents. These reasons, combined with their large database, make subtilisins attractive for protein engineering. Hence, extensive engineering studies have been conducted on the *Bacillus* subtilisins, and more than 500 site-directed mutants have been produced to alter specific enzyme properties, such as pH profile, thermal stability, or

substrate specificity. Finally, the reversal of proteolysis has opened an interesting approach to \rightarrow protease-catalyzed peptide synthesis [E. E. Sterchi, W. Stöcker (Eds.), *Proteolytic Enzymes: Tools and Targets*, Springer, Berlin, 1999].

Proteolytic enzymes, a widely used term in literature for \rightarrow peptidases.

Proteome, the entirety of proteins expressed in a tissue, body fluid or an organism.

Proteomics, investigation of the entirety of the proteins produced by a cell, tissue or organ under a set of certain conditions. The \rightarrow proteome, the protein equivalent of the genome, is a quantitative protein pattern determined by the development state and environmental parameters. Changes in protein expression can be observed by proteome analysis, which usually is a differential approach investigating two different states. It relies on two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) followed by protein staining, and tryptic digestion. The tryptic peptides are extracted, desalted and concentrated using C-18 Zip-Tips (filtration through C-18 RP material). The peptide fragments are then analyzed by mass spectrometry and the observed masses matched against databases of known proteins or proteins predicted on the basis of annotated genomes (fingerprint analysis). 2D-PAGE usually combines isoelectric focusing (separation according to pI) with SDS- polyacrylamide gel electrophoresis (separation according to molecular mass) and allows the simultaneous resolution of more than 5000 proteins (depending on gel size and pH gradient). However, as usually more than 10 000 different proteins are expressed by a cell at the same time, resolution often remains incomplete.

"Gel-free" methods such as the multi-dimensional protein identification technology (MuDPIT) represent alternatives to the 2D-PAGE-based strategies. The proteome is digested by, e.g., trypsinization, and the resulting peptides are bound to a cation-exchange HPLC column (first dimension), from where they are successively eluted with increasing salt concentrations onto a reversed-phase (RP) HPLC column (second dimension), where the peptides are separated according to hydrophobicity. As in the fingerprint analysis, the proteins can be identified by alignment of the peptide masses with a database to match proteins predicted by the annotated genome [F. Lottspeich, *Angew. Chem. Int. Ed.* **1999**, *38*, 2476; J. M. Walker (Ed.), *The Proteomics Protocols Handbook* Humana Press, Totowa, N.J., **2005**; A. Görg et al., *Proteomics* **2004**, *4*, 3665; T. Kislinger et al., *J. Am. Soc. Mass. Spectrom.* **2005**, *16*, 1207; J.-C. Sanchez, G. L. Corthals, D. F. Hochstrasser (Eds.), *Biomedical Applications of Proteomics* Wiley-VCH, Weinheim, **2006**; J. C. Smith, et al., *Anal. Chem.* **2007**, *79*, 4325].

Prothrombin, *thrombogen, factor II*, the zymogen of the serine protease \rightarrow thrombin. Prothrombin occurs in all vertebrates, and is activated after initiation of the coagulation cascade at the site of vascular injury. Prothrombin consists of the thrombin domain, a Gla domain, and two kringle domains [J. Stenflo et al., *Proc. Natl. Acad. Sci. USA* **1974**, *71*, 2730; K. G. Mann et al., *Methods Enzymol.* **1981**, *80*, 286].

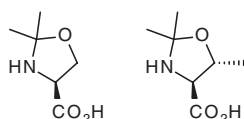
Pseudobiopolymers, non-natural biopolymers, comprising compounds such as antisense nucleotides, neo-glycoconjugates, and different classes of peptide analogues (\rightarrow pseudopeptides). The latter are composed of non-peptidic molecules in a repetitive manner similar to peptides. Moreover, some of them fold to give

stable, reproducible secondary structures mimicking protein secondary structures such as helices, sheets, or turns. They often are characterized by metabolic stability, resemble peptidic structures, and some of them might be applied therapeutically. The \rightarrow peptoids, \rightarrow peptide nucleic acids, and \rightarrow β -peptides are important representatives of this class of compounds. Oligomers of aza-amino acids (hydrazine carboxylates) have been named \rightarrow azatides. Oligosulfonamides, \rightarrow hydrazinopeptides (composed of α -hydrazino acids) and \rightarrow aminoxy peptides, composed of α -aminoxy acids, serve as β -peptide analogues with respect to the backbone atom pattern. \rightarrow Oligocarbamates, \rightarrow oligopyrrolinones, oligosulfones, \rightarrow γ -peptides, \rightarrow oligoureas, \rightarrow vinylogous peptides, vinylogous oligosulfonamides, and peptides derived from carbohydrate amino acids form further classes of pseudobiopolymers. Gellman coined the term "foldamers" for any polymer that reproducibly adopts a specific ordered conformation.

Pseudopeptides, a collective term for non-natural, non-peptide biopolymers (\rightarrow pseudobiopolymers), that resemble or mimic peptides and proteins. Among others, oligo-(*N*-alkylglycines) (\rightarrow peptoids), \rightarrow β -peptides and \rightarrow γ -peptides, \rightarrow hydrazinopeptides, \rightarrow aminoxy peptides, oligosulfonamides, \rightarrow oligocarbamates, \rightarrow peptide nucleic acids (PNA), pyrrole-imidazole polyamides, and \rightarrow oligopyrrolinones belong to this class of compounds [P. E. Nielsen, *Pseudo-Peptides in Drug Discovery*, Wiley-VCH, Weinheim, **2004**].

Pseudo-prolines, building blocks for peptide synthesis, where a Ser or Thr residue is reversibly protected as a cyclic *N,O*-ketal (proline-like oxazolidine) to be eventually cleaved with TFA. The incorporation of Ser or Thr residues as the corresponding

pseudo-proline derivatives in strategic positions of a \rightarrow difficult sequence prevents the undesired formation of secondary structures during synthesis, and leads to improved synthetic efficiency in Fmoc SPPS. The pseudo-prolines also found application as switching elements in the \rightarrow switch peptides [G. Tuchscherer et al., *Biopolymers (Pept. Sci.)* **2007**, 88, 239].



Pseudo-prolines derived
from Ser and Thr
Pseudo-prolines

Psoriasisin, *human psoriasisin*, S100A7, a member of the S100 family of calcium-binding proteins richly expressed in keratinocytes of patients suffering from psoriasis. At present, the exact physiological function of human psoriasisin in many human cell types remains to be investigated. It has been assumed that this protein may play an important role in innate immune defense against microbial infections. The total chemical synthesis of psoriasisin by \rightarrow chemical ligation has been described [X. Li et al., *Biochemistry* **2005**, 44, 14688].

Psty, polystyrene.

PTC, phenylthiocarbamoyl.

PTH, phenylthiohydantoin or parathyroid hormone.

Purification techniques, methods for the purification of peptides and proteins. Analysis and purification of naturally occurring peptides and of synthetic peptides makes use of different separation techniques. Partitioning of the analyte between a solution and a solid phase is the most exploited principle. Ion-exchange and electrophoresis methods

relying upon the existence of charged forms in aqueous solution are frequently used. Separation methods based on molecular size, adsorption chromatography, especially salt-promoted adsorption chromatography, and \rightarrow affinity chromatography are further important methods. Thin-layer chromatography, the simplest technique for amino acid or peptide analysis, is performed in various solvent systems. Free peptides can be examined by paper electrophoresis or by thin-layer electrophoresis in acidic solvent (dilute acetic acid) or under basic conditions. The introduction of high-performance liquid chromatography (HPLC), both on an analytical and a preparative scale, was a breakthrough in the separation and analysis of peptides and proteins. For \rightarrow reversed-phase HPLC, the column material is derivatized using alkylsilanes with four to 18 carbon atoms (referred to as C-4 to C-18 columns). Ion-exchange chromatography (IEC) is easy to use for protein purification due to its high scale-up potential. Size-exclusion chromatography (SEC), also named gel filtration chromatography when performed in aqueous solvent systems or gel permeation chromatography for polymer separation in non-aqueous solvents, is of somewhat limited resolving power in peptide purification, but continues to be an efficient separation method for proteins. In affinity chromatography, a low-molecular-weight biospecific ligand is linked via a spacer to an inert, porous matrix, such as agarose gel, glass beads, polyacrylamide, or crosslinked dextrans. Peptides often take over the role of the immobilized biospecific ligand. Fusion proteins, conjugates of the target protein with a carrier protein (\rightarrow streptavidin, protein A, glutathione S-transferase) or with a \rightarrow His tag can be easily purified on columns with immobilized biotin (streptavidin) or Strep-tag

(streptavidin), IgG (protein A), \rightarrow glutathione (glutathione *S*-transferase), or on a column loaded with Ni^{2+} -NTA complexes (His tag) [C. K. Larive et al., *Anal. Chem.* **1999**, 71, 389; P. Cutler (Ed.), *Protein Purification Protocols*, Humana Press, Totowa, N.J., **2004**; L. R. Bonner, *Protein Purification*, Taylor & Francis, New York, **2007**].

PyAOP, 7-azabenzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate.

PyBOP, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate.

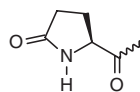
PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate.

Pyl, pyrrolysine (one-letter symbol O).

Pyroglutamic acid, *pyrrolidone carboxylic acid*, *5-oxoproline*, *pyrrolid-2-one-5-carboxylic acid*, *pGlu*, $<\text{Glu}$, *Glp*, *Pyr*, $<\text{E}$, an internal cyclic lactam of glutamic acid, representing a condensation of the α -amino group with the γ -carboxyl group. Pyroglutamic acid occurs as the *N*-terminal residue of naturally occurring \rightarrow pyroglutamyl peptides. In contrast, pyroglutamyl formation is a serious side reaction in peptide synthesis. The cyclization is catalyzed by weak acids. However, it is not a problem using Fmoc/ Bu^t chemistry, since basic conditions are maintained throughout chain elongation.

Pyroglutamyl peptides, peptides bearing \rightarrow pyroglutamic acid residues at the *N*-terminal position of the peptide chain. Pyroglutamyl acid formation of *N*-terminal glutamine residues catalyzed

by glutamine cyclase is an example of \rightarrow post-translational modification. The aminolytic cyclization of an *N*-terminal glutamine ($\text{R} = \text{NH}_2$) in peptides irreversibly gives terminated pyroglutamyl peptides. Naturally occurring pyroglutamyl peptides include *eisenin* ($<\text{Glu-Gln-Ala-OH}$), *pelvetin* ($<\text{Glu-Gln-Gln-OH}$) from algae, or the liberins \rightarrow thyroliberin, and \rightarrow gonadoliberin, as well as other peptides including \rightarrow physalaemin, and \rightarrow neurotensin. The pyroglutamyl peptide bond in biologically active pyroglutamyl peptides can be selectively cleaved by high concentrations of aqueous methanesulfonic acid for structural examinations [J. Kobayashi et al., *Chem. Pharm. Bull.* **2006**, 54, 827].



Pyroglutamyl peptides

Pyrrolysine (Pyl, O), the twenty-second genetically encoded, proteinogenic amino acid. It occurs in some methanogenic Archaea, has first been isolated from *Methanosarcina barkeri*, and appears to be limited to the *Methanosarcinaceae* and the Gram-positive *Desulfotobacterium hafniense*. Unlike \rightarrow selenocysteine, the 21st proteinogenic amino acid, pyrrolysine is charged directly onto a dedicated tRNA by a cognate aminoacyl-tRNA synthetase [B. Hao et al., *Science* **2002**, 296, 1462; J. A. Krzycki, *Curr. Opin. Microbiol.* **2005**, 8, 706]

PYY, peptide tyrosine tyrosine.

Q

QC, glutaminyl cyclase.

QqTOF, quadrupole/time-of-flight.

QRFP, a 43-peptide amide bearing an N-terminal pyroglutamyl residue and the C-terminal RFamide consensus motif. This novel \rightarrow RFamide peptide is implicated in food intake and aldosterone release from the adrenal cortex in the rat. QRFP is conserved in humans, cattle, rat, and mouse. The term QRFP is derived from pyroglutamylated arginine-phenylalanine-amide peptide [S. Fukusami et al., *J. Biol. Chem.* **2003**, 278, 46387; C. Kutzleb et al., *Curr. Prot. Pept. Sci.* **2005**, 6, 265].

QSAR, quantitative structure–activity relationship.

Quaternary structure, the spatial arrangement of two or more polypeptide chains associated by non-covalent interactions, or

in special cases linked by disulfide bonds, forming definite complexes.

8-Quinolyl ester (OQ), a special type of \rightarrow active ester featuring an additional proton-accepting group that stabilizes a hydrogen-bonded transition state during aminolysis. This led to high aminolytic activity and an extensive decrease in racemization-prone oxazolone formation [H.-D. Jakubke, A. Voigt, *Chem. Ber.* **1966**, 99, 2944].

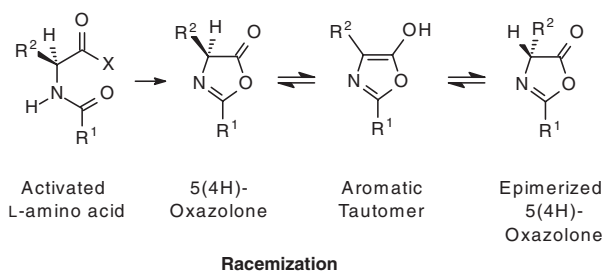
Quinqueginsin, a homodimeric protein ($M_r \sim 53$ kDa) with inhibitory activity against human immunodeficiency virus (HIV), fungi, ribonuclease, and cell-free translation. Quinqueginsin has been isolated from the roots of American ginseng *Panax quinquefolium*. The inhibitory action towards HIV-1 reverse transcriptase was potentiated after chemical modification with succinic anhydride [H. X. Wang, T. B. Ng, *Biochem. Biophys. Res. Commun.* **2000**, 269, 203].

R

Rab proteins, *Ras-like proteins from rat brain*, guanosine triphosphate phosphatases (GTPases) belonging to the Ras superfamily of GTPases. Rab proteins form the largest branch, with more than 60 members in humans. Most of Rab proteins are ubiquitous, but some are cell-type or tissue-specific. Results of *in vivo* and *in vitro* studies have concluded that Rab proteins cycle between a GTP-bound active and a GDP-bound inactive form, which results in dramatic changes in their three-dimensional structure. Furthermore, Rab GTPases cycle between membrane and cytosolic localizations. Their membrane association function is achieved through two geranylgeranyl moieties covalently attached to two cysteines at the C-terminus. This post-translational modification requires the interplay of the GTPase with Rab geranylgeranyl-transferase (RabGGTase) and its accessory protein REP (Rab escort protein) [H. R. Bourne et al., *Nature* **1990**, 348, 125; P. J. Casey, M. Seabra, *J. Biol. Chem.* **1996**, 271, 5289; J. B. Bock et al., *Nature* **2001**, 409, 839].

Racemization, *epimerization*, loss of stereochemical information at C $^{\alpha}$ -atom. While the expression racemization is used in organic chemistry for the complete conversion of a single enantiomer into the racemate, it is often used in peptide chemistry for partial or total epimerization at one chiral C $^{\alpha}$, irrespective of whether a mixture of diastereomers or enantiomers is formed. The correct stereochemistry is important for the biological activity of a peptide or protein. Hence, racemization must

be minimized in the synthesis of peptides. The stereochemical integrity of a synthetic peptide very much depends on the degree of epimerization during coupling steps or other types of reaction that are sensitive toward racemization. If only 2% epimerization occurs upon incorporation of each amino acid residue during peptide synthesis of a 20-peptide, the inseparable mixture of diastereomers theoretically contains only 66.8% of the peptide with the correct stereochemistry. Racemization may occur by direct enolization of a carboxy-activated amino acid. Base-catalyzed racemization has been observed under highly basic coupling conditions or during ester saponification, while acid-catalyzed racemization occurs upon treatment of *N*-substituted *N*-methyl amino acid derivatives with strong acids. Racemization during coupling reactions mainly is caused upon amino acid activation by the formation of stereochemically labile 5(4*H*)-oxazolones (2-oxazolin-5-ones, azlactones) as reaction intermediates. The propensity toward 5(4*H*)-oxazolone formation strongly correlates with the activation potential of the carboxy-activating group and the electronic properties of the *N* $^{\alpha}$ -acyl residue due to the nucleophilic capacity of the carbonyl oxygen. Preactivation of amino acids with coupling reagents sometimes is accompanied by racemization and, hence, should be avoided when, for example, racemization-prone building blocks are to be incorporated. 5(4*H*)-Oxazolones display a much higher tendency towards enolization and, consequently, racemization, than protected amino acids themselves, because the enol



form is part of an aromatic oxazole structure. Peptide chain assembly starting from the C-terminus using urethane-type protecting groups is regarded as being devoid of racemization.

Radiosumin, a dipeptide isolated from the freshwater blue-green alga *Plectonema radiosum* (NIES-515). It is composed of the two unusual building blocks 2-amino-3-(4-amino-2-cyclohexen-1-ylidene)propionic acid and 2-amino-3-(4-amino-2-cyclohexylidene)propionic acid. The structure has been confirmed by total synthesis. It exhibits a high inhibitory effect against trypsin, and moderate activity against plasmin and thrombin [H. Matsuda et al., *J. Org. Chem.* **1996**, 61, 8648; T. Shioiri, Y. Hamada, *Synlett* **2001**, 184].

RAFT, regioselectively addressable functionalized template.

Ramachandran plot, a graphical x/y-representation of accessible regions of the peptide torsion angles φ / ψ .

RAMP, receptor activity modifying protein.

Ranakinin, KPNPERFYGL¹⁰Ma, an 11-peptide amide isolated from the brain of the frog *Rana ribibunda*. Ranakinin shows similarities to \rightarrow physalaemin, and is a preferred agonist for the NK-1 tachykinin receptor [M. G. Kodjo et al., *Endocrinology* **1995**, 136, 4535].

Ranalexin, FLGGLIKIVP¹⁰AMICAVTK KC²⁰ (disulfide bond: C¹⁴–C²⁰), an antimicrobial 20-peptide isolated from the skin of the American bullfrog *Rana catesbeiana*. Ranalexin resembles structurally \rightarrow polymyxin, based on a similar 7-peptide ring system. It is thought to act via the formation of ion channels, which are pores spanning the membranes of bacteria [P. D. Clark et al., *J. Biol. Chem.* **1994**, 269, 10849; E. Vignal et al., *Eur. J. Biochem.* **1998**, 253, 221].

Ranamargarin, DDASDRAKKF¹⁰YGLMa, a 14-peptide amide isolated from the skin of the Chinese frog *Rana margaratae*. Its activity profile resembles that of \rightarrow substance P and \rightarrow physalaemin [L. Q. Tang et al., *Regul. Pept.* **1988**, 22, 182].

Rana RFamide (Rana-RFa), \rightarrow Neuropeptide R-RFa.

Ranatachykinins (RTK), a group of tachykinin-like peptides isolated from bullfrog brain and gut. RTK A, KPSPDRFYGL¹⁰Ma, RTK B and RTK C were named for their source *Rana catesbeiana* and their homology to the \rightarrow tachykinin family. RTK A causes strong effects in the guinea-pig ileum and rat duodenum contractility assays similar to \rightarrow eledoisin. All of the RTK elicited Ca²⁺ elevations in Chinese hamster ovarian cells [K. Kangawa et al., *Regul. Pept.* **1993**, 46, 81; S. A. Perrine et al., *J. Med. Chem.* **2000**, 43, 1741].

Ranatensin, <EVPQWAVGHF¹⁰Ma, a 11-peptide amide belonging to the → ranatensin family. Ranatensin was first isolated from the skin of the American leopard frog *Rana pipiens*. Ranatensin shows vasoactive and myotropic activity [T. Nakajima et al., *Fed. Proc.* **1970**, 29, 282; T. Nakajima, *Trends Pharmacol. Sci.* **1981**, 2, 202].

Ranatensin family, a subfamily of the → bombesin-like family. To this family belong → ranatensin, → litorin, and → neuromedin B.

Ranatuierins, antimicrobial peptides first isolated from the skin of the American bullfrog, *Rana catesbeiana*. Nine peptides, named Ranatuierins 1–9, showing antimicrobial activity towards *Staphylococcus aureus* were isolated. *Ranatuierin 1*, SMLLS VLKNL¹⁰GKVGLGFVAC²⁰KINKQC (disulfide bond: C²⁰–C²⁶), shows the broadest activity spectrum against *S. aureus*. Later, further members of these → ranid frog peptides were described, such as *Ranatuierin-2SEa*, GFISTVKNL¹⁰TNVA GTVIDT²⁰IKCKVTGGC, *Ranatuierin-2SEb*, AIMDTIKDTA¹⁰KTVAVGLLNK²⁰LKCKITGC, and *Ranatuierin-2SEc*, GIMDTIKD TK¹⁰TVAVGLLNKL²⁰KCKITGC. However, these three peptides with antimicrobial and histamine-releasing activities were isolated from skin secretions of the frog *Rana sevos*a [J. Goraya et al., *Biochem. Biophys. Res. Commun.* **1998**, 250, 589; C. Graham et al., *Peptides* **2006**, 27, 1313].

Random coil conformation, an unordered conformation usually characterized by a strong negative circular dichroism (CD) band just below 200 nm.

Random screening, a stochastic approach for lead structure retrieval in the drug development process. In → high-throughput screening thousands of compounds can be

tested per day in biological assays. A combinatorial library for random screening may contain large mixtures or arrays of very highly diverse structures. Screening results are hence often difficult to analyze. Today, random screening of large compound libraries is recommended to be accompanied by focused screening with library design based on the target structure.

Random sampling, an approach in molecular modeling for conformational energy searching that relies on stochastic probing (Monte Carlo simulation). Different conformations are examined at random – in contrast to systematic searching – in order to explore the conformational space of a molecule.

Ranid frog peptides, histamine-releasing and antimicrobial peptides from the skin secretion of the North American dusky gopher frog, *Rana sevos*a. Ranid frog peptides comprise four families, namely esculentin-1, esculentin-2 (→ esculentins), → brevenin-1 and → ranatuierin-2. The peptides have been named according to the accepted terminology as esculentin-1SEa, etc., reflecting the peptide family name, the species of origin (SE for *sevos*a), and the isotype (a) [C. Graham et al., *Peptides* **2006**, 27, 1313].

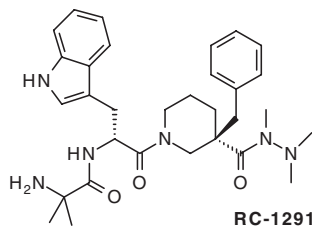
Ras inhibitory peptide (RIP), H-Val-Pro-Pro-Pro-Val-Pro-Pro-Arg-Arg-Arg¹⁰-OH, a 10-peptide corresponding to the sequence 1149–1158 of the guanine nucleotide-releasing factor hSos1. The latter is essential for the control of Ras activity. RIP specifically inhibits the binding of hSos1 to the protein human Grb2 which binds to activated receptor tyrosine kinase [N. Li et al., *Nature* **1993**, 363, 85].

Ras proteins, a superfamily of plasma membrane-bound GTP-binding proteins that are involved in signal transduction

pathways controlling cell growth, differentiation, apoptosis, and other events. *H-ras*, *N-ras*, and *K-ras* are identified as human ras genes. *K-ras* is spliced to give two different variants, *K-ras4A* and *K-ras4B*. Each of the three functional ras genes encode highly related proteins known as Ras p21 proteins that contain 188 or 189 residues. Whereas, the first 85 residues of mammalian p21 Ras proteins of known sequences are identical, the following 80 residues differ slightly, with at least 85% homology between any pair. The remaining part of the protein is highly variable except for the last four amino acids bearing the CAAX motif (C = Cys; A = any aliphatic amino acid; X = variable residue) which is present in all members of the Ras protein family. The Ras p21 proteins are involved in the regulation of oncogenic, mitogenic, and development signaling pathways. The synthesis of the Ras protein occurs in the cytosol, and is localized to the inner plasma membrane only after a series of post-translational modifications. The attachment of lipophilic groups to the C-terminus is a prerequisite for biological function. Especially, farnesylation is necessary for membrane localization and its activity. Farnesylation of the cysteine residue of the CAAX motif occurs after the proteolytic cleavage of AAX followed by methyl esterification at the newly formed C-terminal Cys residue. Farnesylation of the appropriate SH group is catalyzed by farnesyltransferase, which transfers a C-15 farnesyl moiety from farnesyl pyrophosphate. After localization to the cell membrane, the Ras p21 proteins bind GTP and GDP and possess intrinsic GTPase activity. Ras acts as a molecular switch that cycles between the GDP-bound "off" and the GTP-bound "on" states. The lifetime of the two states is determined by *guanine nucleotide exchange factors* (GEFs) and *GTPase-*

activating proteins (GAP). Oncogenic versions of Ras contain point mutations which cause blocking of the GTPase activity in the presence and absence of GAP. The resulting accumulation of Ras in the active form leads to uncontrolled cell growth, and this plays an important role in malignant transformations [M. Barbacid, *Annu. Rev. Biochem.* **1987**, 56, 779; D. R. Lowy, B. M. Willumsen, *Annu. Rev. Biochem.* **1993**, 62, 851; D. M. Leonard, *J. Med. Chem.* **1997**, 40, 2971; A. Wittinghofer, H. Waldmann, *Angew. Chem. Int. Ed.* **2000**, 39, 4192; N. Mochizuki et al., *Nature* **2001**, 411, 1006; O. Rocks et al., *Science* **2005**, 307, 1746].

RC-1291, *Pseudotripeptide RC-1291*, (*R,R*)-2-amino-*N*-[2-[3-benzyl-3-(*N,N'*-trimethylhydrazinocarbonyl)piperidin-1-yl] -1-(1-*H*-indol-3-ylmethyl)-2-oxo-ethyl] -2-methylpropionamide, a → ghrelin agonist binding to and stimulating the → growth hormone secretagogue receptor. RC-1291 is currently under clinical evaluation for cancer cachexia. This complex metabolic syndrome manifests itself in progressive weight loss, anorexia, and persistent erosion of body cell mass in response to a malignant growth. A practical synthesis of RC-1291, starting from the *N*-terminal building block, was developed for this clinical candidate in 2006 [M. Ankersen, *US Patent* 6,576,648 B2, **2003**; K. A. Kern, J. A. Norton, J. Parenter. *Enteral Nutr.* **1988**,



12, 286; B. J. Paul et al., *Org. Proc. Res. Dev.* **2006**, 10, 339].

Reagent mixture method, a method to incorporate variable amino acids in \rightarrow combinatorial peptide synthesis. A mixture of activated building blocks is used in excess for acylation of the peptide chain either in solution synthesis or in SPPS. In order to safeguard equimolar incorporation, isokinetic mixtures are employed, where differences in reactivity between the reactants are accounted for by adjusting the stoichiometric ratio.

Receptor, a protein on the cell membrane or within the cytoplasm or cell nucleus capable of binding its ligand (L) according to the law of mass action ($R + L \rightarrow [RL]$). The binding parameter of a radio-labeled ligand to a receptor can be determined from a plot of bound ligand (B)/free Ligand (F) versus bound ligand ($B/F = (B_{\max} - B)/K_L$). This is known as a Scatchard plot, named after its originator, George Scatchard. K_L is operationally defined as the ligand concentration at which the receptor is half-maximally occupied by ligand, and can be determined from tangential slope, $-1/K_L$. Receptors occur in different types, depending on their ligand and function. Many hormone receptors and neurotransmitter receptors are transmembrane proteins which reside and operate typically within a plasma membrane of a cell, but also in the membranes of some subcellular compartments and organelles. *G protein-coupled receptors* (\rightarrow G proteins) are also known as seven transmembrane receptors (7TM receptors) and act as receptors for, e.g., \rightarrow angiotensins, \rightarrow cholecystokinin, \rightarrow glucagon, \rightarrow secretin, \rightarrow somatostatin, and \rightarrow chemokines. *Receptor tyrosine kinases* detect ligands and propagate signals through tyrosine kinases of intracellular domains such as receptors of \rightarrow

insulin, \rightarrow erythropoietin, and \rightarrow insulin-like growth factors. *Guanylyl cyclase receptors* are, e.g., receptors for \rightarrow guanylin, \rightarrow ANP, and other natriuretic peptides. Hormone-receptor interactions stimulate the synthesis and activation of specific enzymes via signaling cascades involving second messengers such as cAMP, cGMP, diacylglycerol (DAG), inositol triphosphate (IP_3), and Ca^{2+} . The release of prostaglandins, steroid hormones, thyroid hormones, peptides, and glycoproteins can also be stimulated by peptide and protein hormones [C. Stanford, R. Horton, *Receptors: Structure and Function*, Oxford University Press, **2001**].

Receptor activity-modifying proteins (RAMPs), transmembrane accessory proteins crucial for plasma membrane expression, and also for the determination of receptor phenotype of various seven-membrane domain G protein-coupled receptors. Three RAMPs, called RAMP1, RAMP2 and RAMP3, have been identified. They are single transmembrane-spanning proteins with the ability to modify receptor processing, glycosylation and presentation on the cell surface. However, the actual function depends on the specific interacting receptor. RAMP1 has 148 residues, a signal sequence and a single transmembrane protein close to the C-terminus. For example, heterodimers consisting of the calcitonin receptor (CTR) and RAMP1 exhibit high affinity for \rightarrow amylin, sCT and \rightarrow calcitonin gene-related peptide (CGRP), but not for hCT. In contrast, CTR/RAMP3 heterodimers show only low affinity for CGRP. The calcitonin receptor-like receptor (CRLR, \rightarrow calcitonin/calcitonin gene-related peptide family) with one of the RAMPs mediates signals of \rightarrow adrenomedullin (ADM) and CGRP. However, adrenomedullin has a greater affinity

on the CRLR/RAMP2 and CRLR/RAMP3 heterodimers compared to CGRP, which primarily signals via the CRLR/RAMP1 heterodimer. Furthermore, it has been shown that \rightarrow intermedin/adrenomedullin-2 (IMD) couples with the CRLR/RAMP receptors for signaling, exhibiting an activity profile distinct from that of ADM and CGRP. The RAMPs represent a new mechanism for receptor modulation that is important for the regulation of physiological responses [L. M. McLatchie et al., *Nature* **1998**, 393, 333; P. M. Sexton et al., *Cell. Signal.* **2001**, 13, 73; W. Born et al., *Recept. Channels* **2002**, 8, 201; M. Morfis et al., *Trends Pharmacol. Sci.* **2003**, 24, 596].

Receptor down-regulation, internalization of a \rightarrow receptor induced by an excess of a peptide hormone, leading to disappearance of the receptor. This results in a temporary stimulation, followed by inhibition of the target cells.

Receptor mapping, identification of structural elements of a peptide which are crucial for binding to a receptor. If the three-dimensional structure of the receptor is unknown, receptor mapping relies on conformational analysis of peptides containing a putative binding sequence, e.g., by NMR and molecular dynamics calculations, combined with an evaluation of their biological activity. A major precondition for such an analysis of the peptide conformation in solution is that the peptide ligand is conformationally constrained, as for example cyclopeptides (\rightarrow spatial screening) or peptides with sterically hindered amino acid components. Such an approach of indirect computer-aided drug design (indirect CADD) is very useful in the process of rational drug design, when the molecular structure of the target is unknown. It allows for the evaluation of structural changes

upon modification, and results in the identification of crucial structural elements of the ligand that are required for high affinity towards the receptor, while generating a "negative imprint" of the receptor, a hypothetical model of the receptor's binding site. In a pharmacological context, receptor mapping means the analysis of synthesis, storage, release, binding of effector molecules (peptides or drugs) on cells or tissue with radioactive tracer molecules, e.g., by positron emission tomography (PET) [R. Spadaccini, P. A. Temussi, *Cell. Mol. Life Sci.* **2001**, 58, 1572].

Recombinant DNA techniques, the synthesis of peptides and proteins based on the principles of molecular biology and gene technology. Proteins and peptides can be expressed on a large scale by recombination and expression of genetic material, e.g., in bacteria, yeast, plant cells, insect cells, and mammalian (including human) cell lines. Gene expression comprises the synthesis of the corresponding mRNA (transcription) and synthesis of the protein (translation). The biosynthesis of a foreign gene product (protein) relies on the recombination of the genetic material of the producing organism with the DNA fragment encoding for the target protein. Eukaryotic genes additionally contain non-coding elements (introns) besides the sequence information encoding for a protein. The precursor messenger RNA (mRNA) formed after transcription is subsequently processed into mature mRNA by splicing, where the introns are removed from the sequence. Consequently, the genomic DNA of eukaryotes is not directly suitable for transfection. DNA complementary to the mature mRNA (cDNA) must be prepared and used for transfection instead. Mature mRNA isolated from the donor cells is used as a template to synthesize

cDNA *in vitro* with the enzyme reverse transcriptase that naturally occurs in retroviruses. Especially → peptide drugs and → protein pharmaceuticals are increasingly becoming the focus of interest. Based on their endogenous functions in the human body, such compounds increasingly find application as therapeutic drugs and influence pathophysiology as well as healing processes. The proteins to be used for therapeutic purposes can be produced in large quantities by recombinant DNA technology. The workflow involves inserting the desired gene encoding the protein together with the appropriate transcriptional regulatory elements and a selector (e.g., an antibiotic resistance gene in the case of a prokaryotic expression system) into an expression vector. Such expression vectors generally employ strong viral or cellular promoters to enhance expression of the recombinant gene. Cultivation of the host organism leads to gene amplification, mRNA synthesis, and protein synthesis. Finally, the recombinant protein must be isolated and purified. Peptides and proteins that do not require post-translational modification (e.g., → insulin) can be produced in prokaryotes. Shorter peptides are often expressed as fusion proteins to protect them from proteolysis and to increase the efficiency. Such fusion proteins contain a cleavage site, e.g., for a protease or cyanogen bromide (cleaves Met) located *N*-terminally in order to liberate the target peptide during work-up. When proper folding, assembly, and post-translational modification of the target protein is a prerequisite, the quality and efficacy can be largely improved when cultivated mammalian cells are employed for production. About 60–70 % of all recombinant protein pharmaceuticals are produced in mammalian cells. For this purpose, Chinese hamster ovary (CHO) cells or human embryo kidney (HEK-293) are used

preferably [F. M. Wurm, *Nature Biotechnol.* **2004**, 22, 1393; G. Gellissen (Ed.), *Production of Recombinant Proteins*, Wiley-VCH, Weinheim, **2004**].

Recombinant protein, *rec. protein*, a protein synthesized by → recombinant DNA techniques.

Red pigment-concentrating hormone (RPCH), today denoted as *Panbo-RPCH*, pGlu-Leu-Asn-Phe-Ser-Pro-Gly-Trp-NH₂, an 8-peptide amide belonging to the → AKH/RPCH peptide hormone family. RPCH is a crustacean color-change hormone discovered in the eye stalks of the prawn *Pandalus borealis* in 1972. It was described as the first neuropeptide from invertebrates. Interestingly, the highly conserved RPCH is the only member of the AKH/RPCH family occurring in Crustacea. However, some insects contain the crustacean form Panbo-RPCH. The major biological function of Panbo-RPCH is the aggregation of pigment granules in the epithelial chromatophores. It is also involved in the stimulation of methyl farnesoate release from mandibular organs, as well as neuromodulatory effects. However, no true metabolic effects of Panbo-RPCH on energy metabolism, as known for → adipokinetic hormones in insects, have been observed in crustaceans [P. Fernlund, L. Josefsson, *Science* **1972**, 177, 173; G. Gäde, *Annu. Rev. Entomol.* **2004**, 49, 93].

Regioselectively addressable functionalized templates (RAFT), oligovalent moieties with chemically distinct functional groups that can be selectively addressed in the preparation of → template-associated synthetic proteins (TASP). RAFT are molecular scaffolds that comprise porphyrins, steroids, calixarenes, glycosides, and a variety of cyclic peptides and peptidomimetics. RAFT

are used, e.g., for chemoselective coupling or ligation with peptide and protein modules, and allow for the attachment of four or more different peptide building blocks in the construction of artificial proteins or receptor mimetics [G. Tuchscherer et al., *Biopolymers* **1998**, 47, 63; G. Tuchscherer et al., *J. Peptide Res.* **1999**, 54, 185; S. Peluso, *ChemBioChem* **2001**, 2, 432].

Relaxin, one of the first peptide hormones to be discovered with structural similarity to \rightarrow insulin. Relaxin is first synthesized as a prohormone that is comprised of a signal sequence and a B-C-A domain configuration. The C-peptide is removed during processing. Rat relaxin consists of an A chain (24 aa) and a B chain (35 aa) linked by two interchain disulfide bonds (Cys_A¹¹–Cys_B¹⁴/Cys_A²⁴–Cys_B²⁶). In addition, the A chain contains an intrachain disulfide bond (Cys¹⁰–Cys¹⁵). In 1926, Hisaw found that the injection of serum from pregnant guinea pigs or rabbits into virgin guinea pigs shortly after estrus induced a relaxation of the pubic ligaments. Relaxin is produced in the reproductive tract of many mammals during pregnancy, and acts to maintain pregnant uterine tissues and relax the pubic ligaments in preparation for birth. Furthermore, it promotes development of the mammary apparatus, thus enabling normal lactational performance. Relaxin modulates nipple development for lactation post partum in rats and mice, whereas in pregnant pigs it is essential for prepartum development of glandular parenchyma. In humans, relaxin is produced and secreted in small amounts during pregnancy, but until now no physiological function for circulating relaxin has been identified. Interestingly, diverse therapeutic actions of relaxin on non-reproductive tissues have been de-

scribed that have clinical implications. For example, relaxin has been shown to promote wound healing and to reduce fibrosis in the heart, kidney, liver, and lung. H2 relaxin can only be applied over short-term (2–4 weeks) periods when administered to experimental models of fibrosis. However, recently it has been reported that mouse relaxin can effectively inhibit collagen deposition and accumulation over long-term treatment periods. Relaxin is a member of the \rightarrow relaxin peptide family. In humans, three genes have been established: *RLN1* (encoding human relaxin-1, H1), *RLN2* (human relaxin-2, H2), and *RLN3* (human relaxin-3, H3). The A chains of H1–H3 consist of 24 aa differing in their sequences, whereas differences also exist in the length of the B chains (H1 and H3: 28 aa; H2: 29 aa). In most other mammals, there exist only two *RLN* genes, encoding relaxin and relaxin-3. In these species, *RLN1* is equivalent to the *RLN2* gene in humans and higher primates, and encodes the relaxin which plays a key role in reproductive processes. Until now, H1 has actually not been found in the human body, and so it is likely to be a pseudogene only. Recently, it has been shown that the newly discovered *RLN3* gene might be the ancestral gene for the relaxin peptide family. Relaxin-3 is specifically expressed in the nucleus incertus of the mouse and rat brain, and acts most likely as an important neuropeptide. The relaxin receptor is a leucine-rich repeat-containing G protein-coupled receptor 7 (LGR7). This receptor and the closely related LGR8 have large extracellular domains containing multiple leucine-rich repeats (LRRs) and an unique LDL receptor-like cysteine-rich motif (LDLR-domain). Although relaxin-3 also interacts with LGR7 and LGR8 in some species, its native receptor is GPCR135, also known as somatostatin- and angiotensin-like peptide

receptor (SALPR) [R. Ivell, A. Einspanier, *Trends Endocrinol. Metab.* **2002**, *13*, 343; R. A. D. Bathgate et al., *Trends Endocrinol. Metab.* **2003**, *14*, 207; S. Y. Hsu, *Trends Endocrinol. Metab.* **2003**, *14*, 303; O. D. Sherwood, *Endocr. Rev.* **2004**, *25*, 205; T. N. Wilkinson et al., *BMC Evol. Biol.* **2005**, *5*, 14; R. A. D. Bathgate et al., *Biochemistry* **2006**, *45*, 1043; C. S. Samuel et al., *Biochemistry* **2007**, *46*, 5374].

Relaxin peptide family, a peptide family in human consisting of seven members comprising three → relaxin peptides (relaxin-1, relaxin-2, relaxin-3) and four → insulin-like peptides (INSL-3, INSL-4, INSL-5, INSL-5). In most other mammals, there are only two *RLN* genes that encode relaxin and relaxin-3. It has been shown that the recently discovered *RLN3* gene is the ancestral gene for the relaxin peptide family. However, the function of relaxin-3 remains to be determined. Its highest expression is in the brain, which suggests a neuropeptide role. The peptide hormones encoded by these genes are structurally related to → insulin. They consist of A and B chains connected by two disulfide bonds, and are formed from a prohormone after proteolytic cleavage of the intervening C chain. The members of the family act on cell membrane G protein-coupled receptors (GPCRs). Leucine-rich-repeat containing G protein-coupled receptor 7 (LGR7) is the receptor for relaxin, whereas LGR8 is the receptor for INSL-3 [S. Y. Hsu, *Trends Endocrinol. Metab.* **2003**, *14*, 303; T. N. Wilkinson et al., *BMC Evol. Biol.* **2005**, *5*, 14; R. A. D. Bathgate et al., in: *Physiology of Reproduction*, Knobil, E., Neill, J. D. (Eds.), 3rd edn., pp. 679–770, Elsevier, San Diego, **2006**].

Relaxin-like factors, → insulin-like peptides.

Release inhibiting hormones, *release inhibiting factors*, → statins.

Releasing hormones, *releasing factors*, → liberins.

RELM, acronym for resistin-like molecules (→ resistin, → FIZZ).

Renin, *angiotensin-forming enzyme*, *angiotensinogenase*, an → aspartic peptidase with highly restricted substrate specificity. The only native substrate is angiotensinogen (→ angiotensins). It cleaves the peptide bond between two Leu residues of the minimally sized angiotensinogen substrate -Pro-Phe-His-Leu↓Leu-Val-Tyr-Ser-. A highly specific inhibitor for human renin is H-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-OH, containing two Phe residues instead of the two Leu residues. Renins of all species are inhibited by → pepstatin. Active renin is produced from prorenin by cleavage of the *N*-terminal propeptide. It consists of two similar domains each containing the catalytical Asp. The mature native renin ($M_r \sim 36\text{--}42$ kDa) is a two-chain protein containing two disulfide bonds and two potential *N*-glycosylation sites formed proteolytically from the native single-chain enzyme. Renin is found in mammals, birds, amphibians, and teleosts. It is expressed mainly in the juxtaglomerular cells of the kidney. After secretion into the blood circulation, it reacts selectively with angiotensinogen to form angiotensin I. Renin acts with aldosterone and several other substances to help balance sodium and potassium levels in the blood and fluid levels in the body, which affects blood pressure [T. Ingami, *J. Hypertens.* **1989**, *7* (Suppl. 2), S3; A. Fukamizu, K. Murakami, *Trends Endocrinol. Metab.* **1995**, *6*, 279].

RER, rough endoplasmic reticulum.

Resilin, a fibrillar protein from the exoskeleton of insects and other arthropods. The protein with a high Gly content, but lacking sulfur-containing amino acids and Trp, is located between the chitin lamellae and is responsible for the elasticity of the arthropod exoskeleton. Resilin is an elastic energy store. Important components of resilin are dityrosine and trityrosines, formed by the crosslinking of Tyr residues of one or more peptide chains; this results in a three-dimensional lattice, forming the rubber-like properties. Resilin contains distinct repetitive domains that appear to confer elastic properties to the protein as in the case with other elastomeric proteins such as \rightarrow elastin, gliadin and spider silks. Resilin was first discovered in the wing-hinges of locust [T. Weis-Fogh, *J. Exp. Biol.* **1960**, 37, 889].

Resistin (FIZZ3), a member of a family of cysteine-rich secreted proteins termed FIZZ or RELM. Resistin is known as adipocyte-specific secretory factor. It is produced in adipose tissue. The name was coined because resistin was reported in 2001 to antagonize insulin action in cells both *in vivo* and *in vitro*, and circulating levels were increased in obese and diabetic mice. Human resistin circulates in blood as a dimer consisting of two linear 92-peptide chains linked by a disulfide bridge at Cys²⁶. Actions of resistin in humans are not well established [C. M. Stephan et al., *Nature* **2001**, 409, 307; U. Smith, *Obes. Res.* **2002**, 10, 61; B. Aruna et al., *Biochemistry* **2003**, 42, 10554; U. Meier, A. M. Gressner, *Clin. Chem.* **2004**, 50, 1511].

RET, resonance energy transfer.

Retropeptide, (1) a peptide analogue in which one or more peptide bonds -CO-NH- is replaced by -NH-CO-; (2) a peptide analogue with reversed sequence related to the parent peptide.

Retroinverso peptide, a peptide analogue in which one or more peptide bonds -CO-NH- is replaced by -NH-CO-, and additionally the α -chiral centers are inverted [M. Chorev, M. Goodman, *Acc. Chem. Res.* **1993**, 26, 266].

Reversed-phase HPLC (RP-HPLC), the most popular "high-performance" or "high-pressure" liquid chromatography variant in which the solid stationary phase is derivatized with non-polar hydrophobic groups so that the elution conditions are the reverse of normal liquid chromatography [W. S. Handcock, *Handbook of HPLC for the Separation of Amino Acids, Peptides, and Proteins*, Volumes 1 and 2, CRC Press, Boca Raton, **1984**; C. T. Mant, R. S. Hodges, *High Performance Liquid Chromatography of Peptides and Proteins: Separation, Analysis, and Conformation*, CRC Press, Boca Raton, **1991**; J. K. Swadesh, *HPLC: Practical and Industrial Applications*, CRC Press, Boca Raton, **2001**].

Reverse proteolysis, \rightarrow proteolysis, \rightarrow protease-catalyzed peptide synthesis.

R_f, retention factor (TLC).

RFamide peptides (RFaP), a large family of bioactive peptides possessing the motif Arg-Phe-NH₂ (RFa) at their C-terminal end. This family also includes the \rightarrow FMRFamide-related peptides (FaRP) that in former time served as an own family. RFaP have been characterized in all groups of invertebrates, and immunohistochemical data had for a long time suggested that they also exist in the CNS of vertebrates. During the early 1980s, the 5-peptide amide H-Leu-Pro-Leu-Arg-Phe-NH₂ isolated from chicken brain, was shown to increase arterial blood pressure and to modulate the electrical activity of brainstem neurons. The two RFaP, \rightarrow neuropeptide FF (NPFF) and \rightarrow neuropeptide AF (NPAF), have been

isolated from the bovine brain. Interestingly, a single gene encodes both neuropeptides. It has also been established that multiple copies of RFaP of various moluscan species may be generated by a single precursor. In 1987, the first *Drosophila melanogaster* RFaP gene was discovered and, at the same time, the 9-peptide amide, H-Asp-Pro-Lys-Gln-Asp-Phe-Met-Arg-Phe-NH₂, was isolated from adult fruitflies. The precursor contains multiple, putative peptide sequences. For example, the 9-peptide sequence mentioned above occurs five times, and the sequence -Thr-Pro-Ala-Glu-Asp-Phe-Met-Arg-Phe- twice, in the precursor protein, besides some similar peptides. The *drosulfakinins* (DSK) show sequence similarity to other RFaP and to gastrin- and CCK-like peptides. The fruitfly sulfakinin peptides *DSK-I*, H-Phe-Asp-Asp-Tyr-Gly-His-Met-Arg-Phe-NH₂, and *DSK-II*, GGD-DQFDDYG¹⁰HMRFa, contain a sulfated Tyr residue (Tyr/Y). *SchistoFLRFa*, also termed *myosuppressin*, H-Pro-Asp-Val-Asp-His-Val-Phe-Leu-Arg-Phe¹⁰-NH₂, from the desert locust *Schistocerca gregaria* shows sequence similarity with the RFaP, but it has a myoinhibitory activity on various visceral muscle preparations. The homologous neuropeptide from extracts of adult fruitflies *Dromyosuppressin* (DMS), H-Thr-Asp-Val-Asp-His-Val-Phe-Leu-Arg-Phe¹⁰-NH₂, contains also the C-terminal sequence -RFa, and only differs from cockroach and locust myosuppressins by the N-terminal residue. It has been localized in fruitfly CNS and gut tissues. Various RFaP have been discovered in mammals, birds, fish, and amphibians. Novel amphibian RFaP are → neuropeptide R-RFa and → neuropeptide 26RFa [C. S. Barnard, G. J. Dockray, *Regul. Pept.* **1984**, *8*, 209; L. E. Schneider, P. H. Taghert, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 1993; J. V. Broeck, *Peptides* **2001**, *22*, 241; N. Chartrel et al.,

Peptides **2006**, *27*, 1110; N. Vyas et al., *Peptides* **2006**, *27*, 990; I. Mertens et al., *Peptides* **2006**, *27*, 1291; T. Osugi et al., *FEBS J.* **2006**, *273*, 1731].

RGD, fibrinogen binding sequence (-Arg-Gly-Asp-).

RGD peptides, peptides containing the sequence -Arg-Gly-Asp- (RGD). The RGD sequence is considered to be a widespread recognition sequence present in proteins of the extracellular matrix (ECM) or of pathogenic bacteria, which is crucial for binding to → integrins. The RGD sequence mediates cell–cell adhesion and cell–ECM contacts. Soluble peptides prevent the interaction between integrin and ECM proteins, while immobilized RGD peptides support cell attachment to surfaces. The recognition of the RGD sequence in a protein or peptide strongly depends on the three-dimensional arrangement of the Arg guanidino group and the Asp carboxylate (pharmacophoric groups). Cyclic, conformationally constrained RGD peptides have been designed according to the → spatial screening approach and display high affinity towards integrins. D-Amino acids, β-amino acids, and N-methyl amino acids may be employed as turn-inducing elements to lock the conformational equilibrium. The peptide cyclo-(-Arg-Gly-Asp-D-Phe-MeVal-) with the generic name Cilengitide[®] is a high-affinity ligand for integrin α_vβ₃, which is involved in angiogenesis, tumor metastasis, and osteoporosis. It shows highly promising results in clinical trials for treatment of glioblastoma, a very aggressive form of brain tumor. Eptifibatide[®] (integrilin), a cyclic peptide with the sequence cyclo^{SS}-(Mpa-Arg-Gly-Asp-Trp-Pro-Cys) and a disulfide bond between 3-mercaptopropionic acid (Mpa) and Cys, is an anticoagulant that

selectively blocks the platelet integrin $\alpha_{11b}\beta_3$ [R. Haubner et al., *Angew. Chem. Int. Ed.* **1997**, 36, 1374; K.-E. Gottschalk, H. Kessler, *Angew. Chem. Int. Ed.* **2002**, 41, 3767; S. Urman et al., *Angew. Chem. Int. Ed.* **2007**, 46, 3976].

α -RglA, GCCSDPRCRY¹⁰RCR (disulfide bonds: C²–C⁸/C³–C¹²), a new $\rightarrow \alpha$ -conotoxin from the Western Atlantic species *Conus regius* that specifically and potently blocks the $\alpha 9\alpha 10$ nicotinic acetylcholine receptor subtype [M. Ellison et al., *Biochemistry* **2006**, 45, 1511].

RIA, radioimmunoassay.

Ribosomal peptide synthesis, biosynthesis of DNA-encoded peptides on the ribosome. The sequence of ribosomally synthesized peptides is encoded by deoxyribonucleic acid (DNA). The gene is transcribed to give messenger RNA (mRNA) that is, if appropriate, spliced and conveys the genetic information from the nucleus to the ribosome. An amino acid reacts with adenosine triphosphate (ATP) under elimination of pyrophosphate to yield a mixed anhydride, the aminoacyl adenylate, which normally remains tightly bound to the enzyme. Such activated amino acids are attached to the 3' end of tRNA, forming the aminoacyl-tRNA, which serves as an adaptor molecule and recognizes base triplets on mRNA. Hence, the translation process requires two steps of molecular recognition – the choice of the correct amino acid for the covalent attachment to a tRNA, and the recognition of the aminoacyl-tRNA by mRNA. Peptide bond formation occurs in the ribosomal \rightarrow peptidyl transferase center that resides in the large ribosomal subunit. Ribosomal peptide synthesis proceeds stepwise from N- to C-terminus by reading the mRNAs in the 5' \rightarrow 3' direction. Many peptides, especially short peptide hormones, are produced as prepro-precursors, that are

subsequently processed by proteolysis [R. Martin, *Protein Synthesis: Methods and Protocols*, Humana Press, Totowa, N.J., **1998**].

Ribosome-inactivating proteins (RIP), proteins widely distributed among higher plants with ribosome-inactivating activity. Due to their N-glycosidase activity, these proteins inactivate ribosomes by cleaving a single adenine from the large rRNA. Thereby protein biosynthesis is arrested at the translocation step. It has been reported that as little as one RIP molecule per cell is capable of turning off protein synthesis. Single-chained type 1 and 2 are 30 and 60 kDa, respectively, while the small RIP are about 10 kDa. Type 2 RIP consists of an A chain and a B chain. The latter has lectin properties, whereas the A chain is termed as a Gal/GalNAc-binding subunit. A typical member of the type 2 RIP is \rightarrow ricin [N. Sharma et al., *Plant. Physiol.* **2004**, 134, 171].

Ricin, a phytotoxin from castor bean plant *Ricinus communis*. Ricin is composed of two hemagglutinins (RCL I and RCL II) and two toxins (RCL III and RCL IV). The latter are dimers consisting of an A chain, *ribosome-inactivating enzyme* (267 aa; M_r \sim 32 kDa) and a B chain, *galactose/N-acetylgalactosamine-binding lectin* (262 aa; M_r \sim 34 kDa) linked together by a disulfide bond. The B chain binds to cell-surface glycoproteins and affects entry into the cell, whereas the A chain carries the toxic activity. It acts on the 60S ribosomal subunit and prevents the binding of elongation factor-2. The inhibition of protein synthesis leads to cell death. Ricin, which belongs to the \rightarrow ribosome-inactivating proteins, is one of the most poisonous naturally occurring substances known [J.-Y. Lin et al., *Nature* **1970**, 227, 292; R. G. Wiley, T. N. Oeltmann, *Ricin and Related Plant Toxins*, in: *Handbook of Natural Toxins*, Volume 6,

R. F. Keeler, A. T. Tu (Eds.), Marcel Dekker, Inc., New York, 1991].

Rigin, H-Gly-Gln-Pro-Arg-OH, a synthetic peptide derived from a fragment of human IgG. It is capable of affecting baseline levels of IL-6 (\rightarrow interleukins) as well as modulating the effects of UV-stimulated overproduction of IL-6. Analogous to \rightarrow tuftsin, rigin shows phagocytosis-stimulating activity [A. Ashish, R. Kishore, *Eur. J. Biochem.* 2000, 267, 1455; R. C. Dutta et al., *Int. Immunopharmacol.* 2001, 1(5), 843].

Rink amide resin, (2,4-dimethoxy)benzhydrylamine resin, a polystyrene handle combination suitable for cleavage of peptide amides with 95% TFA [H. Rink, *Tetrahedron Lett.* 1987, 28, 3787].

RNA, ribonucleic acid.

RNase, ribonuclease.

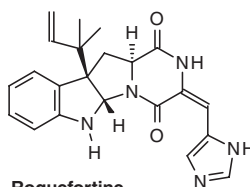
ROE, rotating frame nuclear Overhauser effect.

ROESY, rotating frame nuclear Overhauser enhanced spectroscopy.

Roquefortine, *roquefortine C*, a modified diketopiperazine produced by a number of *Penicillium* species. It is a common fungal metabolite, and is widely distributed in a range of blue cheeses. This diketopiperazine is derived from the condensation of tryptophan and histidine residues, and modified by heterocyclization and isoprenyl addition. Interestingly, roquefortines A and B are structurally different from roquefortine C, and belong to the isofumigaclavines, whereas roquefortine D possesses the same core structure as roquefortine C [P. M. Scott et al., *Experientia* 1976, 32, 140; B. Clark et al., *J. Nat. Prod.* 2005, 68, 1661].

Roquefortine E, an isoprenylated diketopiperazine isolated from an Australian

soil isolate of the ascomycete *Gymnoascus reessii* Baranetzki, together with the known co-metabolite \rightarrow roquefortine. In contrast to roquefortine C, this new member did not possess any discernible antibacterial activity, but did display weak cytotoxic activity to mammalian cells, as did roquefortine C [B. Clark et al., *J. Nat. Prod.* 2005, 68, 1661].



RP, reversed-phase.

RPCH, red pigment-concentrating hormone.

Rubredoxins (Rd), small iron-containing proteins occurring in various sulfur-metabolizing bacteria and archaea involved in electron transfer. Sometimes Rd are classified as iron-sulfur proteins. However, they do not contain inorganic sulfide. Rubredoxin from *Clostridium pasteurianum* ($M_r \sim 6$ kDa; 52–54 aa) shows functional similarity to \rightarrow ferredoxin but contains, in contrast to the latter, only one iron bound by the sulfur atoms of four cysteine residues. The iron–sulfur complex shows tetrahedral symmetry. The 3-D structures of a number of rubredoxins have been solved. The folds belong to the $\alpha + \beta$ class, with two α -helices and two to three β -strands [W. Lovenberg, B. E. Sobel, *Proc. Natl. Acad. Sci. USA* 1965, 54, 193; M. Frey et al., *J. Mol. Biol.* 1987, 197, 525].

Rudinger, Josef (1924–1975), a noted peptide chemist and founder of the European Peptide Symposia, together with Geoffrey Young, starting in Prague in 1958. He was born in Jerusalem, educated in Czechoslovakia and England, and in 1949 returned to

Prague as a member of a research group which later became the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences, and began to work on peptides. He was not only an outstanding peptide chemist, but in particular was a true citizen of the world, permanently helping to build lasting friendships among peptide scientists from countries with widely different political regimes. When the Czechoslovak reform movement was suppressed in August 1968, he emigrated to Switzerland and was appointed to a full professorship at the ETH in Zurich. In commemoration of his role in the foundation of the EPS, and of the diverse contributions he made – both by his own work on neurohypophyseal hormones and basic peptide methodology, and indirectly through his selfless stimulation of others in many countries of the world – the *Josef Rudinger Memorial Lecture* was established in 1984 (→ European Peptide Society) [J. H. Jones, Editorial, *The Life and*

Work of Josef Rudinger, *J. Peptide Sci.* **2004**, *10*, 393].

Rugosin A-like insulintropic peptide, KG AAKGLLEV¹⁰ASCKLSKSC, a 19-peptide with insulin-releasing activity isolated from the skin secretions of the frog *Rana saharica* [L. Marenah et al., *Peptides* **2005**, *26*, 2117].

Ruheman's purple, the intensively colored violet dye formed during the reaction of ninhydrin with α -amino acids.

Rusticyanin (Rc), a member of blue copper proteins (BCP) which are relatively small, soluble electron-transfer proteins. Rc possesses a β -barrel structure and is arranged in a so-called "Greek key" topology. It shows the highest redox potential (680 mV) of the BCP family, and is particularly efficient in stabilizing the copper (I) ion [F. Nunzi et al., *Biochem. Biophys. Res. Commun.* **1994**, *203*, 1655; L. A. Alcaraz et al., *Protein Sci.* **2005**, *14*, 1710].

S

SA, symmetrical anhydrides.

Saa, sugar amino acids.

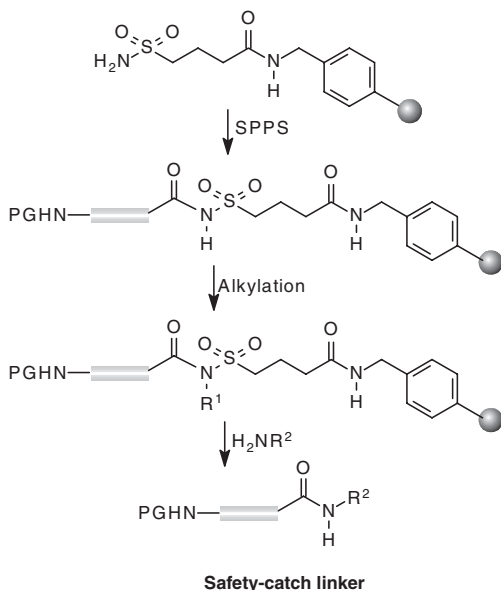
SABR, structure–activity–bioavailability relationships.

Safety-catch linker, a linker moiety (\rightarrow handle) that is stable under the conditions of peptide synthesis, but must be activated for cleavage. The two chemical states of safety-catch linkers differ either by real orthogonality or by the kinetics of the cleavage reaction. The most popular safety-catch linkers are based on sulfonamides, where the first amino acid is anchored in the form of an *N*-acyl sulfonamide, which is stable towards acidic and basic reaction conditions. Upon *N*-alkylation of the *N*-acyl sulfonamide with either diazomethane or iodomethane, a secondary *N*-acyl

sulfonamide is formed. This conversion provides an activated C-terminus of the peptide which may react with diverse nucleophiles, including the *N*-terminus for combined cyclization-cleavage. C-terminal thioesters, subsequently to be used for ligation purposes, are obtained on thiolysis of peptides bound to a safety-catch linker [F. Guillier et al., *Chem. Rev.* **2000**, *100*, 2091; P. Heidler, A. Link, *Bioorg. Med. Chem.* **2005**, *1*, 585].

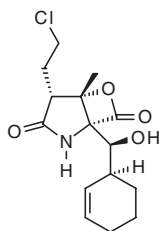
Sakakibara tactics, \rightarrow Boc/Bzl/Pac chemistry.

Salinamides, cyclodepsipeptides (\rightarrow depsipeptides) isolated from *Streptomyces* sp. CNB-091, an actinomycete isolated from the surface of the jellyfish *Cassiopeia xamachana* collected in the Florida Keys.



The first discovered *salinamides* A and B were composed of seven amino acids and two non-amino acid building blocks. They showed moderate antibiotic activity against Gram-positive bacteria, and exhibited potent topical anti-inflammatory activity. *Salinamide D* contains D-Val in place of D-Ile in salinamide A, whereas *salinamides C* and *E* are monocyclic depsipeptides which are likely methylated byproducts of salinamide A biosynthetic intermediates [B. S. Moore et al., *J. Org. Chem.* **1999**, 64, 1145].

Salinosporamide A, NPI 0052, a microbial product of *Salinispora tropica* strain CNB-392 that acts as a potent \rightarrow proteasome inhibitor. Salinosporamide A is structurally related to \rightarrow omuralide, the β -lactone derived from \rightarrow lactacystin, and is more effective as a proteasome inhibitor than omuralide. Furthermore, it exhibits cytotoxicity against many tumor cell lines, especially against Velcade[®] resistant multiple myeloma cells [V. Caubert, N. Langlois, *Tetrahedron Lett.* **2007**, 48, 381].

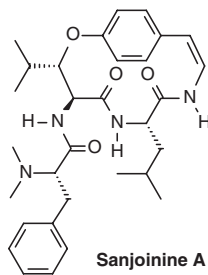


Salinosporamide A

SALMFamide peptides, a family of neuropeptides isolated from species belonging to the phylum *Echinodermata*. *SALMFamide-1* (S1) H-Gly-Phe-Asn-Ser-Ala-Leu-Met-Phe-NH₂ and *SALMFamide-2* (S2) SGPYSFNSSL¹⁰TFa are the first members of this family found in the radial nerve cords of the starfish (class *Asteroidea*). S1 and S2 are present in the in-

nervation of a variety of starfish organs, including the cardiac stomach and tube feet. Furthermore, seven putative SALMFamide neuropeptides, named SpurS1 to SpurS7, have been discovered by sequencing the genome of the sea urchin *Strongylocentrotus purpuratus*. SpurS1–3 have the C-terminal sequences Thr-Phe-NH₂ or Ser-Phe-NH₂, which are identical or similar to the C-terminal sequence of the starfish SALMFamide S2 [M. R. Elphick et al., *Pep-tides* **1991**, 12, 455; M. R. Elphick, M. C. Thorndyke, *J. Exp. Biol.* **2005**, 208, 4273].

Sanjoinine A, *franguloline*, a cyclopeptide alkaloid. Sanjoinine A is the major bioactive component responsible for the sedative properties of “Sanjoin”, a plant seed of clinical importance in oriental medicine. Using a novel cycloetherification procedure, the asymmetric total synthesis of Sanjoinine A was described in 1999 [B. H. Han et al., *Pure Appl. Chem.* **1989**, 61, 443; L. Laib, J. Zhu, *Tetrahedron Lett.* **1999**, 40, 83].



Sanjoinine A

Sansalvamide A, a cyclodepsipeptide (\rightarrow depsipeptides) isolated from the marine fungus of the genus *Fusarium*, collected off Little San Salvador Islands (Bahamas). It is composed of four amino acids (two Leu, Phe, Val) and one hydroxy acid, (S)-2-hydroxy-4-methylpentanoic acid. Sansalvamide A shows significant cancer cell cytotoxicity, with a mean IC₅₀ value of 27.4 $\mu\text{g mL}^{-1}$ against the National Cancer

Institute's cell-line panel. The solid-phase synthesis of the antitumor antibiotic sansalvamide A was described in 2000 [G. N. Belofsky et al., *Tetrahedron Lett.* **1999**, 40, 2913; Y. Lee, R. B. Silverman, *Org. Lett.* **2000**, 2, 3743].

Saposins, a family of four small heat-stable glycoproteins derived from the large precursor protein prosaposin (70 kDa). The saposins A–D are involved as cofactors in sphingolipid catabolism [Y. Kishimoto et al., *J. Lipid Res.* **1992**, 33, 1255; A. M. Vaccaro et al., *Neurochem. Res.* **1999**, 24, 307].

Saposin-like proteins (SAPLIP), a diverse family of lipid-interacting proteins characterized by a conserved pattern of cysteine residues. They show various cellular functions of which most are only partly understood. More than 200 different SAPLIP have been found in relevant databases occurring from amoebozoans to mammals [R. S. Munford et al., *J. Lipid Res.* **1995**, 36, 1653; H. Bruhn, *Biochem. J.* **2005**, 389, 249].

SAR, structure–activity relationship.

Sar, sarcosine (*N*-methylglycine).

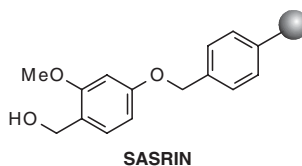
Sarafotoxins (SRTX), CSCKDMDTKE¹⁰CLNFCHQDVI²¹W (SRTX-a) (disulfide bonds: C¹–C¹⁵/C³–C¹¹), a family of vasoactive peptides initially isolated from the venom of *Atractaspis engaddensis*. The highly toxic peptides (SRTX-a, -b, -c, -e) are structurally and functionally related to endothelins (ET). Each of the members of the ET-SRTX family contains four Cys, and about 60–70% of their 21 amino acid residues are identical. The SRTX cause strong vasoconstriction of coronary arteries. Death after intoxication with SRTX peptides is the result of cardiac ischemia or infarction. Sarafotoxins and sarafotoxin-like peptides are produced by various snake

species of the genus *Atractaspis*. Long-SRTX are by three amino acids longer than the previously described SRTX. One of the six isoforms, termed SRTX-m, induces toxicity in mice, mostly due to vasoconstriction, and shows a lower toxicity and potency than the more potent SRTX described to date, SRTX-b from *A. engaddensis* [Y. Kloog et al., *Science* **1988**, 242, 268; F. Ducancel, *Toxicon* **2002**, 40, 1541; M. A. F. Hayashi et al., *Peptides* **2004**, 25, 1243].

Saralasin, H-Sar-Arg-Val-Tyr-Val-His-Pro-Ala-OH, [Sar¹, Val⁵, Ala⁸]angiotensin II, a noncompetitive antagonist of angiotensin II (→ angiotensins). Saralasin shows blood pressure-lowering activity in humans, and has found diagnostic application in renin-dependent hypertension. It inhibits the pressor effects of angiotensin II in rats. It has been reported that saralasin could be protective against acute pancreatitis [W. Wienen et al., *Mol. Pharmacol.* **1992**, 41, 1081; S. W. Tsang et al., *Regul. Pept.* **2003**, 111, 47].

Sarmesin, H-Sar-Arg-Val-Tyr(Me)-Ile-His-Pro-Phe-OH, a synthetic 8-peptide acting as a competitive antagonist of the angiotensin II receptor (→ angiotensins) in rat smooth muscle preparations [M. N. Scanlon et al., *Life Sci.* **1984**, 34, 317; W. Wienen et al., *Mol. Pharmacol.* **1992**, 41, 1081].

SASRIN (Super Acid Sensitive ResIN), a highly acid-labile resin. Cleavage of peptides after synthesis from SASRIN can be performed, in high yield, by treatment of the peptidyl-resin with 1% TFA in



dichloromethane [M. Mergler et al., *Tetrahedron Lett.* **1988**, 29, 4005].

Sauvagine (SVG), <EGPPISIDLS¹⁰LELL RKMIEI²⁰EKQEKEKQQA³⁰ANNRLLLDTI a⁴⁰, a 40-peptide amide originally isolated from the leaf-frog *Phyllomedusa sauvagei*. Sauvagine belongs to a family of related peptides including → corticoliberin, → urotensin I, and → urocortin. It possesses only about 40% sequence similarity with the primary structure of rat urocortin, and about 50% with urotensin-I. Sauvagine causes a number of pharmacological activities on diuresis, and on the endocrine glands and cardiovascular system [C. Montecucchi et al., *Hoppe-Seyler's Z. Physiol. Chem.* **1979**, 360, 1178; P. C. Montecucchi et al., *Int. J. Pept. Protein Res.* **1982**, 20, 139; D. A. Lovejoy, R. J. Balment, *Gen. Comp. Endocrinol.* **1999**, 115, 1].

SBzl, thiobenzyl.

SCAL, safety catch acid-labile linker or safety catch amide linker.

Scatchard plot, → receptor.

Scavenger, a compound to trap reactive intermediates. When cleaving protecting groups of the *tert*.-butyl or benzyl type, scavengers such as anisole, thioanisole, dimethyl sulfide, or triisopropylsilane must be added to the reaction mixture in order to avoid side reactions of the intermediate carbenium ions.

SchistoFLRFamide, *myosuppressin*, → FMRFamide-related peptides.

Schistomyotropins (Scg-MT), neuropeptides from the CNS of the desert locust (*Schistocerca gregaria*). The peptides were isolated from the methanolic extract of about 7000 brains of these insects. The primary structures were elucidated as follows: *schistomyotropin-1* (Scg-MT-1)

GAAPAAQFSP¹⁰RLa, *schistomyotropin-2* (Scg-MT-2) TSSLFPHPR¹⁰La. Scg-MT-1 belongs to the FXPRLa family, whereas Scg-MT-2 is only related to this family and displays 10-fold less activity compared to Scg-MT-1 in stimulating cockroach hindgut motility [D. Veelaert et al., *Biochem. Biophys. Res. Commun.* **1997**, 241, 530].

Schizotrin A, an antifungal cyclic undecapeptide from cyanobacterium *Schizotrix* (TAU strain IL 89-2) with activity against *C. albicans* and *C. tropicalis* [I. Pergament, S. Carmelli, *Tetrahedron Lett.* **1994**, 35, 8473].

Schlack-Kumpf method, also called the *isothiocyanate method*, a method for C-terminal sequence analysis of peptides and proteins. The C-terminus is converted with acetic anhydride into a 5(4H) oxazolone. Upon reaction with ammonium thiocyanate or with the new derivatizing reagent triphenylgermanyl isothiocyanate (TPG-ITC), 1-acyl-2-thiohydantoins are formed, with the peptidyl residue being the acyl group. The peptidyl residue is then cleaved to give the 2-thiohydantoin derived from the C-terminal amino acid, which is subsequently analyzed [P. Schlack, W. Kumpf, *Hoppe-Seyler's Z. Physiol. Chem.* **1926**, 154, 125; J. Li, S. Liang, *Anal. Biochem.* **2002**, 302, 108].

SCL, synthetic combinatorial libraries.

Scyliorhinin I (Scy I), H-Ala-Lys-Phe-Asp-Lys-Phe-Tyr-Gly-Leu-Met¹⁰-NH₂, a tachykinin (→ tachykinin family) with limited structural similarity to mammalian → substance P. Scy I is a 10-peptide amide isolated from the intestine of the dogfish *Scyliorhinus caniculus*, with tachykinin-like activity. Scy I is the only known tachykinin that shows high affinity for both NK-1 and NK-2 binding sites, and low affinity for NK-3 binding sites [J. M. Conlon et al.,

FEBS Lett. **1986**, *200*, 111; R. Patacchini et al., *Eur. J. Pharmacol.* **1993**, *250*, 311].

SDV, styrene divinylbenzene.

SDS, sodium dodecylsulfate.

Sea anemone toxins, toxic peptides isolated from the venom of sea anemones. Sea anemones contain short neuropeptides such as \rightarrow Antho-Kamide, \rightarrow Antho-RIamide I, Antho-RFamide (pGlu-Gly-Arg-Phe-NH₂), Antho-RNamide (L-3-phenyl-lactyl-Leu-Arg-Asn-NH₂), Antho-RPamide I (H-Leu-Pro-Pro-Gly-Pro-Leu-Pro-Arg-Pro-NH₂) and II (pGlu-Asn-Phe-His-Leu-Arg-Pro-NH₂), Antho-RW amide I (pGlu-Ser-Leu-Arg-Trp-NH₂), and II (pGlu-Gly-Leu-Arg-Trp-NH₂). The real sea anemone toxins are divided into three types that have been thoroughly investigated and classified according to their size and mode of action. There are neurotoxins ($M_r = 3\text{--}5$ kDa) like \rightarrow anthopleurin A which act on voltage-gated sodium channels, besides neurotoxins ($M_r = 3.5\text{--}6.5$ kDa) which address voltage-gated potassium channels, and the pore-forming cytolytins (actinoporins), highly basic proteins ($M_r = 16\text{--}20$ kDa) that are able to form pores through membranes [G. Anderluh, P. Macek, *Toxicon* **2002**, *40*, 111; T. Honma, K. Shiomi, *Mar. Biotechnol.* **2006**, *8*, 1].

Sec, selenocysteine (one-letter symbol U).

SEC, size-exclusion chromatography.

Second messenger, intracellular mediators of the externally received hormonal message, e.g., cAMP, cGMP, Ca²⁺, inositol-1,4,5-triphosphate (IP₃), diacylglycerol (DG).

Secondary structure, different types of well-defined peptide conformations with periodic or aperiodic character, that oc-

cur in peptides and proteins besides unordered parts. The most prominent secondary structure elements are \rightarrow helices, \rightarrow β -sheets and \rightarrow turns. The preferred conformation of a peptide chain is governed by the energetically favored torsion angles φ , ψ , and ω , combined with additional stabilization by hydrogen bonds, hydrophobic interactions, salt bridges, dipole effects, etc. Substituents at the amide bond can be positioned to give either *cis* ($\omega = 0^\circ$) or *trans* ($\omega = 180^\circ$) configuration (\rightarrow peptide bond), as the partial double bond character of the amide bond confers a significant rotational barrier.

Secondary structure mimetics, building blocks that induce a discrete \rightarrow secondary structure in a peptide, in most cases turns or helices.

Secretases, three proteases (α -, β - and γ -secretase) implicated in the etiology of \rightarrow Alzheimer's disease. They are responsible for the formation of \rightarrow amyloid- β by proteolytic cleavage of the precursor protein APP [W. P. Esler, M. S. Wolfe, *Science* **2001**, *293*, 1449].

Secretin, HSDGTFTSEL¹⁰SRLREGAR LQ²⁰RLLQGLVa (human secretin), a 27-peptide amide released by gastric acid from S cells in the duodenum. It was originally discovered in the duodenal mucosa as a hormone enhancing the secretion of bicarbonate, enzymes, and K⁺ from the exocrine pancreas. Together with other peptides, secretin forms the \rightarrow secretin family. For a long time, secretin was believed to exist only as the 27-peptide amide. During the mid-1980s, the immediate precursor of amidated S-27, the glycine-extended S-28, and S-30, extended by Lys-Arg, were identified in porcine gut extracts as additional secretins with full biological activity. Although

the existence of S-28 and S-30 was not surprising, the discovery of S-71 was unexpected. The secretin gene encodes *prepro-secretin*, consisting of 132 to 134 residues, depending on the species. The precursor protein is normally processed to the three bioactive secretin peptides of almost similar size (S-27, -28, and -30) by endoproteolytic cleavages and variable C-terminal trimming. In contrast, the bioactive S-71 is produced after RNA splicing, whereas the middle sequence of *prepro-secretin* is removed on the gene level. S-71 contains the sequence of non-amidated S-27, followed by a Gly-Lys-Arg extension and a further C-terminal extension of 41 residues. Human and rat secretin receptors show 81% identity, and are coupled with G proteins. The activation of the receptor stimulates the adenylate cyclase/protein kinase A cascade and enhances Ca^{2+} concentration in various cellular systems [V. Mutt et al., *Eur. J. Biochem.* **1970**, *15*, 513; G. Gafvelin et al., *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 6781; G. G. Nussdorfer et al., *Peptides* **2000**, *21*, 309].

Secretin family, a member of the gastroenteropancreatic peptide families. This family comprises \rightarrow secretin, \rightarrow glucagon, \rightarrow glucagon-like peptides (GLP-1 and GLP-2 both encoded by one gene), \rightarrow vasoactive intestinal polypeptide (VIP) and \rightarrow peptide histidine isoleucine amide (both encoded by one gene), \rightarrow growth hormone-releasing hormone, \rightarrow glucose-dependent insulinotropic polypeptide (also referred to as gastric inhibitory polypeptide, GIP), and \rightarrow pituitary adenylyl cyclase-activating polypeptides (PACAP). Helospectine I and II and helodermin from the toxins of *Heloderma horridum* and *Heloderma suspectum*, respectively, and the \rightarrow exendins are not

present in mammals [J. F. Rehfeld, *Physiol. Rev.* **1998**, *78*, 1087].

Secretogranins, \rightarrow chromogranins.

Secretoneurin (SN), a 33-peptide derived from secretogranin II (chromogranin C, \rightarrow chromogranins). SN is widely distributed throughout the central and peripheral nervous systems. Known functions of SN include chemotaxis of monocytes and endothelial cells, and inhibition of endothelial cell proliferation. In addition, SN is a potent chemoattractant for human eosinophils. Since it can be co-released with \rightarrow substance P and \rightarrow calcitonin gene-related peptide from sensory afferent c-fibers by capsaicin, it might represent another member of the group of inflammatory neuropeptides [R. Kirchmair et al., *Neuroscience* **1993**, *53*, 359; S. Dunzendorfer et al., *Blood* **1998**, *91*, 1527; C. J. Wiedermann, *Peptides* **2000**, *21*, 1289].

Segetalins, cyclic peptides from higher plants. They have been used to activate blood flow and promote milk secretion and to treat amenorrhea and breast infections in China. Segetalins A and B have been isolated from the seeds of *Vaccaria segetalis* (Caryophyllaceae). Segetalins B, G, and H show estrogen-like activity. The syntheses of various segetalins have been described [H. Morita et al., *Tetrahedron* **1995**, *51*, 5987; P. Sonnet et al., *Tetrahedron Lett.* **2003**, *44*, 3293].

Segment condensation, *segment coupling*, \rightarrow convergent synthesis.

Segment coupling, \rightarrow segment condensation.

Selenocysteine (Sec, U), $\text{HSeCH}_2\text{-CH}(\text{NH}_2)\text{-COOH}$, the twenty-first encoded amino acid which was discovered during the late 1980s. Sec is similar in reactivity

and is isosteric to cysteine. However, the one key difference is that it has a reduced pK_a (5.2) with the consequence that it is deprotonated under physiological conditions. Therefore, most known selenoproteins are involved in redox reactions, e.g., *E. coli* formate dehydrogenase H (FDH_H), where Sec is part of the catalytic mechanism. Selenocysteine is an amino acid building block in several dozen naturally occurring proteins, such as glutathione peroxidase, thioredoxin reductase, iodothyronine 5'-deiodinase, and artificial selenoproteins that catalyze a variety of interesting reactions. For example, a novel eukaryotic selenoprotein has been found in the haptophyte alga, *Emiliania huxleyi*, which requires selenium for growth. The Sec residue is ribosomally incorporated into proteins by a cognate aminoacyl-transfer RNA pair, Sec-tRNA^{Sec}, via read-through of an internal, in-frame UGA codon. The latter is specified by a particular (in the mRNA) UGA codon which is normally the *opal* stop codon. However, efficient suppression of the stop codon requires a specific translation factor and specific recognition elements within the mRNA. Alternatively, cysteine auxotrophs can be used to create artificial selenoproteins in which all cysteine residues are selectively replaced by Sec. In bacteria, Sec-tRNA^{Sec} is synthesized via an indirect, two-step mechanism starting with aminoacylation of Ser-tRNA synthetase to generate Ser-tRNA^{Sec}. In the next step, this misacylated tRNA intermediate is converted to Sec-tRNA^{Sec}, catalyzed by a new Sec synthase in eukarya and archaea. The selenocysteine-mediated native chemical ligation (→ chemical ligation) and expressed protein ligation (→ biochemical ligation) based on the reaction of → C-terminal peptide α -thioester with peptide fragments containing an N-terminal Sec residue gives also selenoproteins [T. C.

Stadtman, *Annu. Rev. Biochem.* **1996**, 65, 83; J. Korle et al., *J. Biol. Chem.* **2000**, 381, 849; R. Quaderer et al., *Helv. Chim. Acta* **2001**, 84, 1197; R. J. Hondal et al., *J. Am. Chem. Soc.* **2001**, 123, 5140; T. Obata, Y. Shiraiwa, *J. Biol. Chem.* **2005**, 280, 18462; J. Yuan et al., *Proc. Natl. Acad. Sci. USA* **2006**, 103, 18923; T. L. Hendrickson, *Nat. Struct. Mol. Biol.* **2007**, 14, 100].

Selenoproteins, → selenocysteine.

Semipermanent protecting groups, → protecting groups of amino acid side-chain functionalities that must be stable to the repetitive treatments necessary, both for the deprotection of the N $^{\alpha}$ -amino protecting group of the growing peptide chain and for repeated coupling reactions.

Separation methods, techniques for the separation of peptides for analytical or preparative purposes (→ purification techniques). Basically, separation during synthesis and separation (purification) after the synthesis must be distinguished. → SPPS is an approach for separation during synthesis, as the growing peptide chain is attached to an insoluble carrier, which allows separation from an excess of starting material and soluble side products. Alternatively, a fluororous tag, a perfluorinated moiety, may be attached to the peptide and the target peptide can be separated from non-tagged compounds by partitioning between organic and perfluorinated solvents or water and perfluorinated solvents. → Reversed-phase HPLC (RP-HPLC) is the most popular HPLC variant used for purification of peptides and proteins after the synthesis. Because of the high chromatographic resolution it is most suitable for the assessment of homogeneity. → Ion-exchange chromatography (IEC) likewise is a commonly practiced method for protein purification, especially

in its HPLC variant. Gel filtration has increasingly been replaced by RP-HPLC. Capillary electrophoresis (CE) relies on the separation of peptides and proteins based on their differential migration in an electric field. Multidimensional separations, such as 2-D gel electrophoresis (e.g., comprising isoelectric focusing combined with polyacrylamide gel electrophoresis) and multidimensional chromatography approaches, such as 2-D-HPLC (e.g., a combination of ion-exchange HPLC with RP-HPLC) are widely used in → proteomics because they are able to efficiently resolve complex peptide mixtures at high resolution, and are compatible with mass spectrometry. → Affinity chromatography relies on the enrichment of a protein with a bioselective ligand chemically bound to an inert matrix retaining the target because of its selective affinity to the ligand. Besides chromatographic and electrophoretic techniques, ultrafiltration (UF) represents a low-pressure method for the rapid concentration of protein solutions by means of a semipermeable membrane. UF typically retains high-molecular-mass compounds. As UF membranes can be tailored with respect to pore size (0.005–0.1 μm) and approximate molecular mass cut-off (1 to 500 kDa), UF can be used for the separation of peptides and proteins which differ significantly in their molecular mass [N. Catsimpoolas, *Methods of Protein Separation*, Plenum Press, 1975; S. Roe, *Protein Purification Techniques: a Practical Approach*, Oxford University Press, 2001].

Sequence analysis, the determination of the → primary structure (amino acid sequence) of a peptide or protein. Prior to sequence analysis the determination of the amino acid composition (→ amino acid analysis) and the number of different

peptide chains in a protein by analysis of N-terminal and/or C-terminal residues (→ end group analysis) is necessary. N-terminal analysis can be performed using several chemical and enzymatic methods. Chemical methods are mostly based on transformation of the N-terminal α -amino function, e.g., with Sanger's reagent (→ dinitrophenyl method) or dansyl chloride (→ dansyl method), followed by hydrolysis, separation and characterization of the terminal amino-acid derivative. In addition, enzymatic cleavage of the N-terminal residue with, e.g., porcine kidney leucyl aminopeptidase (LAP), aminopeptidase I (API) or aminopeptidase M is also feasible. According to the → Akabori method, all amino acids not located at the C-terminus are converted into hydrazides. Cleavage of cystine disulfide bonds is required to cleave disulfide-linked peptides. N-Terminal sequence analysis is performed according to the → Edman degradation, while C-terminal sequence analysis is feasible following the → Schlack–Kumpf method. Mass spectrometry has proved to be a very useful method for the analysis of peptides and proteins, especially in the rapidly developing area of → proteomics. MALDI-ToF-MS and ESI-MS offer alternatives to the classical Edman peptide sequencing. N-terminal → ladder sequencing is based on a modified Edman procedure, whereas C-terminal ladder sequencing is based on the same principle and initially was combined with C-terminal sequence analysis either by carboxypeptidase treatment or the → Schlack–Kumpf method coupled with MALDI-MS analysis of the truncated peptides. The soft desorption of MALDI or ESI MS techniques does not induce fragmentation processes, and allows the transfer of high-molecular-mass polypeptide ions into the gas phase. Short peptides can be directly sequenced

(→ MS *de-novo* sequencing), for example by MALDI-ToF MS techniques via post-source decay (PSD), whilst prior cleavage to provide suitable fragments is an imperative prerequisite for proteins and longer polypeptides. Peptides generated proteolytically can be identified by MS after degradation by carboxypeptidase. In tandem mass spectrometry (MS/MS, or MSⁿ), single ions are selected by mass and further fragmented by employing collision-induced dissociation (CID) followed by analysis of the resulting fragments. In → proteomics the protein of interest is digested by treatment with a protease (e.g., trypsin), and the resulting peptide fragments (peptide fingerprint, peptide mass map) are identified by searching against databases [A. S. Brown, *Protein/Peptide Sequence Analysis: Current Methodologies*, CRC Press, 1988, J. M. Walker, *The Protein Protocols Handbook*, Humana Press, 2002; B. J. Smith, *Protein Sequencing Protocols*, Humana Press, Totowa, N.J., 2003].

Serine peptidases, *serine proteases* the most studied class of → peptidases. They have a reactive serine residue, for example, the hydrolysis of a peptide substrate involves an → acyl enzyme intermediate in which the hydroxyl group of Ser¹⁹⁵ (chymotrypsin numbering system) is acylated by the acyl moiety of the substrate, thus releasing the amine fragment of the substrate as the first product. The formation of the acyl enzyme is the slow step in peptide bond hydrolysis, but acylenzyme often accumulates in the hydrolysis of ester substrates. The acyl enzyme thus formed will be the same for a series of substrates which differ in their leaving group. The active site of serine peptidases is complementary in structure to the transition state of the reaction, a structure which is very close to the tetrahedral adduct of Ser¹⁹⁵ and the carbonyl

carbon of the peptide substrate. Indeed, transition-state binding catalysis provides the catalytic power of the appropriate serine peptidase. During the course of formation of the tetrahedral intermediate a conformational distortion causes the carbonyl oxygen of the scissile peptide bond to move deeper into the active site to occupy the oxyanion hole. The resulting oxyanion is hydrogen-bonded to the backbone of NH groups of Gly¹⁹³ and Ser¹⁹⁵, whereas the NH group of the peptide bond preceding the scissile bond forms a hydrogen bond to the backbone carbonyl of Gly¹⁹³. Decomposition of the tetrahedral intermediate forming the acylenzyme intermediate and the amine product occurs under the driving force of proton donation from the N3-Atom of His⁵⁷ through general acid catalysis. The *N*-terminal part of the cleaved peptide chain (amine product) will be released in the next step and replaced by a water molecule, and forming a second tetrahedral intermediate. The latter then decomposes to the reaction's carboxyl product (C-terminal portion of the cleaved peptide chain) and the active enzyme. Generally, all the serine peptidases employ the same catalytic three amino acid units to hydrolyze peptide bonds. The diversity of serine peptidases such as → trypsin, → chymotrypsin, and → kallikreins results entirely from the way in which they accommodate their specific substrates [A. J. Barrett, N. D. Rawlings, *Arch. Biochem. Biophys.* 1995, 318, 247].

Serine proteases, → serine peptidases.

Serine (Ser, S), α -amino- β -hydroxypropionic acid, HO-CH₂-CH(NH₂)-COOH, C₃H₇NO₃, M_r 105.09 Da, a proteinogenic amino acid.

Serpins, a superfamily of structurally homologous proteins comprising approximately 800 members. The majority of the

serpins are serine proteases inhibitors, from which the name derives. In addition, inhibitors of cysteine proteases and some non-inhibitory proteins must also be included based on their structural homology. A characteristic three-dimensional structure of the members of the serpin family consists of three β -sheets, nine helices, and the reactive center loop exposed on the surface. Selected members of the serpins are α_1 -proteinase inhibitors, \rightarrow maspin, plasminogen activator inhibitor, α_1 -antichymotrypsin, α_1 -antitrypsin, \rightarrow antithrombin III, \rightarrow ovalbumin, and neuroserpin. Serpins are involved in various processes, such as inflammation, fibrinolysis, coagulation, apoptosis, protein folding, neoplasia, viral pathogenesis, and complement activation. Serpins have metastable native structures. Especially, serpin variants which have resulted from mutations show a tendency to undergo conformational changes, leading to latent forms and polymers. The latter are involved in various conformational diseases, termed *serpinopathies*, that are associated with conditions such as angioedema, emphysema, thrombosis, liver disease, and dementia [J. A. Irving et al., *Genome Res.* **2000**, *10*, 1845; G. A. Silverman et al., *J. Biol. Chem.* **2001**, *276*, 33293; D. A. Lomas, R. Mahadeva, *J. Clin. Invest.* **2002**, *110*, 1585; E. Marszal, A. Shrake, *Arch. Biochem. Biophys.* **2006**, *453*, 121].

Serum albumin, \rightarrow albumins.

Sex peptide (SP), a male peptide in *Drosophila melanogaster* inducing the post-mating responses when injected into virgin females. SP is synthesized in the accessory glands. A second male peptide is the *ductus ejaculatorius peptide 99B* [H. Liu, E. Kubli, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 9929].

Shaker peptides, \rightarrow conotoxins.

β -Sheet, a periodic \rightarrow secondary structure element. Hydrogen bonds in a β -sheet are formed between two adjacent polypeptide chains to give either a parallel β -sheet with the torsion angles $\phi = -119^\circ / \psi = 135^\circ$, or an antiparallel β -sheet with $\phi = -139^\circ$ and $\psi = 135^\circ$. β -Pleated sheets are found in silk fibroin and other β -keratins (\rightarrow keratins), and also in several domains of globular proteins, where they may occur in a twisted, curled, or backfolded form.

Sheppard tactics, \rightarrow Fmoc/Bu^t chemistry.

Shiga toxin, a bacterial toxin produced by *Shigella dysenteriae* belonging to the AB₅ toxins family. It is structurally related to verotoxin and cholera toxin. Shiga toxin is composed of two subunits. The monomeric A-subunit has a N-glycosidase activity causing inhibition of protein synthesis and cell death. The B-subunit is a homopentamer which is responsible for receptor binding, internalization and intracellular transport of the holotoxin [E. A. Meritt, W. G. Hol, *Curr. Opin. Struct. Biol.* **1995**, *5*, 165; D. G. Pina et al., *Biochim. Biophys. Acta* **2007**, *1768*, 628].

ShI, a sodium channel neurotoxin from the sea anemone *Stichodactyla helianthus*. ShI is a member of the \rightarrow β -defensin-fold family [W. R. Kem et al., *Biochemistry* **1989**, *28*, 3483; A. M. Torres, P. W. Kuchel, *Toxicon* **2004**, *44*, 581].

Shy A, a *Streptomyces* protein (195 aa; M_r \sim 20.7 kDa) belonging to a new family of membrane-associated proteins involved in morphological differentiation in actinomycetes [S.-F. Tseng et al., *Biochem. Biophys. Res. Commun.* **2006**, *343*, 369].

Sialyl-Lewis X (SLeX), the tetrasaccharide α -NeuAc-2,3- β -Gal-1,4-(α -L-Fuc-1,3)- β -GlcNAc-1,3-OR, one of the most important carbohydrates in humans. SLeX is

amino acid, and formally composed of a carbamic acid (*N*-carboxy group) and a carboxylic acid (carboxy group) to give a mixed anhydride. Their practical application in peptide synthesis suffers from the high tendency towards ring-opening polycondensation, with the consequence that *N*-carboxy anhydrides can only be employed under carefully controlled reaction conditions. Alternatively, hexafluoroacetone can be used as a reagent to simultaneously protect the *N* α -group and activate the carboxy group of an amino acid. The resulting derivatives (\rightarrow bis(trifluoromethyl)-1,3-oxazolidin-5-one approach) can be efficiently employed in peptide synthesis. Reaction of the activated lactone moiety with the *N*-terminus of a peptide releases hexafluoroacetone from the *N,O*-ketal. Racemization does not occur during this procedure, and the activated derivatives are stable for storage. A different recent example of a simultaneous *N* α -protection and carboxy group activation is the reaction of amino acids with *O*-propargyl-*O*'-pentafluorophenyl carbonate (Poc OPfp). This reaction brings about Poc-protection (propargyloxycarbonyl-protection) of the *N* α -group with intermediate formation of a mixed anhydride that readily forms the pentafluorophenyl ester in a one-pot reaction. After peptide coupling, the Poc-group can be cleaved using benzyl triethylammonium tetrathiomolybdate [R. Ramesh et al., *Org. Lett.* **2006**, 8, 1933].

Site-directed mutagenesis, an important method for the predetermined exchange of an amino acid in a protein. Site-directed mutagenesis relies on the replacement of a single nucleotide or a group of nucleotides in DNA encoding for a protein, with the consequence that a single amino acid or even a longer epitope of the protein is replaced, deleted, or inserted. The target DNA

sequence is cloned into a double-stranded vector. After separation of the two DNA strands, a synthetic oligonucleotide comprising approximately 20 bp is allowed to hybridize to one of the single strands of the vector. The synthetic oligonucleotide contains, in the middle, the mutated deleted or inserted DNA sequence. There is a mismatch in binding during the first cycle because of the mutation. However, the elongated strand based on the synthetic oligonucleotide which contains the mutation is present in the same concentration as the original template after the first round, and then amplified [M. Smith, *Angew. Chem. Int. Ed.* **1994**, 33, 1214; J. Braman (Ed.), *In Vitro Mutagenesis Protocols*, Humana Press, Totowa, N.J., **2002**].

Size-exclusion chromatography (SEC), a method for the separation and purification of peptides and proteins. Size-exclusion chromatography brings about the separation of molecules according to their hydrodynamic volume. An SEC column is packed with porous particles of fairly defined pore size. Molecules that are too large to penetrate the pores will elute faster than smaller molecules that diffuse into the pores. Consequently, the sample is fractionated according to molecular size. SEC is also named gel filtration chromatography (GFC), which specifically refers to the separation of biopolymers in an aqueous mobile phase. The alternative term gel permeation chromatography (GPC) is related to the application in non-aqueous separation systems. SEC mostly uses soft polymer gels as a stationary phase in the form of packed columns. The most popular matrices are Sepharose (agarose), Sephacryl (co-polymer of allyl dextran and *N,N'*-methylene-bisacrylamide), Bio-gel P (co-polymer of acrylamide and *N,N'*-bisacrylamide), Bio-gel A (agarose), or

polyether gels [H. G. Barth et al., *Anal. Chem.* **1998**, *70*, 251].

SLC, sublethal concentration.

Sleeper peptide, → conantokins.

S-linked glycopeptides, peptides with an oligosaccharide moiety attached to a Cys residue across an *S*-glycosidic bond. The replacement of the anomeric oxygen or nitrogen of an *N*- or *O*-glycan by sulfur gives an *S*-linked glycopeptide. *O,S*-acetals are known to be chemically more stable than the corresponding *O,O*-acetals or *O,N*-acetals. They are resistant to the action of glycosidases, while being tolerated by most biological systems [D. A. Thayer et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 4596].

SMPS, simultaneous multiple peptide synthesis.

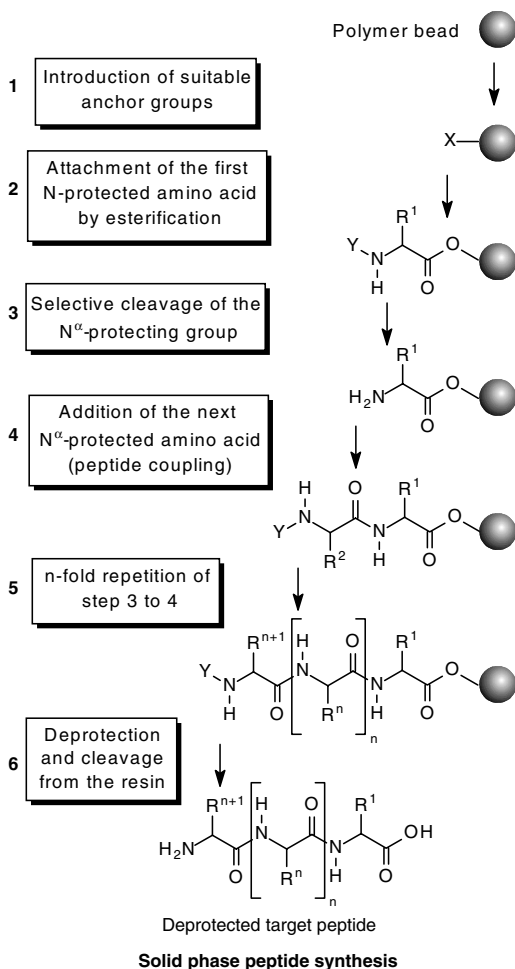
Sodefrins, peptide pheromones from the red-bellied newt. The 10-peptide H-Ser-Ile-Pro-Ser-Lys-Asp-Ala-Leu-Leu-Lys¹⁰-OH was first isolated from the abdominal gland of the male newt *Cynops pyrrhogaster*, while [Leu³,Gln⁸]sodefrin occurs in *C. ensicauda*. The sodefrins are potent conspecific female-attracting pheromones, and act primarily on the lateral nasal sinus cells [S. Kikuyama et al., *Science* **1995**, *267*, 1643; T. Nakada et al., *Front. Neuroendocrinol.* **2006**, *27*, 149].

Solid-phase chemical ligation, → chemical ligation.

Solid-phase combinatorial peptide synthesis, → combinatorial peptide synthesis, → solid-phase peptide synthesis.

Solid-phase peptide synthesis (SPPS), a strategy for the synthesis of peptides, with the growing peptide chain immobilized to

a solid phase facilitating separation procedures. As in → solution-phase synthesis, the peptide chain in SPPS is assembled starting from the C-terminus. In most cases the first amino acid of the target peptide is connected across its carboxy group to an insoluble polymer that may easily be separated from excess reagents and side products by filtration. The polymeric support must be chemically inert, mechanically stable, insoluble in the solvents used, and easily separated by filtration. In order to attach the first amino acid of the peptide to be synthesized, a sufficient number of reactive sites must be present. For most purposes polystyrene resins crosslinked with 1–2% divinylbenzene are employed. However, a great variety of other resin materials has been developed during the past decades in order to improve on mechanical stability, swelling properties, loading capacity, diffusion properties, and solvation. Crosslinked poly(dimethylacrylamide) is more hydrophilic than polystyrene, which favors peptide synthesis because of the improved swelling properties. Hydrophilic tentacle polymers are obtained by grafting polyethylene glycol (PEG) onto polystyrene beads. The PEG part of the polymer confers improved hydrophilicity and high solvation (TentaGel). Sintered polyethylene, cellulose, silica and chitin have also been used as support materials. The resin material must be chemically functionalized with linkers (→ handles) to allow attachment of the first amino acid of the projected peptide. Such handles can be tailored with respect to stability and cleavage conditions, as the polymeric support can be interpreted as a giant protecting group, usually for the C-terminus. The first amino acid is coupled to the resin across, e.g., ester or amide bonds. Depending on the nature of the linker and amino acid, care must be taken in this step to avoid racemization. After cleavage



of the N^{α} -protecting group the next protected amino acid is coupled. Again, the temporary N^{α} -protecting group is cleaved and corresponding steps are repeated until the required peptide sequence has been assembled. At the end of the synthesis the peptide is cleaved from the resin and purified. In most cases, cleavage from the resin and cleavage of the semi-permanent side-chain-protecting groups is brought about simultaneously. However, in special cases, for example in the synthesis of backbone

cyclic peptides, only the linker is cleaved to generate a side-chain-protected peptide soluble in organic solvents. While the peptide is bound to the resin, reagents and amino acid building blocks are employed in excess to safeguard complete reaction. The efficiency of the coupling reaction and the iterative cleavage of the temporary N^{α} -protecting groups must be exceptionally high because the separation of \rightarrow truncated sequences and deletion sequences from the target peptide after the synthesis is

extremely tedious, or often impossible. The repetitive character of solid-phase peptide synthesis and the simple technical operation allow automation. The first solid-phase peptide synthesizer was constructed by R. B. Merrifield, who also described the ingenious concept of peptide synthesis on a solid support for the first time in 1963. He was awarded the Nobel Prize in Chemistry in 1984 for the unique invention that has revolutionized peptide chemistry, and even organic chemistry, during the past decades. Convergent peptide synthesis – the coupling of peptide segments – can also be employed in SPPS (→ convergent solid-phase peptide synthesis). Today, solid-phase peptide synthesis can also be used for the synthesis of, e.g., → cyclic peptides. In this case, the first amino acid is either attached to the resin across its side chain functionality, or by using a → backbone amide linker. Alternatively a → safety-catch resin may be employed that allows for cyclization and cleavage from the resin in one step. C-terminally modified peptides containing other C-terminal end groups than the usual carboxylic acid or carboxamide functionalities can also be obtained. Moreover, strategies for SPPS in aqueous solvents have been developed. For that purpose, resin materials that are swellable in aqueous or aqueous-ethanolic solutions are required besides water-soluble coupling reagents [S. A. Kates, F. Albericio (Eds.), *Solid-Phase Synthesis*, Marcel Dekker, New York, **2000**; J. Alsina, F. Albericio, *Biopolymers* **2003**, 71, 454; K. Hojo et al., *Protein Peptide Lett.* **2006**, 13, 189].

Solid-phase sequencer, an apparatus for peptide/protein → sequence analysis. Automated primary structure determination of peptides and proteins using the solid-phase sequencing method is based on cova-

lent C-terminal immobilization of the peptide on a suitable support. The reagents for → Edman degradation are then consecutively added. As the protein or peptide is covalently attached to the solid support, byproducts and excess reagents can be removed as in solid-phase peptide synthesis by washing, without loss. The method of solid-phase sequence analysis has to compete with liquid film (spinning-cup) sequencing (→ spinning-cup sequencer) in which the protein is degraded in a liquid film, and also with the → gas-phase sequencer in which the protein is absorbed onto a glass-fiber disc.

Solid-to-solid conversion, an approach to → protease-catalyzed peptide synthesis in which the starting materials and products are in the form of suspended solids. Theoretical analysis shows that the thermodynamic favorability of solid-to-solid conversions is independent of the solvent used, at fixed water activity. This concept may have wide application for the direct reversal of peptide hydrolysis starting from undissolved reactants, even in aqueous media. The reaction will proceed until the excess solid of at least one reactant has been completely consumed [P. J. Halling et al., *Enzyme Microb. Technol.* **1995**, 17, 601; M. Erbdinger et al., *Biotechnol. Bioeng.* **1998**, 59, 68].

Solution-phase synthesis, the synthesis of peptides in solution. Despite the dominance of → solid-phase peptide synthesis (SPPS), solution-phase synthesis still is of importance for the synthesis of peptides on a larger scale, including the preparation of peptide pharmaceuticals. Peptide synthesis in solution may follow either linear or convergent strategies. The linear synthesis is mostly employed for small peptides and peptide segments

up to about five amino acids that can be synthesized in solution without major problems. In contrast, SPPS is much more successful for the linear synthesis of longer peptides. Convergent peptide synthesis (CPS) in solution is mainly employed for the large-scale production of small to medium-size peptides that are produced on an annual scale of several hundreds of kilograms, such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and HIV protease inhibitors, as well as GnRH analogues, oxytocin, and desmopressin. A major advantage of solution-phase synthesis is that the reaction intermediates can be purified and characterized at each step of the reaction sequence. The assembly of the target molecule in solution-phase synthesis utilizes purified and well-characterized segments, whereas in SPPS such a purification of the intermediates is not possible. Hence, the desired final product may be obtained at a higher purity when following the solution-phase strategy. However, such purification and separation measures at each synthetic step are much more time-consuming compared to SPPS.

Somamide A, a 19-membered macrocyclic depsipeptide isolated from assemblages of the marine cyanobacteria *Lyngbya majuscula* and *Schizothrix* sp. from the Fijian Islands. The structure is characterized by a 3-amino-6-hydroxy-2-piperidone (Ahp) unit, a (Z)-2-amino-2-butenic acid building block, and a sulfoxide function was confirmed by total synthesis in 2002 [L. M. Nogle et al., *J. Nat. Prod.* **2001**, *64*, 716; F. Yokokawa, T. Shioiri, *Tetrahedron Lett.* **2002**, *43*, 8673].

Somatoliberin, *somatotropin-releasing hormone*, (**SRH**) → growth hormone-releasing hormone (GRH).

Somatomedins (SM), previous term for → insulin-like growth factors (IGF) [J. J. van Wyk et al., *Recent Prog. Horm. Res.* **1974**, *30*, 259; W. H. Daughaday et al., *Endocrinology* **1987**, *121*, 1911].

Somatostatin (SST), *somatotropin release-inhibiting hormone*, (**SIH**), *somatotropin release inhibiting factor* (**SRIF**), AGCKNF FWKT¹⁰FTSC (disulfide bond: C³–C¹⁴), a heterodetic, cyclic 14-peptide released by the hypothalamus. SST is a potent inhibitor of → growth hormone (GH) release, but not of growth hormone synthesis. SST also inhibits the secretion of several other hormones, such as glucagon, thyrotropin, insulin, cholecystokinin, and gastrin. In addition, it is a regulator of many other biological processes. Six somatostatin receptor (SSTR) subtypes and multiple postreceptor signaling systems have been described. SSTR-2 (rat) seems to be the dominant SSTR that influences GH release from the somatotrope. Signal transduction comprises G protein-coupled reduction in L- and T-type voltage-sensitive Ca²⁺ influx/channels and increased K⁺ channels. SST is synthesized as prepro-SST, which is processed at the C-terminus to form SST-14. Besides the hypothalamus, SST-14 and SST-like peptides (including SST-28) have been found in the stomach, pancreas, and also in the central and peripheral nervous systems, thymus, gastrointestinal tract, ovaries, and even in plants (tobacco, spinach). SST infusions have been applied to the treatment of bleeding peptic ulcers and gastrointestinal lesions, for the preventive treatment of stress ulcers, and in the healing of fistulae of the small intestine and gallbladder. Many analogues have been synthesized and tested to identify some with higher selectivity and a longer half-life. [D-Trp⁸]SST, [D-Cys¹⁴]SST, and [D-Trp⁸, D-Cys¹⁴]SST show different abilities

to inhibit the production of GH, insulin or glucagon. Furthermore, *octreotide*, H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol (disulfide bond: Cys²–Cys⁷) is 70-fold more potent than SST in inhibiting somatotropin release *in vivo* 15 min after administration, and it is characterized by a long duration of action after intramuscular administration. This analogue is used in the treatment of somatotropin- and thyrotropin-secreting pituitary tumors, carcinoid tumors, and in further indications. More recently, two additional analogues, namely *lanreotide*, H-D-βNal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-ol (disulfide bond: C²–C⁷), and *vapreotide*, H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-OH (disulfide bond: C²–C⁷) have become available for clinical use. Radiolabeled somatostatin analogues such as ⁹⁰Y-DOTA-Tyr³-octreotide (⁹⁰Y-DOTATOC) with the β-emitter ⁹⁰Y have been developed for radiotherapy [P. Brazeau et al., *Science* **1973**, 179, 77; C. Johansson et al., *Digestion* **1981**, 22, 126; C. H. S. McIntosh, *Life Sci.* **1985**, 17, 2043; D. K. Reed et al., *Endocrinology* **1999**, 140, 4739; Y. C. Patel, *Front Neuroendocrinol.* **1999**, 20, 157; C. Scarpignato, I. Pelosini, *Chemotherapy* **2001**, 47 (Suppl. 2), 1; J. van der Hoek et al., *Curr. Pharm. Des.* **2005**, 11, 1573; A. M. Comaru-Schally, A. V. Schally, *Int. J. Oncol.* **2005**, 26, 301].

Somatostatin family, a member of the gastroenteropancreatic peptide families. Somatostatin, and → corticostatin belong to this family.

Somatotropin, → growth hormone.

Somatotropin release inhibiting peptide, → somatostatin.

Somatotropin-releasing hormone, → somatoliberin.

Somatotropin-releasing peptides, → growth hormone-releasing peptides.

Sortases (Srt), bacterial transpeptidases found in Gram-positive bacteria. They catalyze a cell wall sorting reaction characterized by the covalent attachment of surface proteins to the cell wall envelope. Srt have been proven to have a key function in the pathogenicity of Gram-positive bacteria. Protein substrates of sortases bear a so-called sorting signal at the C-terminus consisting of the LPXTG motif (X = any amino acid), a hydrophobic region, and a tail of charged residues. *Sortase A* (Srt A) from *Staphylococcus aureus* catalyzes the Thr-Gly bond cleavage within the sorting motif, forming a threonyl thiol ester with the active site Cys residue. The resulting intermediate undergoes nucleophilic attack from the N-terminal pentaglycine moiety of the cell wall peptidoglycan (Lipid II). In subsequent reaction steps, the precursor protein becomes polymerized into mature peptidoglycan. The principle of sortase-catalyzed transpeptidation has been used as an additional variant of → biochemical protein ligation (→ sortase-mediated protein ligation) [S. K. Mazmanian et al., *Science* **1999**, 285, 760; B. A. Frankel et al., *Biochemistry* **2005**, 44, 11188].

Sortase-mediated protein ligation, an enzyme-based variant of biochemical protein ligation. Using the principle of sortase A-mediated transpeptidation (→ sortases, Srt), peptides with one or more N-terminal glycines can function as nucleophilic amino components in the ligation process. This enzymatic ligation procedure is highly selective due to both the low tolerance of Srt for deviation in the LPXTG recognition motif, and the limited occurrence of the latter in proteins. However, as the ligation product contains the crucial recognition motif (just like the carboxy

component), the former is also a potential substrate along with the byproduct bearing the P'1-Gly residue in the *N*-terminal position. Under these conditions it must be assumed that it is possible for the reaction to attain equilibrium. In order to reach yields >50%, the equilibrium should be shifted to the product side by manipulations that are equal to those applied in \rightarrow equilibrium-controlled enzymatic synthesis. The synthesis of various polypeptides, including biologically active nucleic acid-peptide conjugates, underline that this approach might be an interesting technique for the ligation of unprotected peptides and proteins [H. Y. Mao et al., *J. Am. Chem. Soc.* **2004**, 126, 2670; S. Pritz et al., *J. Org. Chem.* **2007**, 72, 3909].

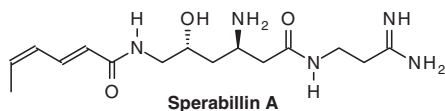
Spantide I, [D-Arg¹,D-Trp^{7,9},Leu¹¹]substance P, an antagonist of \rightarrow substance P [K. Folkers et al., *Br. J. Pharmacol.* **1984**, 83, 449].

Spatial screening, a strategy developed by H. Kessler et al. for \rightarrow receptor mapping. Spatial screening is applied in the search for an unknown active conformation of the recognition sequence present in a ligand. Spatial screening comprises the synthesis of a library of stereoisomeric \rightarrow cyclic peptides containing a peptide sequence that is assumed to be recognized by a receptor (recognition sequence). The cyclic peptides used in the spatial screening approach additionally contain a building block that induces or stabilizes the secondary structure, as for example a D-amino acid, an *N*-alkyl-amino acid, or a β -amino acid. While, for example, a hexapeptide displays several interconverting conformations with different turn geometry, the presence of a building block with conformational bias locks the overall conformation of the peptide. A cyclic peptide has less conformational flexibility than its lin-

ear parent and, hence, less degrees of freedom. If binding to a receptor is still possible for the constrained cyclopeptide, the binding event is entropically favored compared to the linear peptide. Such peptides are assumed to be conformationally homogeneous, and the three-dimensional (spatial) orientation of the functional groups present in the amino acid side chains of the recognition sequence can be determined by NMR spectroscopy. The solution conformation and the receptor-bound conformation are assumed to be similar because of the conformational constraints [R. Haubner et al., *Angew. Chem. Int. Ed.* **1997**, 36, 1374; F. Schumann et al., *J. Am. Chem. Soc.* **2000**, 122, 12009; J. Chatterjee et al., *J. Am. Chem. Soc.* **2006**, 128, 15164].

SPCL, synthetic peptide combination library.

Sperabillins, pseudopeptide antibiotics produced by *Pseudomonas fluorescens* YK-437 showing potent *in vivo* activity. The structure of sperabillin A was elucidated as 3-[(3*R*,5*R*)-3-amino-6-(2*E*,4*Z*)-2,4-hexadien-5-ylamino]-5-hydroxyhexanoylamino]propanamide dihydrochloride. Sperabillin B bears a methyl moiety at the C-6 position of sperabillin A, whereas sperabillins C and D are (2*E*,4*E*)-isomers of the 2,4-hexadienoyl moiety of sperabillin A and B, respectively. The total syntheses have been described [N. Katayama et al., *J. Antibiot. (Tokyo)* **1992**, 45, 10; S. G. Davies et al., *Chem. Commun.* **2003**, 2132; L. Allmendinger et al., *SYNLETT* **2005**, 2615].



Speract, H-Gly-Phe-Asp-Leu-Asn-Gly-Gly-Gly-Val-Gly¹⁰-OH, a sperm-activating 10-peptide isolated from sea urchin eggs.

Speract stimulates the respiration, motility, and cyclic nucleotide metabolism of sea urchin spermatozoa. It induces calcium oscillations in the sperm tail [D. L. Garbers et al., *J. Biol. Chem.* **1982**, 257, 2734; C. D. Wood et al., *J. Cell Biol.* **2003**, 161, 89].

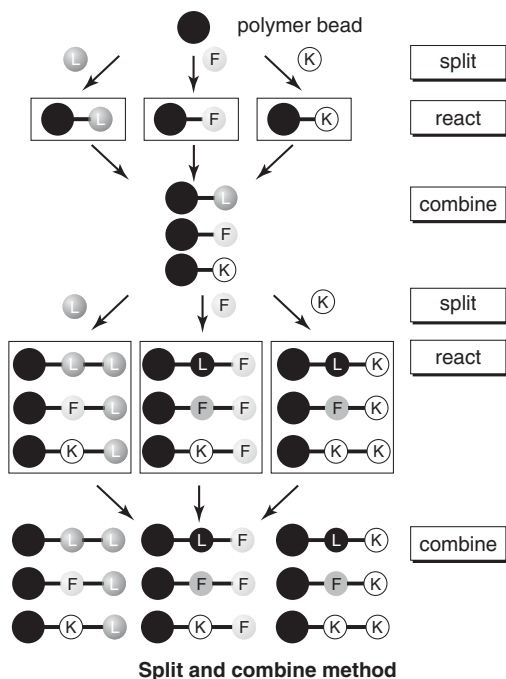
Spider venom peptides, toxic peptides from spiders that mainly modulate neurotransmission. Spider venoms are rich in neurotoxins that influence ion channels, interfere with neurotransmitter exocytosis, or affect neurotransmitter binding. The most important families are the atracotoxins (36–68 amino acids) and the latrotoxins. Many spider venom peptides are translated as pre-peptides and post-translationally modified, e.g., by disulfide bridge formation and C- or N-terminal modification. Because of the high diversity of its constituents, the spider venom is sometimes regarded as a biogenic structurally constrained combinatorial peptide library where nearly all amino acids of the mature sequence may be mutated, with the exception of a few strictly conserved cysteine residues responsible for the three-dimensional fold of the toxin [G. Estrada et al., *Nat. Prod. Rep.* **2007**, 24, 145].

Spinning-cup sequencer, → liquid-phase sequencer.

Spiruchostatins, cyclic → depsipeptides isolated from *Pseudomonas* sp. with potent inhibitory activity against histone deacetylases (HDAC). Spiruchostatin A is a bicyclic depsipeptide containing (3*S*,4*R*)-statine, D-Cys, D-Ala, and (*E*)-3-hydroxy-7-thio-4-heptenoic acid. It is structurally similar to the HDAC inhibitor FR-901228 (FK-228), which is in advanced clinical trials as an anticancer agent. The total synthesis of spiruchostatin A has been described [T. Doi et al., *Tetrahedron Lett.* **2006**, 47, 1177].

Splenopentin (SP-5), H-Arg-Lys-Glu-Val-Tyr-OH, a 5-peptide with sequence similarity to thymopentin (→ thymopoietin) [T. Audhya et al., *Proc. Natl. Acad. Sci. USA* **1984**, 81, 2847].

Split and combine method, *split and mix method*, an approach in combinatorial peptide synthesis. The split and combine method employs solid-phase peptide synthesis for the assembly of peptide libraries in the form of mixtures. It uses either Boc or Fmoc tactics, and relies on the fact that one single polymer bead contains only peptides with the same sequence (one bead, one compound library). A certain amount of polymer resin, large enough to safeguard that the number of beads exceeds the number of library members, is used. Prior to coupling of the first amino acid residue the amount of resin is divided (“split”) into equal portions, the number of portions corresponding to the number of different amino acids to be coupled in this position. After coupling of the corresponding amino acid in separate containments, the whole material is combined, washed, deprotected at N^α, and then again divided (“split”) into portions. The whole procedure is repeated until the full-length peptides have been assembled. Peptide libraries obtained according to the split and combine method may be used directly for screening purposes, where active peptides present on a single bead are, e.g., revealed by a color reaction. When applying the split and combine method together with chemical encoding (molecular tagging), the peptide sequence present on a single bead can be identified by the tag molecules additionally present on this bead. Chemical encoding relies on the fact that tagging molecules (e.g., fluorinated aromatic compounds) are reacted with the bead in parallel to the peptide coupling. The combination of the



different aromatic compounds eventually provides information on the peptide sequence [Á. Furka et al., *Int. J. Pept. Protein Res.* **1991**, 37, 487; K. S. Lam et al., *Chem. Rev.* **1997**, 97, 411].

Spot synthesis, the parallel synthesis of single compounds on cellulose or polymer strips relying on the deposition of solvent drops containing reagents or building blocks to bring about coupling or de-protection. The C-terminal amino acid is connected across an ester bond and a linker molecule to the hydroxyl groups of cellulose. Residual reactive positions of the cellulose are subsequently deactivated. All further steps are performed as in Fmoc SPPS. Washing, and cleavage of the N^α -protecting group, is performed by submersing the whole cellulose sheet into the corresponding washing, capping, or cleavage solution. The peptides obtained in a spa-

tially resolved manner on a cellulose sheet are usually not cleaved from this support; rather, the sheets with bound peptides can be treated and tested in biological assays like Western blot membranes. An array between 96 and several thousands of peptides can be created on a single cellulose sheet in a highly parallel manner [R. Frank, *J. Immunol. Methods* **2002**, 267, 13].

SPPS, → solid-phase peptide synthesis.

ssDNA, single-stranded DNA.

SST, somatostatin.

Sta, statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methyl-heptanoic acid.

Statherin, *human salivary statherin*, an acidic Tyr-rich phosphopolypeptide secreted mainly by salivary glands. Statherin is a 43-peptide ($M_r \sim 5.4$ kDa), and inhibits calcium phosphate precipitation from

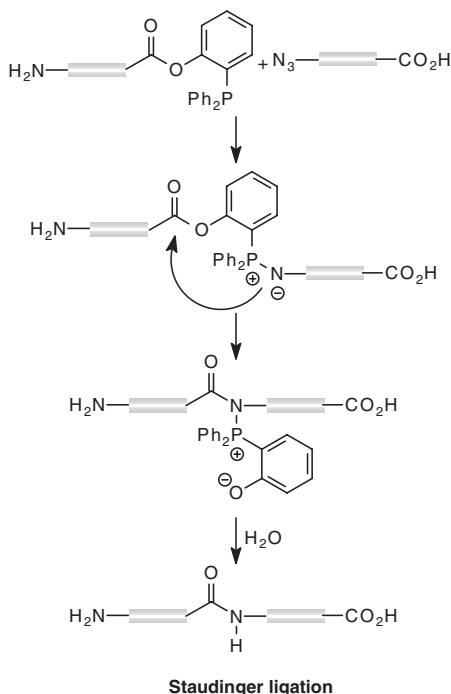
human parotid saliva. It shares important functions together with other salivary phosphoproteins in providing an environment for recalcification and tooth enamel stabilization. Furthermore, statherin possesses high affinity for calcium phosphate minerals such as hydroxyapatite. Circular dichroism studies of both the synthetic and native statherin revealed that it adopts an amphiphilic helical conformation of the *N*-terminus connected to a long poly-L-proline type II segment that, in turn, is linked to an extended β -strand [D. H. Schlesinger et al., *Int. J. Peptide Protein Res.* **1989**, 34, 374; T. L. Gururaja, M. J. Levine, *Peptide Res.* **1996**, 9, 283].

Statine (Sta), (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, an unusual amino acid occurring as a building block, e.g., in \rightarrow pepstatin [D. H. Rich et al., *J. Org. Chem.* **1978**, 43, 3624].

Statins, release inhibiting factors, release inhibiting hormones, neurohormones synthesized in the small-cell region of the hypothalamus and transported via the bloodstream to the anterior pituitary. Members of the statins include \rightarrow melanostatin, \rightarrow somatostatin, and \rightarrow prolactostatin. They inhibit the secretion of melanotropin, somatotropin, and prolactin, respectively. Together with the corresponding \rightarrow liberins, the statins regulate the levels of the three pituitary hormones.

Staudinger ligation, a bio-orthogonal method for coupling unprotected fragments (\rightarrow chemical ligation). The Staudinger ligation relies on the Staudinger reaction between a phosphine and an azide. The primarily formed aminophosphoranes are characterized by a highly nucleophilic nitrogen atom that readily reacts with many different electrophiles. The traceless Staudinger ligation utilizes, e.g., esters

or thioesters carrying an additional phosphine moiety. The phosphine forms the iminophosphorane upon reaction with an azide, followed by an intramolecular attack of the iminophosphorane nitrogen onto the ester or thioester. In such a way an amide bond is formed where the azide formally serves as the amino component while the thioester or ester acts as the acyl component [M. Köhn, R. Breinbauer, *Angew. Chem. Int. Ed.* **2004**, 43, 3106].

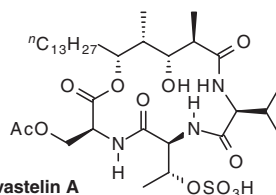


Stein, William H., (1911–1980), American biochemist and winner of the Nobel Prize in Chemistry 1972 (shared with \rightarrow Moore and \rightarrow Anfinsen) for his contribution to the understanding of the connection between chemical structure and catalytic activity of the active center of the ribonuclease molecule. Stein received his Ph.D. in 1938, and in the same year joined the staff of the Rockefeller Institute of Medical

Research in New York. In 1954 he was promoted to a professorship therein. Stein and Moore developed methods for the quantitative analysis of amino acids, their automation, and the application in peptide and protein chemistry.

Stereochemical peptide analysis, the investigation of the stereochemistry of peptides. The stereochemical integrity of a peptide is crucial for molecular recognition, intermolecular interactions, and biological activity. Methods for the analysis of the stereochemical integrity of peptides with respect to the occurrence of peptide stereoisomers are of high relevance for investigations involving biologically active peptides, and especially for the quality control of pharmaceutical peptides. → Racemization (epimerization) is always a concern in peptide synthesis as it results in the undesired formation of diastereomers. Consequently, the assessment of the stereochemical characteristics of a target peptide also with respect to optimization of the synthetic strategy is of major importance. Direct enantiomer analysis is, in principle, possible by using chiral stationary phases in chromatography where a chiral selector is immobilized onto a solid support. A similar situation applies to the addition of a chiral selector in capillary zone electrophoresis, or a chiral shift reagent in NMR spectroscopy. However, in the analysis of the stereochemical integrity of a synthetic peptide it is mainly diastereomer analysis that is a major issue. As diastereomers can be distinguished on the basis of their different physico-chemical properties, special enantiomerically pure selectors are usually not necessary. Nevertheless, chiral selectors may be helpful even for the separation of diastereomers, as the relatively small differences in the physico-chemical properties of diastereomers can be enhanced by

using chiral selectors. HPLC is the premier method for such analysis, besides thin-layer chromatography, gas chromatography, capillary zone electrophoresis, and NMR spectroscopy. Cyclodextrins, macrocyclic glycopeptide antibiotics (e.g., teichoplanin), polysaccharides, polymers of amino acids (e.g., poly-L-alanine, poly-L-leucine, or poly-L-phenylalanine) are used as chiral selectors in HPLC columns. Even proteins have been used as chiral discriminators [C. Czerwenka, W. Linder, *Anal. Bioanal. Chem.* **2005**, 382, 599].



Stevastelin A

Stevastelins, cyclic → depsipeptides isolated from a culture broth of *Penicillium* sp. NK374186 comprising stevastelin A, B, B3, and C3. They show potent immunosuppressive activity by blocking human T-cell activation, without affecting the phosphatase activity of → calcineurin. This mode of action is different from that of the well-known immunosuppressants → FK506-binding proteins and → cyclosporin A. The stevastelins are expected to be new immunosuppressants, as well as useful biochemical probes [K. Kurosawa et al., *Bull. Chem. Soc. Jpn.* **2006**, 79, 921].

Stichodactyla toxin (ShK), RSCIDTIPKS¹⁰ RCTAFQCKHS²⁰ MKYRLSFCRK³⁰ TCGTC (disulfide bonds: C³–C³⁵/C¹²–C²⁸/C¹⁷–C³²), a 35-peptide (M_r 4055 Da) originally isolated from the sea anemone *Stichodactyla helianthus*. The ShK-neurotoxin inhibits the specific binding of dendrotoxin I to rat brain membranes. ShK acts as a voltage-dependent K⁺ channel (A channel)

blocker, and may become a useful molecular probe for studying potassium channels [J. Pohl et al., *Lett. Pept. Sci.* **1994**, 1, 29; O. Castaneda et al., *Toxicon* **1995**, 33, 603].

Streptavidin, a tetrameric protein (M_r 60 kDa) from *Streptomyces avidinii* with a high affinity to biotin ($K \sim 10^{-15}$ M). Streptavidin is used in various laboratory techniques for detecting biotinylated molecules, and is preferred to \rightarrow avidin due to its more favorable isoelectric point and lack of glycosylation. It belongs to the protein superfamily \rightarrow calycins [N. M. Green, *Methods Enzymol.* **1990**, 184, 51; S. Freitag et al., *Protein Sci.* **1997**, 6, 1157; A. Skerra, T. G. Schmidt, *Methods Enzymol.* **2000**, 326, 271].

Streptokinase, an extracellular protein (415 aa, M_r 47 kDa) produced by various strains of β -hemolytic streptococci. Streptokinase is not generally considered to be a proteolytic enzyme, but is one of the most potent exogenous activators of human \rightarrow plasminogen. Complexes of streptokinase with human plasminogen can hydrolytically activate other plasminogen molecules to \rightarrow plasmin which then dissolves blood clots alone [L. A. Schick, F. J. Castellino, *Biochem. Biophys. Res. Commun.* **1974**, 57, 47; K. W. Jackson, J. Tang, *Biochemistry* **1982**, 21, 6620].

Stresscopin, \rightarrow urocortins.

Stresscopin-related peptides, \rightarrow urocortins.

Structure-based molecular design, *computer-aided molecular design* (CAMD), *computer-aided drug design* (CADD), approaches for lead structure identification and optimization in the drug development process. The rational design of a lead structure in drug development basically relies upon the three-dimensional structure of

the target protein that must be addressed by the drug molecule. Molecular docking algorithms are frequently used to postulate the binding site of a small molecule as a potential ligand. For this purpose, software has been developed, implementing surface complementary matching, fragment growing, random sampling, simulated annealing, and genetic algorithms. However, at least in the early stages of a medicinal chemistry project, an X-ray structure of the target protein is not yet available. Under such circumstances a homology model of the target protein may be used. Such models can be created by computation on the basis of sequence similarities between the protein of interest and a second protein, the structure of which has already been determined. Indirect CADD relies on structure-activity relationship data of ligands of the target for which the 3-dimensional structure is yet unknown. Systematic substituent variation of a lead structure is correlated with biological data, eventually leading to the identification of crucial structural elements that are required for the ligand to achieve high affinity receptor binding (\rightarrow receptor mapping, pharmacophore mapping, ligand-based design). In indirect CADD, conformational analysis is a valuable tool in the design especially of new peptide drugs. \rightarrow Spatial screening may also be employed. Linear, flexible peptides are generally inappropriate for the rational design process as they are usually too flexible and the solution structure can not be determined, e.g., by NMR techniques. Cyclic peptides or peptides that contain conformationally constrained acids (proline, proline analogues, *N*-methyl amino acids, C^α -dialkyl amino acids, etc.) are particularly suited for conformational analysis by NMR spectroscopy in combination with molecular

dynamics simulations. In addition to the structural considerations in the molecular design process, issues such as absorption, delivery, metabolism, excretion, and toxicity can be predicted by ADME/toxicity modeling. CADD strategies can also be used to filter large compound databases or libraries of candidate compounds in the frame of virtual screening (*in-silico* screening). For such purposes, software has been developed capable of analyzing and collecting pharmacophore patterns in a fully automated manner [T. Langer, G. Wolber, *Pure Appl. Chem.* **2004**, 76, 991].

Stuart-Factor, Stuart Prower-Factor, Thrombokinin, Factor X, a serine protease and constituent of the blood coagulation cascade. It is either be activated by factor IX_a (intrinsic pathway) or by Factor VII_a (extrinsic pathway). In complex with Factor V as the cofactor it cleaves prothrombin at Arg-Thr and Arg-Ile to give active thrombin.

Styelins, beside → clavanins, α-helical antimicrobial 32-peptides from the tunicate *Styela clava*. The styelins A–E show considerable sequence homology to *pleurocidins*, antimicrobial peptides of the flounder *Pseudopleuronectes americanus*. Styelin D contains 12 post-translationally modified residues which enhance its bactericidal activity at acidic pH and high salinity [I. H. Lee et al., *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **1997**, 118, 515; R. I. Lehrner et al., *Integr. Comp. Biol.* **2003**, 43, 313].

Substance K, → neurokinins.

Substance P (SP), RPKPQQFFGL¹⁰Ma, an 11-peptide amide exerting a wide spectrum of biological effects. SP is a mammalian member of the → tachykinin family. It belongs to a large number of peptides occurring both in the gastrointestinal tract and in the brain. SP is released from

the precursor protein β-prepro-tachykinin. Tachykinin activity is mediated by the G protein-coupled receptors NK₁, NK₂, or NK₃. Stimulation of the smooth muscle, salivary secretion, and lowering of the blood pressure due to vasodilation are important biological actions, besides other effects mediated preferentially via the NK₁ receptor. SP acts as a neurotransmitter in various brain regions, suppresses the action of morphine and endorphins, and plays a protective role against stress-determined disturbances. From structure–activity relationships it can be concluded that the C-terminal 5-peptide represents the biologically active epitope. Acylated SP-(7–11) compounds are the shortest SP analogues while retaining biological activity. <Glu-Phe-Phe-Gly-Leu-Met-NH₂ is one of the most active analogues in the vasodepressor-response assay. SP plays important roles in pathological processes, such as nociception, inflammation, cancer, and psychiatric disturbances. The development of antagonists, including non-peptide antagonists, has opened new avenues for pharmacological research with high therapeutic importance. *Spantide I*, [D-Arg¹, D-Trp^{7,9}, Leu¹¹] SP is the standard antagonist that binds preferentially to the NK₁ and NK₂ receptors. It shows a weak spasmogenic and a poor histamine-releasing effect [S. von Euler, B. Pernow (Eds.), *Substance P*, Raven Press, New York, **1977**; B. Pernow, *Pharmacol. Rev.* **1983**, 35, 85; Z. Gao, N. P. Peet, *Curr. Medicinal Chem.* **1999**, 6, 374; S. E. Leeman, S. L. Ferguson, *Neuropeptides* **2000**, 34, 249; S. Harrison, P. Geppetti, *Int. J. Biochem. Cell. Biol.* **2001**, 33, 555; D. J. Turner et al., *Ann. Surg.* **2007**, 245, 408].

Substrate mimetic approach, *substrate mimetics-mediated synthesis*, an approach to → protease-catalyzed peptide synthesis using substrates that mimic the specific

amino acid side-chain functionality of the appropriate P1 amino acid (\rightarrow peptidases) in dependence of the catalyzing enzyme. First \rightarrow 4-guanidinophenyl esters (OGp) of acylamino acids also containing proline, D-alanine, or β -alanine in the specificity-determining P₁ position have been used for irreversible trypsin-catalyzed peptide synthesis. By theoretical docking simulations it could be demonstrated that this leaving-group moiety binds in place of the specific basic side-chain functionality of common acyl donors largely independent of its C-terminal amino acid. Acylation of the enzyme by the unspecific acyl residue results from the reverse recognition of these substrates. Consequently, if there are no arginine or lysine residues in the educts to be coupled, peptide ligation occurs irreversibly and independent of the S₁ specificity of the enzyme. Improvements in the synthesis of guanidino- and amidinophenyl esters and their application in trypsin-catalyzed synthesis have initiated an extension of this approach to other arginine-specific proteases such as thrombin and the prokaryotic cysteine protease, clostripain. Moreover, special forms of this new artificial enzyme substrates act also as acyl donors for proteases specific for hydrophobic amino acids such as α -chymotrypsin or subtilisin, and even Glu-specific enzymes such as V8 protease. These results qualify the strategy of substrate mimetics as a powerful concept for programming the enzyme specificity in the direction of a more universal application of proteases in biocatalysis. This approach of protease-mediated ligation has been used successfully for the condensation of \rightarrow peptoid fragments [V. Schellenberger et al., *Biotechnol. Bioeng.* **1991**, 38, 104; F. Bordusa et al., *Angew. Chem. Int. Ed.* **1997**, 36, 2473; B. Yoo, K. Kirshenbaum, *J. Am. Chem. Soc.* **2005**, 127, 17132].

Subtiligase, a double mutant of subtilisin BPN' used for ligation of esterified peptides site-specifically onto the N-terminal amino function of peptides or proteins in aqueous solution (\rightarrow protease-catalyzed peptide synthesis). It has been used for the synthesis of RNase A, and also for cyclization of linear peptide esters [T. K. Chang et al., *Proc. Natl. Acad. Sci. USA* **1994**, 91, 12544; D. Y. Jackson et al., *J. Am. Chem. Soc.* **1995**, 117, 819].

Subtilin, a member of the Type A \rightarrow lantibiotics with a pentacyclic structure similar to \rightarrow nisin. Subtilin is a 32-peptide (M_r 3317 Da) produced from *Bacillus subtilis*, and has antimicrobial activity against both the vegetative cells of a broad range of Gram-positive bacteria as well as against the outgrowth of *Bacillus* spp. and *Clostridium* spp. endospores [R. W. Jack, G. Bierbaum, H.-G. Sahl, *Lantibiotics and Related Peptides*, Springer-Verlag, Berlin, Heidelberg, New York, **1998**; M. Kleerebezem et al., *Peptides* **2004**, 25, 1415].

Suc, succinoyl.

Sulfatation factor, \rightarrow somatomedins.

Super acid-sensitive resin, \rightarrow SASRIN.

Supramolecular nanotubes, tubular peptide nanostructures (\rightarrow peptide-based nanotubes). Such non-covalently connected structures are, e.g., formed by stacking of cyclopeptides with alternating D- and L-configured amino acid building blocks. The planes of the amide groups in the cyclopeptide are oriented perpendicular to the ring plane [M. R. Ghadiri, *Adv. Mater.* **1995**, 7, 675; N. Ashkenasy et al., *Small* **2006**, 2, 99].

Surfactin, a branched cyclic lipopeptide from *Bacillus subtilis*. The 3-hydroxy-12-methyltridecanoic acid, (CH₃)₂CH-(CH₂)₈CH(OH)-CH₂-COOH, is linked via an amide bond to the N-terminal Glu of

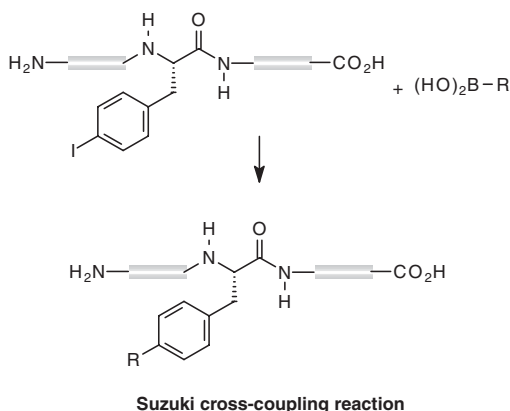
the peptide part Glu-Leu-D-Leu-Val-Asp-D-Leu-Leu, and the cycle is formed by an ester bridge between the carboxy group of the terminal Leu residue to the β -hydroxy group of the tridecanoic acid. Surfactin is the most powerful bio-detergent so far detected, based on its pronounced amphiphilicity. The biosynthesis of surfactin is catalyzed non-ribosomally by the action of a large multienzyme complex consisting of four modular building blocks, termed surfactin synthetase. Surfactin shows also promising properties as an antiviral and anti-Mycoplasma agent [F. Peypoux et al., *Appl. Microbiol. Biotechnol.* **1999**, 51, 553].

Suzukacillin peptides (SZ), a peptaibol antibiotic, termed suzukacillin A, was first isolated from the culture broth of the mold *Trichoderma viride*, strain 1037, exhibiting membrane modifying and lysing properties similar to those of \rightarrow alamethicin. Later, a peptide mixture named SZ-A was obtained by crystallization from crude SZ which was isolated from the culture broth of *T. viride*, strain 63 C-I. Two major groups of peptides named SZ-A and SZ-B could be separated. The major peptide SZ-A4 (21% of all peptides) has the sequence: Ac-Aib-Ala-Aib-Ala-Aib-Ala-Gln-Aib-Lx-Aib¹⁰-Gly-Aib-Aib-Pro-Vx-Aib-Vx-Gln-Gln-Pheol

(Lx: L-Leu or D-Leu; Vx: L-Val or D-Iva; Pheol: L-phenylalaninol). In addition, 15 acetylated SZ- peptides with C-terminal alcohol moieties have been characterized [G. Jung et al., *Biochim. Biophys. Acta* **1976**, 433, 164; C. Krause et al., *J. Peptide Sci.* **2006**, 12, 321].

Suzuki cross-coupling reaction, the Pd-catalyzed cross-coupling of an iodoaromatic moiety with an arylboronic acid. The Suzuki reaction has been employed to modify shorter peptides and the WW domain portion of the protein Pin1 (residues 6–39) (\rightarrow peptidyl prolyl *cis/trans* isomerases) in aqueous solution (Na_2PdCl_4 as the catalyst) under mild conditions, without changing its structure and function. Conjugation of fluorophores was achieved by coupling appropriate arylboronic acid derivatives to a *p*-iodophenylalanine residue in the peptide [S. Kotha, K. Lahiri, *Biopolymers* **2003**, 69, 517; A. Ojida et al., *Tetrahedron Lett.* **2005**, 46, 3301].

Sweet proteins, proteins and peptides that elicit sweet taste. Thaumatin, monellin, mabinlin, brazzein, egg lysozyme, and neoculin (previously named curculin) have been identified as sweet-tasting proteins. New G protein-coupled receptors have been



identified as receptors of sweet taste (T1R1, T1R2, and T1R3). Heterodimers of T1R2 and T1R3 have been proposed to constitute a functional sweet-taste receptor. Sucrose, low-molecular-weight sweeteners (e.g., acesulfam K, saccharin, \rightarrow aspartame, cyclamate), and the sweet-tasting proteins neothame, monellin and thaumatin similarly interact with the same receptor. Interestingly, there is no sequence homology between the sweet-tasting proteins, and also little structural similarity. It was suggested recently on the basis of molecular modeling studies that the sweet-taste receptor has multiple binding sites for such agonists. The molecular interaction of the receptor with sweet proteins seems to be different from that of low-molecular-weight sweeteners. Moreover, knockout of TRPM5 (a taste TRP ion channel) or PLC2 (a phospholipase C selectively expressed in taste tissue) abolishes sweet, amino acid, and bitter taste reception, indicating a complex interplay between different types of taste receptor [P. A. Temussi, *Cell. Mol. Life Sci.* **2006**, 63, 1876; Masuda, N. Kitabatake, *J. Biosci. Bioeng.* **2006**, 102, 375; R. K. Palmer, *Mol. Interv.* **2007**, 7, 87].

Switch peptides, isopeptide intermediates obtained by SPPS. The method is applicable to \rightarrow difficult sequences arising from aggregation phenomena. It relies on the synthesis of Ser or Thr isopeptide intermediates with a final O-N acyl migration step. The principle is identical to the \rightarrow O-acyl isopeptide method, also termed \rightarrow click peptide or \rightarrow depsipeptide peptide method developed independently by different groups [M. Mutter et al., *Angew. Chem. Int. Ed.* **2004**, 43, 4172; G. Tuchscherer et al., *Biopolymers* **2007**, 88, 239].

Symmetric anhydrides, highly reactive amino acid derivatives suitable for pep-

tide bond formation. They are readily obtained upon reaction of two equivalents of N^α -protected amino acid with one equivalent of carbodiimide or phosgene. Symmetric anhydrides may be isolated, but can also be used for peptide coupling, without further purification. The applicability of the method suffers from the fact that only a maximum yield of 50% referring to the N^α -protected amino acid can be obtained.

Synaptojanin 1, a phosphatidylinositol 5'-phosphatase involved in clathrin-mediated endocytosis [P. S. McPherson et al., *Nature* **1996**, 379, 353].

Syndecan-3, *N-syndecan*, a member of the syndecan family of membrane-intercalated proteoglycans. Syndecan-3 is a transmembrane heparan sulfate proteoglycan expressed predominantly in the nervous system in a developmental manner. It has been suggested to have a function in the development and plasticity of neuronal connections by linking extracellular signals to the regulation of the cytoskeleton. In addition, it has been reported that syndecan-3 modulates the activity of \rightarrow agouti protein and \rightarrow agouti-related protein (AGRP). It is an ancillary protein of the \rightarrow melanocortin system. Syndecan-3 has been shown in pharmacological assays to augment AGRP antagonism of α -MSH at the \rightarrow melanocortin receptor MC4R, suggesting that syndecan-3 might function as an AGRP co-receptor [O. Reizes et al., *Cell* **2001**, 106, 105; M. Kaksonen et al., *Mol. Cell. Neurosci.* **2002**, 21, 158; O. Reizes et al., *Ann. N. Y. Acad. Sci.* **2003**, 994, 66].

Synucleins, a family of small, soluble proteins expressed primarily in neural tissues and in certain tumors. This family comprises α -, β -, and γ -synuclein. All members have in common a highly conserved α -helical lipid-binding motif. They occur

not outside vertebrates, although they show some conserved structural similarities with plant "late-embryo-abundant" proteins. α -Synuclein (140 aa) is an acidic neuronal protein, highly expressed in brain tissues, and is primarily found in the presynaptic terminals of neurons. Furthermore, it is expressed in hematopoietic cells, and also found in other tissues, e.g., heart, skeletal muscle, placenta, and pancreas, but it is less abundant than in the brain. α -Synuclein has been detected as a major component of intracellular fibrillar protein deposits (Lewy bodies) in several neurodegenerative diseases, such as Parkinson's disease, \rightarrow Alzheimer's disease, diffuse Lewy body disease, and multiple systemic atrophy. Despite progress having been made in understanding the pathological function of α -synuclein in neurodegenerative illnesses, its biological role remains to be clarified. β -Synuclein lacks 11 central hydrophobic residues compared with its family members, and shows the properties of a random coil. γ -Synuclein occurs primarily in the peripheral nervous system and retina, but its expression in breast tumors functions as a marker for tumor progression. Interestingly, it has been reported that the synucleins are able to penetrate into live cells [R. Jakes et al., *FEBS Lett.* **1994**, 345, 27; J. M. George, *Genome Biol.* **2002**, 3, 3002; V. N. Uversky et al., *J. Biol. Chem.* **2002**, 277, 11970; K. J. Ahn et al., *J. Neurochem.* **2006**, 97, 265].

Syringomycins, small cyclic lipodepsipeptides produced by *Pseudomonas syringae* pv. *Atrofaciens*. They are composed of a closed ring of nine amino acid building blocks bonded to a fatty acid hydrocarbon tail. The main members are syringomycin E

(SE), syringomycin G (SG), syringomycin 25A (S25A), and syringomycin 25B (S25B). The injection of both SE and S25A in wheat leaves caused necrotic symptoms. SE formed voltage-sensitive ion channels, and altered protein phosphorylation and ATPase activity [V. Vassilev et al., *Plant Physiol.* **1996**, 45, 316; A. Feign et al., *J. Membr. Biol.* **1996**, 149, 41].

Systemin, parent compound of a family of functionally related plant peptides with 15–20 amino acids. The tomato systemin (Lycopersicon esculentum systemin, LeSys, AVQSKPPSKR¹⁰DPPKMQTD) was the first peptide signaling molecule to be identified in plants. It is involved in the attenuation of defense responses as a consequence of wounding by herbivorous insects. Systemin was first isolated in 1991 from the leaves of tomato plants, based on its ability to induce an accumulation of protease inhibitors that interfere with the protein digestion of attacking pests. Interestingly, the inducing activity of systemin is not only restricted to protease inhibitors, but also extends to the expression of about 20 proteins involved in plant defense. In the meantime, similar peptides have been found in other species of the Solanaceae that differ only in some positions of the sequence from LeSys. Systemin is first formed as a larger precursor and, after release from prosystemin, is secreted into the apoplast in response to the wound stimulus. A second subfamily is formed by the hydroxyproline-rich systemin glycopeptides (HypSys) [C. A. Ryan, G. Pearce, *Annu. Rev. Cell Dev. Biol.* **1998**, 14, 1; A. Schaller, *Plant Mol. Biol.* **1999**, 40, 763; G. I. Lee, G. A. Howe, *Plant. J.* **2003**, 33, 567].

T

T20, also called *enfuvirtide* and **Fuzeon®**, Ac-YTSLIHSLIE¹⁰ESQNQQEKNE²⁰QQLLELNKWA³⁰SLWNWFa, a synthetic 36-peptide amide acting as an antiviral drug substance. T20 is derived from the ectodomain of HIV-1 gp41, and has been the first representative of a family of anti-retroviral agents that inhibit viral entry. It binds to the first heptad-repeat region (HR1) of envelope glycoproteins 41 of human immunodeficiency virus type 1 (HIV-1), a protein that is critical for the fusion of the virus with the cell membrane. T20 is currently synthesized by a combination of solid- and solution-phase procedures in a production scale of nearly 4000 kg a year involving over 100 chemical steps. In Phase 1 and 2 clinical trials, T20 reduced the plasma viral load and was tolerated when given as short-term monotherapy or as long-term combination therapy [C. Wild et al., *AIDS Res. Hum. Retroviruses* **1993**, 9, 1051; A. B. Lazzarin et al., *N. Engl. J. Med.* **2003**, 348, 2186; B. L. Bray, *Nat. Rev. Drug Discov.* **2003**, 2, 587; V. Marx, *Chem. Eng. News* **2005**, 83, 16].

Tachykinins (TK), preferentially 10- or 11-peptides characterized by a conserved C-terminal pentapeptide amide consisting of -Phe-Xaa-Gly-Leu-Met-NH₂ (Xaa: Phe, Tyr, Val or Ile), but their length ranges between 9 and 42 aa. The tachykinin peptides are phylogenetically ancient and well conserved throughout evolution. Numerous structurally related tachykinin peptides such as *tachykinin-related peptides (TKRP)* and *invertebrate tachykinins (inv.-TK)* have been discovered from mammals, birds,

reptiles, amphibia, and fish, as well as from invertebrates (→ tachykinin family). The discovery of a third preprotachykinin gene (TAC4) has more than doubled the number of tachykinins. In addition, three orphan tachykinin gene-related peptides are characterized on TAC4, in rabbit (endokinin-1), and in humans (→ endokinins). The TK are actively involved in the central and peripheral nervous systems, as well as in the cardiovascular and immune systems [H. Satake et al., *Zool. Sci.* **2003**, 20, 533; J.-C. Beaujouan et al., *Peptides* **2004**, 25, 339; N. M. Page, *Cell. Mol. Life Sci.* **2004**, 61, 1652; L. Liu, E. Burcher, *Peptides* **2005**, 26, 1369; N. M. Page, *Peptides* **2005**, 26, 1356].

Tachykinin family, one of the largest peptide families occurring in nature. The sequence of tachykinins from mammals, birds and reptiles are quite similar, whereas tachykinin peptides from amphibians and fish are fairly diverse. The → mammalian tachykinins comprise → substance P (SP), the → neurokinins A (NKA) and B (NKB), and two elongated versions of NKA, neuropeptide γ (NP γ) and neuropeptide K (NPK), the → endokinins A–D, and → hemokinin-1. Members of the non-mammalian tachykinins are, for example, → bufokinin, → eledoisin, → physalaemin, → kassinin, and → uperolein. A characteristic feature of the tachykinins is the conserved C-terminal pentapeptide amide motif (→ tachykinins). The amino termini of the tachykinins are quite variable, but classes of vertebrate tachykinins with structural similarities

have been termed as SP-like, NKA-like, and NP γ -like tachykinins. Multiple receptors, termed NK₁, NK₂, and NK₃, of the mammalian peptides belong to the superfamily of G protein-coupled receptors that have distinct pharmacological features. The only known tachykinin that shows high affinity for both NK₁ and NK₂ receptors and low affinity for the NK₃ binding site is \rightarrow scyliorhinin I. Multiple isoforms of the toad NK₁ receptor and their specific pharmacological properties have been elucidated, but the existence of orthologues of NK₂ and NK₃ receptors is still unresolved [V. Erspamer et al., *Peptides* **1981**, 2 (Suppl. 2), 7; C. J. Swain, in: *Progress in Medicinal Chemistry*, G. P. Ellis, D. K. Luscomber, A. W. Oxford (Eds.), p. 57, Elsevier, Amsterdam, **1998**; Z. Gao, N. P. Peet, *Curr. Medicinal Chem.* **1999**, 6, 374; H. Satake et al., *Zoolog. Sci.* **2003**, 20, 533; J.-C. Beaujouan et al., *Peptides* **2004**, 25, 339; N. M. Page, *Peptides* **2005**, 26, 1356; L. Liu, E. Burcher, *Peptides* **2005**, 26, 1369].

Tachykinin gene-related peptides, \rightarrow tachykinins.

Tachyplesins, bicyclic peptides containing 16 to 18 residues from the horseshoe crab. They are processed from a 77-residue precursor protein. *Tachyplesin I*, KWCFRVCYRG¹⁰ICYRRCRa (disulfide bonds: C³–C¹⁶/C⁷–C¹²), and the other tachyplesins contain two disulfide bridges which stabilize a rigid structure of two antiparallel β -sheets and a β -turn segment. Tachyplesins are stored in high concentrations in the crab hemocytes. They are active against Gram-negative and Gram-positive bacteria. Tachyplesins show similarity in size, charge and overall structure to the \rightarrow protegrins. In 2005, it was reported that tachyplesin functions not only as an antimicrobial compound, but also as a secondary

secretagogue of LPS-induced hemocyte exocytosis, leading to the amplification of the innate immune reaction at sites of injury [S. Iwanaga et al., in: *Antimicrobial Peptides*, H. G. Boman, J. Marsh, J. A. Goode (Eds.), p. 160, Ciba Foundation Symposium 186, Chichester, John Wiley & Sons, **1994**; K. Matsuzaki, *Biochim. Biophys. Acta* **1999**, 1462, 1; A. Ozaki et al., *FEBS J.* **2005**, 272, 3863].

Tagging, a method of library encoding by attachment of readable “tags” to the resin bead at each coupling step of synthesis (\rightarrow peptide libraries).

Talpha 1, \rightarrow thymosin α_1 .

Tamandarins, cyclodepsipeptides (\rightarrow depsipeptides) isolated from an ascidian of the family *Didemnidae*. The name is attributed to the Brazilian village of Tamandare, near where the organisms were collected. The tamandarins consist of nine residues forming a 21-membered ring containing two ester linkages and a three-residue chain. The structures of tamandarin A and B closely resemble that of the \rightarrow didemnins, and have been confirmed by total synthesis. Tamandarin A exhibits very similar activities against human cancer cell lines compared to didemnin B. However, it is expected to be extremely toxic like didemnin B [B. Liang et al., *Org. Lett.* **1999**, 1, 1319; H. Vervoort et al., *J. Org. Chem.* **2000**, 65, 782; M. M. Joullie et al., *Tetrahedron Lett.* **2000**, 41, 9373].

TANDEM, *Triostin A N-Demethylated*, a synthetic analogue of \rightarrow triostin A. TANDEM is a bisintercalator with the capability to bind to 5'-TpA sequences on DNA by DNase footprinting [T. L. Ciardelli et al., *J. Am. Chem. Soc.* **1978**, 100, 7648; J. P. Malkinson et al., *J. Org. Chem.* **2005**, 70, 7654].

TASP, template-assembled synthetic protein.

TAT(47–58)peptide, YGRKKRRQRR¹⁰RD, a positively charged arginine-rich 12-peptide derived from the 86-aa protein TAT that is involved in the replication of human immunodeficiency virus type 1 (HIV-1). TAT(47–58)peptide is known for a peptidic delivery factor as a → cell-penetrating peptide on mammalian cells. Furthermore, TAT(47–58)peptide shows antifungal activity against pathogenic fungal cells without hemolytic effect on human erythrocytes [E. Vives et al., *J. Biol. Chem.* **1997**, 272, 16010; H. J. Jung et al., *Biochem. Biophys. Res. Commun.* **2006**, 345, 222].

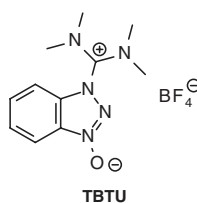
TAT fragment, → cell-penetrating peptides.

TAT-mediated transduction, translocation of peptides and proteins across cell membranes mediated by TAT protein. Macromolecules in excess of 500 Da cannot enter cells by passively crossing the cell membrane due to their size and hydrophilic nature. However, many proteins and peptides having evolutionary selected to perform specific functions are an therapeutic agent to treat a variety of human diseases. In 1994, the first example of the possible therapeutic usefulness offered by TAT-mediated protein transduction were demonstrated by delivery of fusion proteins by conjugation to the TAT transduction domain and other protein transduction domains (→ cell penetrating peptides). The addition of a cationic 9-peptide from the HIV-1 TAT protein to the sequence brings about rapid entry into cells and tissues. The TAT protein (Trans-acting Activator of Transcription) can translocate easily across mammalian cell membranes, and may be used to transport macromolecular cargo into cells for the treatment of multiple diseases, including cancer and stroke.

TAT-fusion proteins have been suggested to be internalized by endocytosis (lipid raft-dependent macropinocytosis) [E. L. Snyder, S. F. Dowdy, *Pharm. Res.* **2004**, 21, 389; J. S. Wadia, S. F. Dowdy, *Adv. Drug Deliv. Rev.* **2005**, 57, 579].

TBAF, tetrabutylammonium fluoride.

TBTU reagent, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, a coupling reagent derived from *N*-hydroxybenzotriazole (HOBt). However, X-ray crystallographic studies revealed that it exists, at least in the solid state, as a zwitterion and is not actually a uronium salt [R. Knorr et al., *Tetrahedron Lett.* **1989**, 30, 1927; L. A. Carpino et al., *Angew. Chem. Int. Ed.* **2002**, 41, 441].



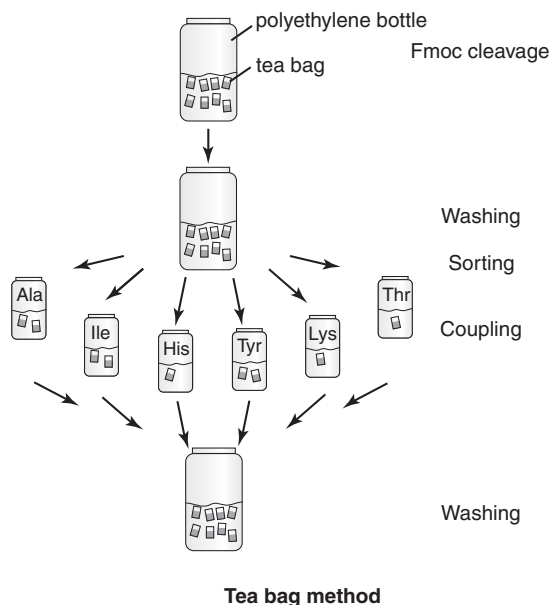
Tce esters (OTce), R-CO-OCH₂CHCl₃, 2,2,2-trichloroethyl esters suitable for protection of the C-terminus in solution-phase peptide synthesis. They can be hydrolyzed under mild conditions that are compatible with acid-labile *N*^α-protecting groups [G. Just, K. Grozinger, *Synthesis* **1976**, 457].

TCL, thin-layer chromatography.

TCR antagonists, peptides capable of binding → MHC proteins and specifically inhibit T-cell activation induced by antigens [S. Vukmanovic, F. R. Santori, *Cell. Immunol.* **2005**, 233, 75].

TEA, triethylamine.

Teabag method, an approach in → combinatorial peptide synthesis that uses parallel



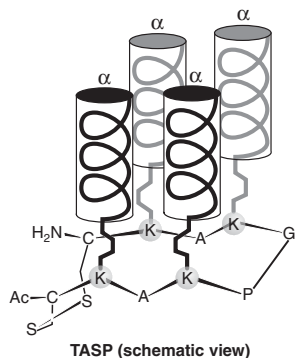
→ SPPS to obtain different compounds on resin material secluded in a porous polypropylene bag. The number of different compounds to be synthesized equals the number of teabags used. Cleavage of temporary protecting groups and washing steps are performed simultaneously for all teabags in one container. The teabags are then sorted, appropriately combined, and coupling of the corresponding amino acid is performed in separate reaction vessels. The method is appropriate for Boc and Fmoc tactics, and usually provides between 30 and 50 mg of each peptide, enough to perform purification steps before subjecting the library to biological testing [R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131].

Teduglutide, ALX-0600, a → dipeptidyl peptidase IV -resistant GLP-2 (→ glucagon-like peptides) analogue improving intestinal function in short bowel syndrome patients [P. B. Jeppesen et al., *Gut* **2005**, *54*, 1224].

Telavancin (TD-6424), a second-generation semisynthetic lipoglycopeptide antibacterial agent based on a → vancomycin scaffold. It exhibits potent *in-vitro* antibacterial action against a broad array of important Gram-positive pathogens [J. L. Pace, G. Yang, *Biochem. Pharmacol.* **2006**, *71*, 968].

Template-associated synthetic proteins (TASP), proteins that have been designed and synthesized *de novo*. Artificial tertiary structures can be constructed by covalent attachment of secondary structure building blocks, e.g., β -sheets, α -helices, and turns, to a topological template. This results in a non-linear architecture of protein modules that is nevertheless able to mimic native proteins. The combination of different secondary structure motifs in TASP provides, e.g., $\beta\alpha\beta$ -structures, helix-bundles, or β -barrel tertiary structures. The design of TASP makes extensive use of molecular modeling techniques. Solid-phase synthesis and spot synthesis have been used to obtain TASP [G. Tuchscherer, M. Mutter,

J. Peptide Sci. **1995**, 1, 3; W. Haehnel, *Mol. Divers.* **2004**, 8, 219].



Template-mediated ligation, an approach to bring two peptide fragments into close proximity. The N-terminus of one peptide and C-terminus of the other peptide are attached to a template, and consequently close to each other so that they can form a peptide bond. The basic principle was created by Brenner et al. using a salicylamide template based on a base-catalyzed intramolecular rearrangement and has been later exploited in \rightarrow thiol capture ligation [M. Brenner et al., *Helv. Chim. Acta* **1957**, 40, 1497].

Temporary protecting groups, \rightarrow intermediary protecting groups usually used for the N^α -amino function of amino acid building blocks during peptide synthesis according to C \rightarrow N strategy such as stepwise \rightarrow SPPS.

Temporins, a group of antibiotic peptide amides isolated from the skin of the European red frog *Rana temporaria* composed of 10–13 aa. The majority of the temporins A–L and temporin-like peptides contain a single basic residue (Arg or Lys), but the primary structure is highly variable. *Temporin A*, TA, FLPLIGRVLS¹⁰GILa, is the most well-known member of these peptides. TA exhibits antibacterial and antifungal activ-

ities. TA is capable to form a transmembrane pore via a barrel-stave mechanism or to form a “carpet” on the membrane surface via a “carpet-like” model. Generally, the temporins are anti-infective peptides with expanding properties [M. Simmaco et al., *Eur. J. Biochem.* **1996**, 242, 788; M. L. Mangoni et al., *Eur. J. Biochem.* **2000**, 267, 1447; W. Kamysz et al., *J. Peptide Sci.* **2006**, 12, 533; M. L. Mangoni, *Cell. Mol. Life Sci.* **2006**, 63, 1060].

Tentoxin, cyclo-(-MeAla-Leu-Me Δ^Z Phe-Gly-), a phytotoxic cyclic peptide isolated from the phytopathogenic fungus *Alternaria alternata*. Tentoxin is a potential natural herbicide that induces chlorosis in many plants, and binds specifically to the soluble part CF₁ of the chloroplastic proton ATPase. At low concentration, tentoxin is a powerful inhibitor, whereas above 10 μ M it stimulates the enzyme both *in vitro* and *in vivo* [M. G. Klotz, *Physiol. Plant.* **1988**, 74, 575; C. Sigalat et al., *FEBS Lett.* **1995**, 368, 253].

Teneurins, a family of transmembrane proteins in vertebrates expressed during pattern formation and morphogenesis. They are homologous to the *Drosophila* pair-rule gene product. Four vertebrate teneurins and a *Caenorhabditis elegans* homologue have been identified to date. They are characterized by an intracellular domain containing polyproline motifs and a long extracellular domain consisting of eight EGF-like repeats, a region of conserved cysteines and unique YD-repeats. The teneurins play fundamental roles in development [B. P. Rubin et al., *Develop. Biol.* **1999**, 216, 195; R. P. Tucker et al., *Int. J. Biochem. Cell Biol.* **2007**, 39, 292].

Teneurin C-terminal associated peptides, a family of neuropeptides with structural similarity to \rightarrow corticoliberin and \rightarrow

calcitonin family. They play a role in the regulation of stress and anxiety [D. A. Lovejoy et al., *Gen. Comp. Endocrinol.* **2006**, *148*, 299].

Teprotide, → ACE inhibitors.

Ternatin, cyclo-[D-*allo*-Ile-MeAla-MeLeu-Leu-MeAla-D-MeAla-(2*R*,3*R*)-3-hydroxy-Leu-], a highly *N*-methylated cyclic 7-peptide isolated from the mushroom *Coriolus versicolor*. Besides the reported antibacterial or antimicrobial activity, (+)-ternatin potently inhibits fat accumulation against 3T3-L1 murine adipocytes [K. Shimokawa et al., *Tetrahedron Lett.* **2006**, *47*, 4445; K. Shimokawa et al., *Bioorg. Med. Chem. Lett.* **2007**, *16*, 4447].

Tertiapin, ALCNCNRIII¹⁰PHMCWKKCKG²⁰Ka (disulfide bonds: C³–C¹⁴/C⁵–C¹⁸/), a 21-peptide amide from the honey bee (*Apis mellifera*). It acts as a blocker of special K⁺ channels. Tertiapin blocks the G protein-gated channel (GIRK1/4) and the ROMK1 channel, with nanomolar affinity. In addition, a potent and selective inhibition of muscarinic K⁺ channels in cardiac myocytes by tertiapin was reported in 2000 [J. Gaultie et al., *Eur. J. Biochem.* **1976**, *61*, 369; W. Jin, Z. Lu, *Biochemistry* **1998**, *37*, 13291; X. Xu, J. W. Nelson, *Proteins Struct. Funct. Genet.* **1993**, *17*, 124; H. Kitamura et al., *J. Pharmacol. Exp. Ther.* **2000**, *293*, 196].

Tertiary amide bonds, amide bonds without a hydrogen substituent at the nitrogen atom. Tertiary amide bonds are found in peptides with proline and *N*-alkyl amino acids, giving rise to a higher propensity for *cis*-peptide bonds (→ peptide bond).

Tertiary structure, the three-dimensional arrangement of secondary structure elements in a protein. Tertiary structure formation is nucleated by supersecondary

structure elements, such as the helix-turn-helix motif, β -hairpin motif, Greek key motif, and $\beta\alpha\beta$ motif.

Textilins (Txln), Kunitz-type serine protease inhibitors from the Australian Common Brown snake *Pseudonaja textilis textilis*. To date, six peptides consisting of ~60 aa have been identified by cloning from venom-gland cDNA. Txln-1 contains 59 aa, and has been suggested as an alternative to → aprotinin for use as an antibleeding agent in surgical procedures [P. P. Masci et al., *Blood Coagul. Fibrinolysis* **2000**, *11*, 385; E.-K. I. Millers et al., *Acta Crystallogr.* **2006**, *F62*, 642].

Tfa, trifluoroacetyl.

TFA, trifluoroacetic acid.

TFE, trifluoroethanol.

TFFH reagent, tetramethyl fluoroformamminium hexafluorophosphate, [(Me₂N)₂CF]⁺PF₆[–], a non-hygroscopic, stable salt suitable for generating acyl fluoride *in situ* (→ Fmoc amino acid fluorides), but also applicable as coupling reagent for solution- or solid-phase peptide synthesis [L. A. Carpino, A. El-Faham, *J. Am. Chem. Soc.* **1995**, *117*, 5401].

TFMSA, trifluoromethanesulfonic acid.

TGF, transforming growth factor.

TH, thymus hormone.

THALWHT, H-Thr-His-Ala-Leu-Trp-His-Thr-OH, a synthetic 7-peptide obtained from a phage display library for the targeting of human airways epithelia [P. J. Jost et al., *FEBS Lett.* **2001**, *489*, 263].

Thanatin, an antifungal 21-peptide produced by *Podisus maculiventris*. It is non-hemolytic and active against *F. oxysporum* and *A. fumigatus* [P. Fehlbaum et al., *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 1221].

Theonellamide F, a bicyclic dodecapeptide isolated from a marine sponge, genus *Theonella*, found at Hachijo Islands. It inhibits the growth of various pathogenic fungi, together with cytotoxicity against L 1210 and P388 leukemia cells [S. Matsunaga et al., *J. Am. Chem. Soc.* **1989**, *111*, 2582; T. Shioiri, Y. Hamada, *Synlett* **2001**, 184].

Theonellapeptolides, a family of tridecapeptide lactones (\rightarrow depsipeptides) isolated from an Okinawan marine sponge *Theonella swinhoei*. The members Ia–e and IId containing high amounts of D-amino acids, N-methyl amino acids, and β -amino acids exhibit cytotoxicity, ion-transport activity for Na⁺ and K⁺ ions, and Na⁺/K⁺-ATPase inhibitory activity. Other theonellapeptolides (III series) exhibiting cytotoxicity have also been isolated from a New Zealand deep water sponge, *Lamellomorpha strongylata* [M. Kobayashi et al., *Chem. Pharm. Bull. (Tokyo)* **1994**, *42*, 1410; S. Li et al., *J. Nat. Prod.* **1998**, *61*, 724; M. C. Roy et al., *Tetrahedron* **2000**, *46*, 9079].

THF, tetrahydrofuran.

Thin-layer chromatography, a separation technique based on a thin layer of solid sorbent. Thin-layer chromatography includes the classical technique of paper chromatography, where the different constituents of a mixture are separated by an eluent on a strip of chromatography paper. The method has been largely replaced by silica gel thin-layer chromatography. A layer of finely ground silica gel or chemically modified silica gel (reversed-phase material) is attached to either a glass plate or an aluminum foil as the support. Thin-layer chromatography basically relies on the different adsorption behaviors of the components of a mixture [P. E. Wall, *Thin-Layer Chro-*

matography: A Modern Practical Approach, Springer-Verlag, **2005**].

Thiocarboxy anhydrides, *N*-thiocarboxy anhydrides, **NTA**, the sulfur analogues of the \rightarrow *N*-carboxy anhydrides (NCA). Because of the higher stability of the corresponding thiocarbamate salts, NTA are more suitable for peptide syntheses than NCA. Acylation reactions with NTA proceed at pH 9–9.5, which prevents the hydrolysis to give hydantoins. Trifunctional amino acids (except lysine and cysteine) do not require side-chain protection. This method has been used for the assembly of several segments of the ribonuclease S-protein that were then combined using the azide method to give the full-length S-protein [R. Hirschmann, R. G. Denkwalter, *Naturwissenschaften* **1970**, *57*, 145].

Thiocarboxy segment condensation, a method for the condensation of peptide segments relying on a C-terminal thiocarboxylate moiety. A C-terminal thiocarboxy group (R-COSH) of an unprotected peptide fragment synthesized by Boc/Bzl SPPS can be selectively activated by silver ions, without affecting side-chain carboxy groups. Application of the method is limited, because thiocarboxylic acids are not stable against oxidation and hydrolysis. Moreover, free side-chain amino groups are prone to react with the activated thiocarboxy group, and peptides containing Cys are not accessible [J. Blake, C. H. Li, *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 1556].

Thioester, derivatives of a carboxylic group obtained, e.g., upon reaction with a thiol. Thioesters are a class of active esters, they readily react with, e.g., amine nucleophiles. C-terminal thioesters of a peptide or protein are important intermediates in \rightarrow

chemical ligation and \rightarrow biochemical protein ligation.

Thioester-forming ligation, the ligation of two unprotected peptide fragments forming a thioester instead of an amide bond between them. It relies on nucleophilic displacement of bromide in an *N*-terminal bromoacetyl residue by a C-terminal thio-carboxylate (R-COSH). Protein analogues have been obtained by this method. However, the thioester bond present in such proteins is unstable above pH 7.

Thioether protection, protection of the methionine thioether side-chain functionality to avoid alkylation and oxidation. The thioether moiety does not cause severe complications during the introduction of amino- or carboxy-protecting groups and coupling reactions. Oxidation to the sulfone takes place only under drastic conditions, but methionine *S*-oxide formation occurs simply on prolonged exposure to air. Methionine is normally used both in Boc and in Fmoc chemistry, without special side-chain protection. Oxidation is avoided in Fmoc chemistry by adding ethyl methyl-sulfide or thioanisole during cleavage and deprotection procedures.

Thiol capture ligation, a variant of \rightarrow template-mediated ligation used for amide bond formation between two unprotected peptide fragments. According to Kemp, a 4-hydroxy-6-mercaptodibenzofuran template with a hydroxy and a thiol substituent has been employed. One peptide is connected with its C-terminus to the hydroxyl substituent, while the other peptide containing an *N*-terminal Cys residue is connected to the template thiol across a disulfide bond. This brings the *N*-terminus of one peptide and C-terminus of the other peptide into close proximity, and the amide bond-forming step occurs as a very rapid in-

tramolecular acyl transfer reaction [D. S. Kemp, *Biochemistry* **1981**, 20, 1793; J. P. Tam et al., *Biopolymers* **2001**, 60, 194].

Thiol protection, masking of the Cys thiol functionality. The high nucleophilicity, the ease of oxidation, and the acidic character of the cysteine thiol group require selective, semipermanent blocking of this functional group during all synthetic operations. Thiol groups of Cys residues often have to be protected to accomplish selective disulfide formation. If more than one intramolecular disulfide bond is present in the target peptide, even orthogonal thiol protecting groups are required. Benzyl and substituted benzyl derivatives (Bzl, Bzl(4-Me), Bzl(4-MeO)) as well as diphenylmethyl (Dpm) and trityl (Trt) groups are frequently used besides acetamidomethyl (Acm), trimethylacetamidomethyl (Tacm), *tert*.-Butyl (*t*Bu), and *tert*.-Butylthio (*t*BuS). *S*-protected Cys derivatives are often prone to racemization, β -elimination, oxidation, and *S*-alkylation [M. Pons et al., *Synlett* **1999**, 172].

Thionins, *PR-13 proteins*, a peptide family of antimicrobial plant proteins containing 45–47 aa with two antiparallel α -helices and an antiparallel double-stranded β -sheet with six to eight cysteines forming disulfide bridges. They constitute an important family of plant toxins showing antifungal and antibacterial activities. Thionins occur in the seeds, stems, roots, and leaves of several plant species, and are classified according to their number of cysteines present [H. Bohlmann, K. Apel, *Annu. Rev. Plant Physiol.* **1991**, 42, 227; L. C. van Loon, E. A. van Strien, *Physiol. Mol. Plant Pathol.* **1999**, 55, 85].

γ -Thionins, a multifunctional class of plant defense proteins with growth inhibition activity toward pathogens. The small cationic

peptides can be classified into four main groups according to their specific functions. γ -Thionins are capable of inhibiting digestive enzymes or acting against bacteria and/or fungi [P. B. Pelegrini, O. L. Franco, *Int. J. Biochem. Cell Biol.* **2005**, *37*, 2239].

Thiopeptide antibiotics, *thiazolyl peptides*, naturally occurring sulfur-containing, highly modified, macrocyclic peptides. They share a number of structural motifs, including several heterocycles such as thiazoles, a dehydropiperidine, a pyridine, oxazoles, and indoles. Nearly all of the thiopeptide antibiotics act as inhibitors of protein synthesis in bacteria. They are secondary metabolites produced by actinomycetes, largely by the genus *Streptomyces*. A representative member of this family is \rightarrow thiostrepton [M. C. Bagley et al., *Chem. Rev.* **2005**, *105*, 685].

Thiostrepton, an important member of the \rightarrow thiopeptide antibiotics because of its biological and medical value. It was first isolated as early as 1954 from *Streptomyces azureus*. It is used in animal health care as a topical antibiotic. However, its application in humans is limited by its low solubility and bioavailability which led to development of drug resistance by the proliferating bacteria. The total synthesis was described in 2005 [Y. Xing, D. F. Draper, *Biochemistry* **1996**, *35*, 1581; K. C. Nicolaou et al., *J. Am. Chem. Soc.* **2005**, *127*, 11159].

Thiotemplate mechanism, the central principle of \rightarrow non-ribosomal peptide synthesis. Non-ribosomal peptide synthetases are multienzyme complexes where every single reaction step in the synthesis of the final product is performed by a specialized protein module. The growing peptide chain is connected to the single modules across a thioester bond. The transfer

of the thioester-activated C-terminus from one module to the amino group of the adjacent amino acid thioester bound to the next module results in a stepwise elongation of the peptide chain [M. A. Marahiel et al., *Chem. Rev.* **1997**, *97*, 2651].

Thioviridamide, a branched cyclopeptide containing five thioamide bonds isolated from the fermentation broth of an actinomycete identified as *Streptomyces olivoviridis*. It consists of 11 amino acids, including two novel amino acid building blocks, β -hydroxy- N^π, N^τ -dimethylhistidinium and S-(2-aminovinyl)cysteine, and an N-terminal 2-hydroxy-2-methyl-4-oxopentanoyl group. Thioviridamide has been reported to induce apoptotic cell death selectively in 3Y1 rat fibroblasts transformed with adenovirus oncogenes [Y. Hayakawa et al., *J. Antibiot.* **2006**, *59*, 6].

Threonine (Thr, T), L-threo- α -amino- β -hydroxybutyric acid, $\text{H}_3\text{C}-\text{CH}(\text{OH})-\text{CH}(\text{NH}_2)-\text{COOH}$, $\text{C}_4\text{H}_9\text{NO}_3$, M_r 119.12 Da, a proteinogenic amino acid with two asymmetric C atoms existing in a *threo*- and an *allo*-form from which the L-threo-form occurs in proteins.

Thrombin, EC 3.4.21.5, *factor IIa*, *fibrinogenase*, a \rightarrow serine protease capable of producing a thrombus or blood clot. Thrombin activates platelets and regulates the behavior of other cells via G protein-coupled protease-activated receptors. It consists of two chains (M_r 36.5 kDa). The A chain (human: 36 aa) of a α -thrombin, without known function, is linked by a single disulfide bond to the catalytic B chain (259 aa) which is homologous to the catalytic domains of trypsin and chymotrypsin. Six additional Cys residues within the B chain form three intrachain disulfide bridges. Furthermore, the B chain is glycosylated on Asn⁶⁰. Thrombin is derived from its

zymogen prothrombin through cleavage by factor Xa in the presence of cofactor Va, Ca^{2+} and a phospholipid surface. Thrombin is the last protease in the coagulation cascade, and cleaves \rightarrow fibrinogen to yield fibrin monomers that polymerize to form the basis of the blood clot. The specificity of thrombin is trypsin-like, but much more restricted with respect to the P_1 residue Arg in substrates and inhibitors. Thrombin also causes platelets to aggregate, modulates neurite growth, and is mitogenic for various cell types [M. T. Stubbs, W. Bode, *Thromb. Res.* **1993**, 69, 1; R. J. Grand et al., *Biochem. J.* **1996**, 313, 353; S. R. Coughlin, *Proc. Natl. Acad. Sci. USA* **1999**, 96, 11023].

Thrombin receptor activator peptides (TRAP), peptides containing sequences derived from the new N-terminus starting with Ser⁴² to Phe⁵⁵ of the seven-transmembrane domain thrombin receptor after \rightarrow thrombin cleavage with the capability of activating platelets directly. Evidence for the proteolytic mechanism of activation is supported by the results that the synthetic peptide TRAP-14, SFLLRNPNDK¹⁰YEPF, is capable of stimulating aggregation of human platelets and Ca^{2+} release in *Xenopus* oocytes expressing the cloned human receptor. Further, TRAP-14 has been found to trigger several intracellular signaling events in human platelets, including phospholipase C and phosphatidylinositol 3-kinase activation, adenyl cyclase inhibition, and phosphorylation of proteins on tyrosine residues. The shorter peptide TRAP-6, H-Ser-Phe-Leu-Leu-Arg-Asn-OH, causes platelet aggregation, mediates tyrosine phosphorylation, inhibits cAMP formation, and increases cytosolic Ca^{2+} concentration [R. R. Vasallo et al., *J. Biol. Chem.* **1992**, 267, 6081; E. Van Obberghen-Schilling et al., *Biochem. J.* **1993**, 292, 667; L. F. Brass et al., *J. Biol. Chem.* **1994**, 269, 2943].

Thrombogen, \rightarrow prothrombin.

Thrombomodulin (TM), a cell-surface glycoprotein (M_r 74 kDa) that binds \rightarrow thrombin and acts as a cofactor in the activation of \rightarrow protein C and its regulation of blood coagulation. TM is predominantly synthesized by vascular endothelial cells and contains six contiguous epidermal growth factor-like domains. TM specifically binds thrombin, leading to a conformation with decreased capability to catalyze clot formation, but with a more than 1000-fold increased capacity to activate protein C. Thus, TM is a linker of endogenous control of coagulation and fibrinolysis. Recent evidence has revealed that TM shows also protein C- and thrombin-independent physiological function, e.g., TM has unique effects on cellular proliferation, adhesion and inflammation, all of which are important steps in atherosclerosis [P. Fuentes-Prior et al., *Nature* **2000**, 404, 449; Y. H. Li et al., *Cardiovasc. Hematol. Agents Med. Chem.* **2006**, 4(2), 183].

Thrombospondins (TSP), a five-member gene family exerting cell-cell and cell-matrix interactions. TSP are related glycoproteins that are synthesized, secreted and incorporated into the extracellular matrix of a variety of cells, e.g., α -granules of platelets following thrombin activation and endothelial cells. They are either trimers or pentamers, and their functions depend on their abilities to interact with various extracellular ligands and cell-surface receptors via the multiple domains that compose each subunit. TSP interact with various blood coagulation factors and anticoagulant factors. *Thrombospondin 1* (TSP 1) is a matrix glycoprotein consisting of three identical, disulfide-linked chains (M_r 450 kDa) originating from platelets and from normal and transformed cells. It is involved in cell migration and proliferation

during embryogenesis and wound repair. The 6-peptide H-Gly-Gly-Trp-Ser-His-Trp-OH acts as a TSP analogue and binds specifically to \rightarrow fibronectin. It inhibits fibronectin-promoted adhesion of breast carcinoma and melanoma cells to gelatin or type I collagen substrates. Further members of the TSP are TSP 2, TSP 3, TSP 4, and cartilage oligomeric matrix protein. TSP 2 has a similar structure to TS 1, but is expressed during different times in development. It acts as an inhibitor of angiogenesis. The other members of the TSP have pentameric structures with a smaller subunit. TSP 3 acts as a developmentally regulated heparin-binding protein, and is predominantly expressed in the developing lung. Recently, genetic investigations have indicated associations of particular single nucleotide polymorphisms in three of the five TSP with cardiovascular disease [M. D. Kosfeld et al., *J. Biol. Chem.* **1991**, 266, 24257; J. M. Sipes et al., *J. Cell Biol.* **1993**, 121, 469; P. Bornstein, *J. Clin. Invest.* **2001**, 107, 929; O. I. Stenina et al., *Arterioscler. Thromb. Vasc. Biol.* **2007**, 27, 1886].

Thymic hormones (TH), *thymus factors*, hormones most likely produced in the thymus epithelium that participate in development of the lymphoid system and maturation of the cellular immune response. Members of the TH are, for example, \rightarrow thymopoietin, \rightarrow thymosins, \rightarrow thymulin, \rightarrow thymopentin and the thymic humoral factor, a polypeptide with M_r 3.2 kDa [J.-F. Bach, in: *Thymic Factor Therapy*, N. A. Byrom, J. R. Hobbess (Eds.), Vol. 16, p. 21; Raven Press, New York, **1984**; T. L. Low, *Thymus* **1990**, 15, 93].

Thymopentin (TP-5), H-Arg-Lys-Asp-Val-Tyr-OH, a synthetic 5-peptide corresponding to the sequence 32–36 of thymopoietin II (\rightarrow thymopoietins). TP-5 exerts the same biological activities as thymopoietin.

It is administered to strengthen the unspecific immune system. Furthermore, TP-5 has been studied for possible application in the treatment of rheumatoid arthritis, AIDS, and other immunodeficiencies. Recently, C-terminally 5-carboxyfluorescein-labeled TP-5 has been described as a fluorescent probe for the thymopoietin receptor [G. Goldstein, T. K. Audhya, *Surv. Immunol. Res.* **1985**, Suppl. 1, 1; S. Onoue et al., *Anal. Sci.* **2006**, 22, 1531].

Thymopoietins (TP), PEFLEDPSVL¹⁰TKE KLK SELV²⁰ANNVTLPAGE³⁰QRKDVYV ELY⁴⁰LQSLTALKR (TP II), a group of peptide hormones from the thymus gland. All members consist of 49 residues with varying residues in positions 1, 2, 34, and 43. For example, TP I is characterized as [Gly¹,Gln²,Ser⁴³]TP II. TP III (spleen) corresponds to [His⁴³]TP II, whereas *splenin* (spleen) corresponds to [Glu³⁴,His⁴³]TP II. The TP induce the differentiation of T lymphocytes. Interestingly, TP II 29–41 shows the same activity as TP II. The active sequence of TP represents \rightarrow thymopentin (TP-5), corresponding to TP-II-(32–36) [D. H. Schlesinger et al., *Cell* **1975**, 5, 367; G. Goldstein et al., *Science* **1979**, 204, 1309; T. Abiko, H. Sekino, *Chem. Pharm. Bull.* **1987**, 35, 2016; S. Onoue et al., *Anal. Sci.* **2006**, 22, 1531].

Thymosin α_1 , *Talpa 1*, Ac-SDAAVDTS SE¹⁰ITTKDLKEKK²⁰EVVEEAEQ, a linear, N-terminally acetylated 28-peptide hormone, secreted by thymus tissue (\rightarrow thymosins) and primarily involved in stimulation of the thymus-dependent immune system. Synthetic thymosin α_1 (Zadaxin[®]) is used for the treatment of HBV and hepatitis, and in combination with low doses of \rightarrow interferon or \rightarrow interleukin (IL-2) it has found application in the treatment of cancer [J. F. Bach, *J. Immunopharmacol.* **1979**, 1, 277; A. Billich, *Curr. Opin.*

Investig. Drug **2002**, 3, 198; E. Garaci et al., *Int. Immunopharmacol.* **2003**, 3, 1145].

Thymosins, polypeptides originally isolated from tissues of vertebrates and postulated to possess hormonal or immunomodulating functions. The designation "thymosins" is related to the first isolation from thymus tissue preparations. α - and β -thymosins are the main members of this peptide family. α -Thymosin includes *prothymosin α* (109 aa), the structurally related *parathymosin a* (101 aa), and the 28-peptide \rightarrow thymosin α_1 . The term β -thymosin is restricted to a group of homologous peptides with an average $M_r \sim 5$ kDa. In mammals, the most commonly occurring member of this group is *thymosin β_4* ($T\beta_4$) containing 43 residues, which is accompanied by $T\beta_9$ (calf), $T\beta_9^{Met}$ (pig), $T\beta_{10}$ (human, horse, rat, cat, mouse) or $T\beta_{13}$ (whale). $T\beta_4$ has been shown to be active in various biological assays, e.g., the terminal deoxynucleotidyl transferase activity *in vivo* and *in vitro* is induced or the hypothalamic secretion of \rightarrow luliberin is stimulated. $T\beta_4$ forms a 1:1 complex with G-actin, thereby sequestering its polymerization and playing an important role in the regulation of the actin polymerization in many cells [T. K. L. Low, A. L. Goldstein, *Thymus* **1984**, 6, 27; W. Voelter, in: *Peptides* 1992, C. H. Schneider, A. N. Eberle (Eds.), p. 103, ESCOM, Leiden, **1993**; E. Garaci et al., *Int. J. Immunopharmacol.* **2000**, 22, 1067; T. Huff et al., *Int. J. Biochem. Cell Biol.* **2001**, 33, 205; J. Marx, *Science* **2007**, 316, 682].

Thymulin, *thymic factor, serum thymic factor, STF*, pGlu-Ala-Lys-Ser-Gln-Gly-Gly-Ser-Asn-OH, a neuroendocrine hormone from the epithelium of the thymus with immunoregulatory actions. It binds to a carrier protein and Zn^{2+} to exert its biological functions. Thymulin plays an essential role in the differentiation of T lymphocytes and

the normalization of the ratio to T-helper cells to suppressor cells. Furthermore, it has been shown to have anti-nociceptive effects in hyperalgesia and in pain of neurogenic origin. The synthesis of thymulin is stimulated by \rightarrow growth hormone [J. F. Bach et al., *Bull. Inst. Pasteur* **1978**, 325; J. J. Haddad et al., *Curr. Med. Chem. Anti-Inflamm. Anti-Aller. Agents* **2005**, 4, 333].

Thyroglobulin (Tg), a globular glycoprotein (M_r 660 kDa) synthesized in the thyroid gland. Thyroglobulin is the precursor protein of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4). During post-translational modification, approximately 20% of the 140 Tyr residues are iodinated using I^- and H_2O_2 , catalyzed by iodoperoxidase, yielding 2,5-diiodo-Tyr residues. Coupling of two modified residues, rearrangement, followed by lysosomal proteolysis, results in the formation of about five or six molecules of T_3 and T_4 . Synthesis of thyroglobulin and release of the thyroid hormone is stimulated by \rightarrow thyrotropin. Tg-specific antibodies are useful in the diagnosis of Hashimoto's thyroiditis or Graves' disease. Tg levels in the blood can be used as tumor marker for special types of thyroid cancer [H. Edelhofer, *J. Biol. Chem.* **1960**, 235, 1326].

Thyroliberin, *thyrotropin-releasing hormone, TRH*, pGlu-His-Pro-NH₂, produced in the paraventricular nucleus of the hypothalamus, stimulates biosynthesis and secretion of \rightarrow thyrotropin (TSH) from the anterior pituitary. It is central in regulating the hypothalamic-pituitary-thyroid (HPT) axis. Furthermore, TRH influences the release of other hormones, e.g., \rightarrow prolactin, \rightarrow growth hormone, \rightarrow vasopressin, \rightarrow insulin, and also the classic neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline). In addition, it is

found in many brain loci outside the hypothalamus, and also outside the CNS in the gastrointestinal tract, pancreas, ovary, placenta, testis, seminal vesicles, retina, and prostate. This widespread distribution of TRH underlines a diverse range of functions also outside the HPT axis. The discovery and characterization of TRH as the first identified hypothalamic-releasing hormone by Guillemin and Schally in 1969 provided ultimate confirmation of the basic principles of neuroendocrinology, and was followed by the discovery of other releasing hormones (\rightarrow liberins). In 1986, the rat prepro-TRH sequence (255 aa; M_r 29 kDa) was identified. The precursor contains an *N*-terminal 25-residue leader sequence, five copies of the TRH progenitor -Gln-His-Pro-Gly- flanked by paired basic amino acids (Lys-Arg or Arg-Arg), four non-TRH peptides between the TRH progenitors, an *N*-terminal flanking peptide, and a C-terminal flanking peptide. In the course of the processing of pro-TRH, Gln-His-Pro-Gly is then amidated, catalyzed by peptidylglycine α -amidating monooxygenase (PAM) using the C-terminal Gly as the amide donor, and the Gln residue undergoes cyclization to pyroglutamate to yield TRH. Besides TRH, other pro-TRH-derived peptides are formed with potential biological functions. In the cryptic region of the prepro-TRH the sequence of the 22-peptide \rightarrow corticotropin release-inhibiting factor has been elucidated. Among the many TRH analogues described, pGlu-3MeHis-Pro-NH₂ shows 800% relative activity with respect to TRH. TRH exerts its biological effects via the stimulation of cell-surface receptors, TRH-R, that belong to the G protein-coupled receptors [R. Guillemin, *Science* **1978**, *202*, 390; A. V. Schally, *Science* **1978**, *202*, 18; E. A. Nillini, K. A. Sevarino, *Endocr. Rev.* **1999**, *20*, 599; G. A. Scalabrino et al., *Neuropharmacology* **2007**, *52*, 1472; S. Engel, M. C.

Gershengorn, *Pharmacol. Ther.* **2007**, *113*, 410].

Thyrotropin, *thyroid-stimulating hormone*, TSH, a α/β glycoprotein (human TSH: α chain: 96 aa; β chain: 112 aa) formed in the adenohypophysis with structural similarities to the \rightarrow gonadotropins. The α chain is identical with the appropriate α chains of both \rightarrow follitropin and \rightarrow lutropin. TSH stimulates synthesis and secretion of the thyroid hormones T₃ and T₄ in the thyroid gland, and the formation of \rightarrow thyroglobulin. The human TSH-receptor consists of 744 residues. The release of TSH is regulated by \rightarrow thyroliberin and inhibited via a negative feedback mechanism by high doses of T₃ and T₄ [J. A. Magner, *Endocr. Rev.* **1990**, *11*, 354; Y. Nagayama, B. Rapoport, *Mol. Endocrinol.* **1992**, *6*, 145].

Thyrotropin-releasing hormone, \rightarrow thyroliberin.

Thz, thiazolidine-4-carboxylic acid (thiaproline).

TLE, thin-layer electrophoresis.

Tmob, \rightarrow 2,4,6-trimethoxybenzyl.

Tmse ester, 2-(trimethylsilyl)ethyl ester, a carboxy protecting group, cleaved by fluoride ions.

TNF, tumor necrosis factor.

TOCSY, total correlation spectroscopy.

TOF, time-of-flight.

4-Toluenesulfonyl group, \rightarrow tosyl group.

Tos, \rightarrow Tosyl group.

Tosyl group (Tos), *4-toluenesulfonyl group*, Tos, a sulfonamide-type protecting group for *N* $^\alpha$, the Arg guanidino group, or the His imidazole nitrogen. It can be cleaved by reduction with sodium in liquid ammonia.

TP, thymopoietin.

TP5, thymopentin.

tPA, tissue plasminogen activator.

t_R, retention time.

trans-Peptide bond, → peptide bond.

Transpeptidases, → transpeptidation.

Transpeptidation, *transamidation*, a reaction involving the transfer of one or more amino acids from one peptide chain to another. This term was first coined by Fruton, in 1950, by analogy with transglycosidation for the papain-catalyzed displacement reaction between Bz-Gly-NH₂ and aniline forming Bz-Gly-NHPh. Of special importance in relation to protease-catalyzed transpeptidation reactions in a preparative scale is the one-step tryptic conversion of porcine → insulin into human insulin, despite the controversial interpretation of the mechanism involved. A bacterial transpeptidase, *serine-type D-Ala-D-Ala carboxypeptidase* (EC 3.4.16.4), also called *penicillin-binding protein 5*, crosslinks the peptidoglycan chains to form rigid cell walls. Further bacterial transpeptidases are → sortases. Tryptic transpeptidation products were observed in → proteome analysis in 2005 [J. S. Fruton, *Yale J. Biol. Med.* **1950**, 22, 263; M. Jamin et al., *Essays Biochem.* **1995**, 29, 1; H. Schaefer et al., *Proteomics* **2005**, 5, 846].

Transducin (G_T), a heterotrimeric (α, β, γ) → G protein (M_r 82 kDa) in the vertebrate eye, transducing visual stimuli by coupling the light-induced conformational change of rhodopsin to the activation of specific phosphodiesterase. G_{T α} activates the cGMP phosphodiesterase that hydrolyzes cGMP to GMP. The resulting drop in the cGMP level causes an electric change in the photoreceptor cell [L. Stryer, *Sci. Am.* **1987**, 257, 42].

Transferrin, also called *siderophilin*, a non-heme protein carrying iron through the blood to the liver, spleen, and bone marrow. Human transferrin (M_r 80 kDa) is a β_1 -globulin and comprises about 5% of the plasma proteins. Cell-surface transferrin receptors deliver transferrin with bound iron to peripheral endosomes by receptor-promoted endocytosis. The release of bound iron is induced by the low pH in the endosomes. The iron-free transferrin (*apoferritin*) remains linked to the receptor and is recycled back to the plasma membrane as a receptor-apoferritin complex. The neutral pH induces the dissociation of apoferritin from the receptor, thus picking up more iron and starting the cycle again [A. Dautry-Varsat et al., *Proc. Natl. Acad. Sci. USA* **1983**, 80, 2258; P. Ponka, C. N. Lok, *Int. J. Biochem. Cell Biol.* **1999**, 31, 1111].

Transforming growth factor- β (TGF- β), a multifunctional protein (M_r ~ 25 kDa) controlling proliferation, differentiation, and other functions in several cell types. TGF- β consists of two identical peptide chains (each 112 aa) linked together by disulfide bridges. TGF- β is regarded as the prototype of the transforming growth factor- β superfamily that regulates cell growth and differentiation *via* the interaction with different membrane receptors. TGF- β potentiates or inhibits the response of most cells to other growth factors, depending on the cell type. Furthermore, TGF- β regulates differentiation of some cell types, e.g., cartilage differentiation *in vitro*. It was originally identified as a → cytokine in transformed fibroblasts. TGF- β is able to regulate both matrix protein synthesis and degradation in a distinctive, profibrotic manner. New strategies to tackle renal fibrosis have been developed in recent years that are centered around the cascade of TGF- β generation,

TGF- β signaling, and matrix protein deposition and degradation. By using human kidney fibroblasts, it has been reported that \rightarrow relaxin blocks TGF- β effects on matrix synthesis and secretion, as well as the transformation of fibroblasts to myofibroblasts [J. Massague, *Cell* **1987**, 49, 437; T. F. Deuel, *Annu. Rev. Cell. Biol.* **1987**, 3, 443; J. Gaedeke, H. Peters, *Kidney Int.* **2005**, 68, 405].

Transforming growth factor- α (TGF- α), a mitogenic protein controlling, together with \rightarrow transforming growth factor- β (TGF- β), the transformation of various cell lines. Rat TGF- α -(1–50), VVSHFNKCPD¹⁰ SHTQYCFHGT²⁰CRFLVQEEKP³⁰ACVCHSGYVG³⁰VRCEHADLLA⁵⁰ (disulfide bonds: C⁸–C²¹ / C¹⁶–C³² / C³⁴–C⁴³) and human TGF- α are single polypeptides with sequence homology (30%) to \rightarrow epidermal growth factor (EGF). TGF- α is formed in excessive amounts in the skin of individuals with psoriasis, a skin disease characterized by epidermal hyperproliferation. TGF- α and other EGF-like proteins are thought to play a role in oncogenesis and wound healing [J. A. Feild et al., *Biochem. J.* **1992**, 283, 91; J. R. Goldenring et al., *Regul. Pept.* **1993**, 43, 37].

Transmissible spongiform encephalopathies (TSE), \rightarrow prions.

Transportan, \rightarrow cell-penetrating peptides.

Trefoil factor family peptides, (TFF peptides), secretory mucin-associated peptides (trefoil peptides) largely found in epithelia of the gastrointestinal tract. They share the TFF domain, a Cys-rich protein module with a consensus structure of 42 amino acids and six conserved Cys residues forming three intramolecular disulfide bridges between Cys¹–Cys⁵, Cys²–Cys⁴, and Cys³–Cys⁶. The TFF pep-

tides play an important role in the formation and repair of the mucous barrier, as well as modulation of mucosal differentiation and immune response [L. Thim, F. E. May, *Cell. Mol. Life Sci.* **2005**, 62, 2956].

Trefoil peptides, \rightarrow trefoil factor family peptides.

Tremerogens, peptide hormones from *Tremella mesenterica* containing a sulfur-linked farnesyl moiety involved in the zytotene stages. For example, *Tremerogen A-13*, EGGGNRGDPS¹⁰GVC^{Farn}, is produced by the a-type cell, whereas *Tremerogen A-10* is formed by the A-type cell. The tremerogens A-9291-I and A-9291-II have been described as sex hormones of *Tremella brasiliensis* [Y. Sakagami et al., *Science* **1981**, 212, 1525; Y. Ishibashi et al., *Can. J. Biochem. Cell. Biol.* **1983**, 61, 796; R. N. Armstrong et al., *Biochemistry* **1984**, 23, 1339].

TRF, time-resolved fluorescence.

TRH, thyrotropin-releasing hormone.

Triadins, a multiprotein family with different distribution of the various splice variants within the sarcoplasmic reticulum (SR). Their function may include involvement in excitation–contraction coupling, in triad targeting, in structural function, or in muscle differentiation. *Triadin*, a glycoprotein ($M_r \sim 95$ kDa) expressed in both skeletal and cardiac muscle, was first identified in rabbit skeletal muscle involved in calcium release for muscle contraction. Recently, it has been reported that triadins are not triad-specific proteins. Two new skeletal muscle triadins may be involved in the architecture of the SR [I. Marty, *Cell. Mol. Life Sci.* **2004**, 61, 1850; S. Vassilopoulos et al., *J. Biol. Chem.* **2005**, 280, 28601].

2,2,2-Trichloroethoxycarbonyl group, (Troc), a urethane protecting group stable toward cleavage conditions of *tert*-butyl-type protecting groups (e.g., Boc). It is cleaved reductively by treatment with zinc [J. B. Aggen et al., *Bioorg. Med. Chem.* **1999**, *7*, 543].

Triflavin, a cysteine-rich polypeptide (M_r 7.6 kDa; 71 aa) isolated from *Trimeresurus flavoviridis* snake venom that belongs to the family of RGD-containing peptides, termed *disintegrins*. Triflavin inhibits the adhesion of tumor cells to matrix proteins through binding to multiple integrin receptors expressed on human hepatoma cells [T. F. Huang et al., *Biochem. J.* **1991**, *277*, 351; J. R. Sheu et al., *Proc. Soc. Exp. Biol. Med.* **1996**, *213*, 71].

Trifluoroacetyl group (Tfa), a carboxamide-type protecting group to be cleaved under alkaline conditions.

Trifluoromethanesulfonic acid (TFMSA), a reagent used in Boc/Bzl tactics as a substitute for liquid HF for final deprotection of semi-permanent benzyl-type protecting groups and cleavage from the resin.

2-(4-Trifluoromethylphenyl)sulfonylethoxycarbonyl group (Tsc), 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl, a base-labile protection group for amines, especially suited for the heteroaromatic pyrrole and imidazole amino acids Trp and His. The Tsc group differs from the 9-fluorenylmethoxycarbonyl (Fmoc) group in decreased sensitivity toward premature cleavage [J. S. Choi et al., *Tetrahedron* **2005**, *61*, 2493].

Trigger factor, \rightarrow FK506-binding proteins.

2,4,6-Trimethoxybenzyl group (Tmob), a protecting group for the thiol functionality of Cys and the ω -carboxamide of Asn or Gln. It is cleaved with trifluoroacetic

acid (TFA), and is favorably employed in SPPS with Fmoc as the temporary protecting group.

Trimethylacetamidomethyl group (Tacm), a type of thiol protecting group with a *N*-acyl *N,S*-acetal moiety, like the \rightarrow acetamidomethyl group (Acm), compatible with both Boc and Fmoc chemistry. The Tacm group is completely stable towards acidolysis, and is cleaved by Hg^{2+} , Tl^{3+} , or I_2 .

Triostin A, a heterodetic cyclodepsipeptide belonging to the quinoxaline antibiotics. It contains two planar aromatic quinoxaline ring systems that are covalently attached to a cyclic octadepsipeptide ring. Both valine and cysteine are *N*-methylated. Triostin A binds sequence specifically to DNA. Beside \rightarrow echinomycin, triostin A is a parent member of an important family of antitumor antibiotics that are in clinical trials. A synthetic analogue is \rightarrow TANDEM, which differs in its structure from triostin A only at the valine residues, which contain no *N*-methyl groups [H. Otsuka, J. Shoji, *Tetrahedron* **1967**, *23*, 1535; K. J. Address, J. Feigon, *Biochemistry* **1994**, *33*, 12386].

Tripeptidyl peptidase II (TPPII), EC 3.4.14.10, an important intermediate exopeptidase in animals that hydrolyzes peptide products of the 26S proteasome (\rightarrow proteasome) into tripeptides. The TPPII from *Arabidopsis* exists as a soluble oligomeric protease complex [B. Tomkinson, *Trends Biochem. Sci.* **1999**, *24*, 355; A. J. Book et al., *Plant Physiol.* **2005**, *138*, 1046].

Triphenylmethyl group (trityl group, Trt), an acid-labile protecting group in Fmoc tactics, e.g., for the side-chain functionalities of Asn, Gln, His, and Cys. The trityl residue is stable to the conditions of coupling and deprotection during Fmoc synthesis. It can be cleaved with dilute acetic acid or

trifluoroacetic acid. Electron-withdrawing substituents as present in 2-chlorotrityl moieties confer increased stability towards acidolysis. The 2-chlorotrityl group is used for carboxy protection, and also as a handle in the \rightarrow 2-chlorotritylchloride resin.

Tris, tris(hydroxymethyl)aminomethane.

Tritrpticin, VRRFPWWPF¹⁰LRR, a 13-peptide, designated to its three consecutive Trp residues, with a broad antimicrobial activity spectrum. It has potential importance as a therapeutic agent for a variety of infectious diseases [C. Lawyer et al., *FEBS Lett.* **1996**, 390, 95; S. T. Yang et al., *Biochem. Biophys. Res. Commun.* **2002**, 296, 1044].

Trityl group, \rightarrow triphenylmethyl group.

TRNOE, transferred nuclear Overhauser effect.

Troc group, \rightarrow 2,2,2-trichloroethoxycarbonyl group.

Trojan horse peptides, \rightarrow cell-penetrating peptides.

Tropomyosin, a protein ($M_r \sim 33$ kDa) present in virtually all eukaryotic cells and in striated muscle. In eukaryotic cells, tropomyosin functions to modulate actin–myosin interactions and to stabilize actin filament structure. In striated muscle, it regulates contractility by blocking myosin-binding sites on actin in the relaxed state. In the activated state, tropomyosin moves away in two steps, one induced by Ca^{2+} binding to \rightarrow troponin and the second by the binding of \rightarrow myosin to \rightarrow actin. Tropomyosin is a homodimer consisting of two 284-aa subunits that wrap around each other, forming a parallel coiled coil of α helices with the exception of the residues at the termini of the chains. The rod-shaped molecules (400 Å in length) are joined head-to-tail, forming cables that

wrap in the groove of the F-actin helix so that one tropomyosin molecule contacts seven consecutive actin monomer units. Furthermore, each tropomyosin molecule binds to a single \rightarrow troponin TnT molecule at its head-to-tail joint [F. G. Whitby et al., *J. Biol. Chem.* **1992**, 227, 441; A. S. Zot, J. D. Potter, *Annu. Rev. Biophys. Chem.* **1987**, 16, 535; W. Lehman et al., *J. Mol. Biol.* **2000**, 302, 593].

Troponin (Tn), the central regulatory protein complex of vertebrate skeletal and cardiac muscle. The troponin complex consists of three subunits: TnC (M_r 18 kDa), a Ca^{2+} -binding protein with about 70% homology to \rightarrow calmodulin, TnI (M_r 24 kDa), with binding capacity to \rightarrow actin, and TnT (M_r 37 kDa) containing the binding site for \rightarrow tropomyosin at its head-to-tail junction. In vertebrate skeletal and cardiac muscle, TnC, through its association with actin and tropomyosin on the thin filament, inhibits the actomyosin interaction at submicromolar Ca^{2+} concentrations and stimulates the interaction at micromolar Ca^{2+} concentrations. Since TnC does not interact directly with actin or tropomyosin, the Ca^{2+} binding signal must be transmitted to the thin filament through the other two subunits, TnI, the inhibitory subunit, and TnT, the tropomyosin-binding subunit. Muscle contraction is initiated by an increase in Ca^{2+} concentration. Ca^{2+} binds to TnC, resulting in a conformational change that causes tropomyosin to move deeper into the thin filament groove, exposing actin's myosin head-binding sites and leading to switch on muscle contraction. TnT is important for the early diagnosis of acute cardiac infarction [K. A. Satyshur et al., *Acta Crystallogr.* **1994**, D50, 40; C. S. Farah, F. C. Reinach, *FASEB J.* **1995**, 9, 755].

TROSY, transversal relaxation-optimized spectroscopy.

Trp, tryptophan.

Trt, triphenylmethyl (trityl).

Truncated sequences, → core sequences, incompletely synthesized peptides. Imperfect conversion during acylation or deprotection of the temporary protecting group in solid-phase synthesis may lead to mismatch sequences that lack some amino acids and truncated sequences (core sequences). They occur, when the accessibility or reactivity of the peptide bound to the solid phase is insufficient (→ difficult sequences). Truncated sequences may be classically identified and quantified by a modified → Edman degradation, also called → preview analysis. Alternatively, mass spectrometry provides efficient tools for the identification of truncated sequences.

Trypsin, EC 3.4.21.4, a prototype of the serine endopeptidases family S 1. It was described and named as the proteolytic activity in pancreatic secretions as early as 1876, and purified by crystallization in 1931. Trypsin strongly prefers to cleave peptide substrates following P1 Arg or Lys residues (→ peptidases). All naturally occurring trypsins are synthesized as proenzymes. The mammalian propeptide (trypsinogen) contains the consensus sequence for cleavage by → enteropeptidase [V. Schellenberger et al., *Biochemistry* **1994**, 33, 4251; J. J. Perona, C. S. Craick, *Protein Sci.* **1995**, 4, 337; L. Hedstrom, *Biol. Chem.* **1996**, 377, 465].

Tryptophan (Trp, W), α -amino- β -indolyl-propionic acid, $C_{11}H_{12}N_2O_2$, M_r 204.23 Da, a proteinogenic amino acid.

TSH, thyroid-stimulating hormone (thyrotropin).

Tufts, H-Thr-Lys-Pro-Arg-OH, a natural phagocytosis-stimulating 4-peptide which

was discovered at Tufts University in 1970. Tufts corresponds to the 289–292 sequence in the CH2 domain of the Fc fragment of *leukokinin*, a leukophilic fraction of a α -globulin. It is released under the catalysis of a specific enzyme (leukokininase) located in the outer membrane of neutrophils. It is assumed (by circumstantial evidence only) that the processing should be performed by the successive action of two enzymes: the splenic tufts endocarboxypeptidase cleaves the Arg²⁹²–Glu²⁹³ bond, whereas the leucokininase cleaves the Lys²⁸⁸–Thr²⁸⁹ bond. The primary biological effect of tufts, after binding to specific cell-surface receptors, is stimulation of the functions of macrophages and polymorphonuclear (PMN) cells. Interestingly, the tetrapeptide H-Thr-Glu-Pro-Arg-OH was isolated from leukokinin of a patient with tufts deficiency. Much attention was paid to the synthesis of various analogues of this short peptide, since its antimicrobial, antiviral, and antitumor activities promise useful therapeutic effects [V. A. Najjar, K. Nishioka, *Nature* **1970**, 228, 672; M. Fridkin, V. A. Najjar, *Crit. Rev. Biochem. Mol. Biol.* **1989**, 24, 1; I. Z. Siemion, A. Kluczyk, *Peptides* **1999**, 20, 645].

Tumor necrosis factor- α (TNF- α), *cachectin*, a single-chain protein (hTNF- α : 157 aa; M_r 17 kDa) containing an intrachain disulfide bridge. TNF- α is a monocyte-macrophage-derived → cytokine first detected by its *in vivo* antitumor activities and *in vitro* cytotoxicity to certain transformed cell lines. Furthermore, it causes a growth-enhancing effect on various cells and thus functions as a bifunctional growth regulator as, for example, IFN- α (→ interferons). TNF- α shares some biological activities with IL-1 (→ interleukins), such as a mediator of inflammatory processes [B. Bharat et al.,

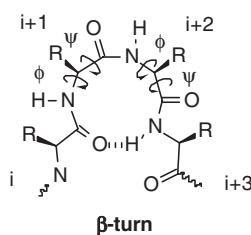
Nature **1985**, 318, 665; K. J. Tracy, A. Cerami, *Annu. Rev. Cell Biol.* **1993**, 9, 317; R. M. Locksley et al., *Cell* **2001**, 104, 487; H. Wajant et al., *Cell Death Differ.* **2003**, 10, 45; A. Corti, P. Ghezzi (Eds.), *Tumor Necrosis Factor: Methods and Protocols*, Humana Press, Totowa, N.J., **2004**; Gulcubuk et al., *J. Vet. Med. A Physiol. Pathol. Clin. Med.* **2006**, 53, 49].

Tumor necrosis factor- β (TNF- β), lymphotoxin, a glycoprotein (171 aa; unglycosylated: $M_r \sim 19$ kDa) produced by mitogen-stimulated lymphocytes. TNF- β causes cytostasis of some tumor cell lines and cytotoxicity of other transformed cells. TNF- β and \rightarrow tumor necrosis factor- α (TNF- α) show 36% sequence homology. Both TNF bind to the same receptors, TNF receptor 1 (M_r 55 kDa) and TNF receptor 2 (M_r 75 kDa), respectively [K. J. Tracey, A. Cerami, *Annu. Rev. Cell Biol.* **1993**, 9, 317; R. M. Locksley et al., *Cell* **2001**, 104, 487; H. Wajant et al., *Cell Death Differ.* **2003**, 10, 45 A. Corti, P. Ghezzi (Eds.), *Tumor Necrosis Factor: Methods and Protocols*, Humana Press, Totowa, N.J., **2004**].

Tumor-associated glycopeptide antigens, glycoprotein structures characteristic for tumor cells. Aberrant protein glycosylation often is observed for autoimmune or infectious diseases and cancer. Tumorigenesis of a cell often coincides with an alteration of oligosaccharide epitopes of glycoproteins presented on the surface of a cell. Examples of such glycoconjugates predominantly expressed on cancer cells are the Ser/Thr O-glycans T_N -antigen (α -GalNAc-), T-antigen (Thomsen-Friedenreich antigen, β -Gal-1,3- α -GalNAc-), sialyl- T_N -antigen (α -NeuNAc-2,6- α -GalNAc-) and sialyl-T-antigen (α -NeuNAc-2,3- β -Gal-1,3- α -GalNAc- and β -Gal-1,3-[α -NeuNAc-2,6-] α -GalNAc-). The \rightarrow sialyl-Lewis X antigen (α -NeuNAc-2,3- β -Gal-1,4-[α -Fuc-1,3-] β -GlcNAc-) and sialyl-Lewis a antigen (α -NeuNAc-2,3- β -Gal-1,3-[α -Fuc-1,4-] β -GlcNAc-), parts of larger oligosaccharide structures, are further representatives. Vaccinations based on synthetic tumor-associated glycopeptides hold potential for targeting the immune system to the cancer cells in order to generate a tumor-specific immune response [C. Brocke, H. Kunz, *Bioorg. Med. Chem.* **2002**, 10, 3085].

lyl Lewis a antigen (α -NeuNAc-2,3- β -Gal-1,3-[α -Fuc-1,4-] β -GlcNAc-), parts of larger oligosaccharide structures, are further representatives. Vaccinations based on synthetic tumor-associated glycopeptides hold potential for targeting the immune system to the cancer cells in order to generate a tumor-specific immune response [C. Brocke, H. Kunz, *Bioorg. Med. Chem.* **2002**, 10, 3085].

Turn, a secondary structure element of non-periodic nature. Turns are found in proteins and peptides. They are classified by the number of amino acids (n) involved, and the dihedral angles φ and ψ of the $n-2$ middle amino acids. γ -Turns are formed by three amino acids, β -turns by four amino acids, and α -turns by five amino acid residues. Turns are often stabilized by a hydrogen bond between the amino group of the C-terminal amino acid and the carboxy group of the N-terminal amino acid.



Turn mimetics, secondary structure mimetics that imitate turns when incorporated into peptides. Most secondary structure mimetics have been designed to imitate a β -turn. Often, bicyclic heterocycles are employed as rigid scaffolds. The design, synthesis, and application of turn mimetics must cope with two problems: (i) not all scaffolds designed as β -turn mimetics actually display the desired properties; and (ii) the synthetic route for the secondary structure mimetic should permit the introduction of appropriate side chains onto the

mimetic scaffold [A. J. Souers, J. A. Ellman, *Tetrahedron* **2001**, 57, 7431].

Tyr, tyrosine.

Tyrocidins, a group of cyclic peptide antibiotics produced from *Bacillus brevis* strains. Derived from *tyrocidin A*, cyclo-(-Val-Orn-Leu-D-Phe-Pro-Phe-D-Phe-Asn-Gln-Tyr¹⁰-), *tyrocidin B* corresponds to [Trp⁶]tyrocidin A, *tyrocidin C* to [Trp⁶, D-Trp⁷]tyrocidin A, and *tyrocidin D* to [Trp⁶, D-Trp⁷, Trp¹⁰]tyrocidin A. The biosynthetic thiotemplate mechanism is similar to that of → gramicidin S, except that three synthesizing enzyme components TycABC are involved. Tyrocidin and gramicidin S primarily act on Gram-positive bacteria, and are used as antibacterial drugs in different formulations (*tyrothricin*) for the topical

treatment of infections, e.g., sore throats. Open-chain analogues of the tyrocidins are without any antibacterial activity.

Tyropeptin A, isovaleryl-L-tyrosyl-L-valyl-DL-tyrosinal, a potent inhibitor of the → proteasome isolated from the culture broth of *Kitasatospora* sp. MK993-dF2. Synthetic derivatives exhibited a 20-fold inhibitory potency enhancement for chymotrypsin-like activity of 20S proteasome compared to tyropeptin A [I. Momose et al., *Biosci. Biotechnol. Biochem.* **2005**, 69, 1733].

Tyrosine (Tyr, Y), α -amino- β -(4-hydroxyphenyl)propionic acid, C₉H₁₁NO₃, M_r 181.19 Da, a proteinogenic amino acid.

Tyrothricin, → tyrocidins.

U

Ubiquitin (Ub), a highly conserved ubiquitous eukaryotic 76 aa protein ($M_r \sim 8.5$ kDa) involved in many cell processes, especially in ATP-dependent protein degradation. Ub is found only in eukaryotic organisms; it occurs neither in eubacteria nor archaeobacteria. It is identical in humans, toad, trout, and *Drosophila*, and this protein differs only in three building blocks between human and yeast. Ubiquitin is synthesized as several tandem repeats (polyubiquitin). Proteins selected for degradation by the 26S \rightarrow proteasome are marked by ubiquitin and proteolytically degraded by the multiprotein complex. The highly conserved ubiquitin–proteasome system plays a pivotal role in protein homeostasis, and is critical in the regulation of normal and cancer-related cellular processes [A. Hershko, A. Ciechanover, *Annu. Rev. Biochem.* **1992**, *61*, 761; A. M. Burger, A. K. Seth, *Eur. J. Cancer* **2004**, *40*, 2217].

UCN, urocortin.

uHTS, ultra-high-throughput screening.

UK, urokinase.

Ultrafiltration (UF), a pressure-driven separation process on the basis of molecular size using a membrane. Suspended solids and solutes of high molecular mass are retained. UF is used for the concentration of protein solutions and for the separation of molecules with significant mass differences. The nature of the membrane determines between compounds which permeate and those which are retained. UF membranes are classified according to the molecular mass limit ("molecular weight

cut-off", MWCO), up to which molecules are allowed to permeate. Instead of applying pressure, the necessary force for ultrafiltration may be exerted by centrifugation (centrifugal ultrafiltration) [R. Ghosh, *Protein Bioseparation Using Ultrafiltration*, Imperial College Press, London, **2003**].

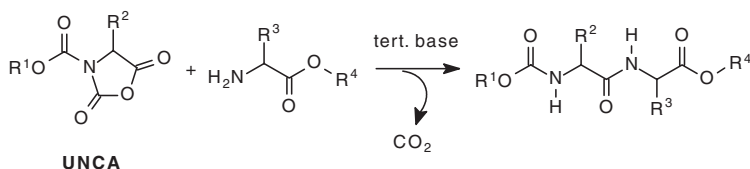
Ultra-high-throughput screening, \rightarrow high-throughput screening.

UNCA, urethane-type protected amino acid *N*-carboxy anhydride.

uPA, urokinase-type plasminogen activator.

Uperolein, <EPDPNAFYGL¹⁰Ma (*uperolein I*), an 11-peptide amide from the skin of the Australian frog *Uperoleia rugosa* belonging to the \rightarrow tachykinin family. Uperolein shows activities similar to those of \rightarrow phyllomedusin. *Uperolein II*, [Ala², Lys⁵, Thr⁶]uperolein I, could be isolated from the same source [A. Anastasi et al., *Experientia* **1975**, *31*, 394].

Urethane-type protected amino acid *N*-carboxy anhydride (UNCA), an \rightarrow *N*-carboxy anhydride (NCA) containing an additional urethane-type protecting group at nitrogen. NCA can be acylated at the ring nitrogen in an aprotic solvent in the presence of a tertiary base to give Boc-, Z-, or Fmoc-protected derivatives (UNCA). They are crystalline compounds, stable in the absence of water, and display high reactivity towards nucleophiles. There is no risk of polymerization, as the amino group formed upon ring opening with a nucleophile is still protected [W. D. Fuller et al., *J. Am. Chem. Soc.* **1990**, *112*, 7414].



Urocortins (Ucn), a group of peptides belonging to the \rightarrow corticotropin-releasing hormone (CRH) family. *Urocortin 1* (Ucn 1), DNPSLSIDLT¹⁰FHLLRTLLEL²⁰ ARTQSQRERA³⁰EQNRIIFDSV⁴⁰ (rUcn), a mammalian 40-peptide closely related to corticoliberin and initially discovered by screening a rat midbrain cDNA library with a probe derived from the fish peptide \rightarrow urotensin I. Ucn 1 is the second endogenous mammalian ligand of the CRH-receptors (\rightarrow corticoliberin). It shares 45% sequence homology with the 41-peptide rat/human CRH. Mouse *urocortin 2* (Ucn 2) and mouse *urocortin 3* (Ucn 3) are 38-peptides showing 34% and 26% homology with r/hCRH and 42% and 18% identity with rUcn 1, respectively. Human Ucn 1 possesses about 44–59% sequence identity with urotensins I found in various fishes. Furthermore, it has only 33% identity with the presumptive closest known non-mammalian homologue \rightarrow sauvagine. Ucn is expressed in specific areas of the brain, but it is also found in other organs notably the heart, placenta, and peripheral blood lymphocytes. Ucn has been reported to have biologically diverse functions in several systems, e.g., stress, reproductive, cardiovascular, appetite, anxiety, and inflammatory responses. In the heart, Ucn has been shown to protect both cultured cardiac cells and the intact heart against the damaging effects of ischemia/reperfusion injury. In this respect, Ucn is capable of activating the PI-3 kinase/Akt pathway and the p42/p44 mitogen-activated protein kinase pathway. In summary, Ucn has beneficial

effects on both cardiac function and on the response of cardiac cells to stress. Ucn 3 is also known as *stresscopin*, and Ucn 2 as *stresscopin-related peptide* [J. Vaughan et al., *Nature* **1995**, 378, 287; F. M. Dautzenberg, R. L. Hauger, *Trends Pharmacol. Sci.* **2002**, 23, 71; D. S. Latchman, *Int. J. Biochem. Cell Biol.* **2002**, 34, 907; J. Tao, S. Li, *Biochem. Biophys. Res. Commun.* **2005**, 332, 923; E. M. Fekete, E. P. Zorilla, *Front. Neuroendocrinol.* **2007**, 28, 1].

Urogastron, \rightarrow epidermal growth factor.

Uroguanylin, NDDCELCVNV¹⁰ACTGLC (hU; disulfide bonds: C⁴–C¹²/C⁷–C¹⁶), a 16-peptide occurring in greatest abundance in the mucosae of the stomach and intestinal tract. It belongs besides \rightarrow guanylin and the bacterial heat-stable (ST) peptides to a family of cGMP-regulating agonists. Uroguanylin activates a common membrane receptor-guanylate cyclase (R-GC) that elicits large increases in the intestinal secretion of chloride and bicarbonate via cGMP. Uroguanylin was first isolated from rat jejunum and opossum urine, respectively. Guanylin and uroguanylin are endogenous peptide hormones that are involved in the regulation of epithelial cell balance in the intestinal epithelium and modulation of Na⁺ balance through actions in the kidney. For uroguanylin, anti-tumor actions in an animal model of human colon cancer have been reported [L. R. Forte Jr., *Pharm. Ther.* **2004**, 104, 137; L. R. Forte Jr., *J. Am. Soc. Nephrol.* **2005**, 16, 291].

Urokinase, \rightarrow urokinase-type plasminogen activator.

Urokinase-type plasminogen activator (uPA), EC 3.4.21.73, *u-plasminogen activator*, *urokinase*, a strong plasminogen activator that specifically cleaves the pro-enzyme/zymogen \rightarrow plasminogen to form the active enzyme \rightarrow plasmin. The serine protease uPA shows an extremely limited substrate specificity. It cleaves the Arg⁵⁶⁰–Val⁵⁶¹ bond within the partial sequence -Cys–Pro–Gly–Arg–Val–Val–Gly–Gly–Cys– comprising the small disulfide-bridged loop in plasminogen, and synthetic substrates based on this sequence. The active enzyme consists of an epidermal growth factor (EGF)-like module and a serine protease domain separated by an unusually long (16 aa) linker region. It is released from a single-chain proenzyme (411 aa) after removal of a 20 aa signal peptide, followed by plasmin or \rightarrow kallikrein cleavage, the Lys¹⁵⁸–Ile¹⁵⁹ bond giving rise to two polypeptides linked together by Cys¹⁴⁸–Cys²⁷⁹. Post-translational modification is performed by glycosylation at Asn³⁰², and fucosylation at Thr¹⁸. The EGF-like module of uPA is the binding determinant to its specific glycolipid-anchored cell-surface uPA-receptor. Urokinase-type plasminogen activator is administered clinically to patients suffering from thrombolytic disorders. A role of uPA/uPA receptor in HIV-1 infection has been described [G. W. Sobel et al., *Am. J. Physiol.* **1952**, 171, 768; K. Dano et al., *Adv. Cancer Res.* **1985**, 44, 139; A. P. Hanson et al., *Biochemistry* **1994**, 33, 4847; M. Alfano et al., *J. Leucocyte Biol.* **2003**, 74, 750].

Uromodulin, a glycoprotein (h: 616 aa; $M_r \sim 85$ kDa) with *in vitro* immunosuppressive properties determined via isolation and characterization of cDNA and ge-

nomic clones. It has been shown that uromodulin is identical to the Tamm–Horsfall glycoprotein, the most abundant protein in normal human urine. It is synthesized in the kidney and acts as a renal ligand for lymphokinin [D. Pennica et al., *Science* **1987**, 236, 83; C. Hession et al., *Science* **1987**, 237, 1479; A. J. Bleyer et al., *Kidney Int.* **2003**, 64, 36].

Uronium reagents, coupling reagents that have found widespread application in peptide synthesis. \rightarrow TBTU, \rightarrow HBTU, and \rightarrow HATU are synthesized from 1-hydroxybenzotriazole (\rightarrow HOBt) or 1-hydroxy-7-azabenzotriazole (\rightarrow HOAt) upon reaction with $[(\text{Me}_2\text{N})_2\text{C}=\text{Cl}]^+$, respectively, in the presence of a tertiary base. However, they have been erroneously classified by structural analogy to \rightarrow BOP as uronium reagents. X-ray crystallographic studies revealed that they exist in the solid state as guanidinium reagents – zwitterions comprising a triazole-*N*-oxide and a guanidinium moiety (*N*-TBTU, *N*-HBTU, *N*-HATU). The “real” uronium reagents *O*-HBTU and *O*-HATU may be obtained by a modified synthetic procedure which strictly avoids tertiary amines by employing K_2CO_3 as the base. The two forms are readily distinguished by a shift in the IR absorption from $\sim 1710\text{ cm}^{-1}$ (*O*-form) to $\sim 1670\text{ cm}^{-1}$ (*N*-form), and by the characteristic ^{13}C NMR signals for the cationic uronium carbon ($\delta \sim 162$ ppm) and the cationic guanidinium carbon ($\delta \sim 152$ ppm). Tertiary bases promote the conversion of the uronium reagents (*O*-form) into the guanidinium reagents (*N*-form). Interestingly, the *O*-form uronium reagents are more efficient coupling reagents than the *N*-form guanidinium reagents. Mechanistically, the carboxylate of a deprotonated amino acid nucleophilically attacks the uronium salt, which results in an

O-acyluronium species that is further converted into the HOBT or HOAT active ester. The guanidinium form is attacked by the carboxylate likewise, and also undergoes an acyl migration to give the active ester. Unlike carbodiimides or phosphonium salt reagents, uronium reagents may irreversibly react with, e.g., N-terminal amino groups to give tetramethylguanidinium derivatives, which is an obstacle in the synthesis of \rightarrow cyclic peptides [F. Albericio et al., *J. Org. Chem.* **1998**, 63, 9678; L. A. Carpino et al., *Angew. Chem. Int. Ed.* **2002**, 41, 441].

Urotensin I (UT I), NDDPPISIDL¹⁰TFHLLRNMI²⁰MARIENEREQ³⁰AGLNRKYLDE⁴⁰Va, a 41-polypeptide from the urophysis of the white sucker, *Catostomus commersoni*. Similar peptides have been found, for example, in shark, carp, trout, trout sole, maggy sole, and European flounder. Urotensin I is part of a family of related peptides including \rightarrow corticoliberin, \rightarrow sauvagine and \rightarrow urocortin in vertebrates, and the diuretic peptides in insects (\rightarrow insect diuretic peptides) [D. A. Lovejoy, R. J. Balment, *Gen. Comp. Endocrinol.* **1999**, 115, 1].

Urotensin II (UT II), ETPDCFWKYC¹⁰V (disulfide bond: C⁵–C¹⁰), a human 11-peptide acting as a potent vasoconstrictor and agonist for the orphan receptor GRP14 (now named U_{II} receptor). The mRNA of UT II was found in the spinal cord. *In situ* hybridization studies led to the conclusion that the urotensin II precursor gene is actively expressed in motor neurons. There is evidence that UT II may exert important physiological functions in humans. UT II and its receptor are widely expressed throughout peripheral tissues including the heart, vasculature, kidney, liver, adrenal, and other sites. Due to this distribution it can be concluded that UT II is a po-

tential regulator of cardiovascular function. It has been designated as the most potent vasoconstrictor known, even more potent than \rightarrow endothelin-1. The plasma UT II level is elevated in renal failure, congestive heart failure, diabetes mellitus, systemic hypertension and portal hypertension by liver cirrhosis. Interestingly, physiological data have provided further evidence that UT II is also a modulator of rapid eye movement (REM) sleep. It directly excites cholinergic mesopontine neurons and increases the rate of REM sleep episodes. Before the discovery of the human peptide, UT II was reported as a hederodetic cyclic 12-peptide (AGTADCFWKY¹⁰CV, disulfide bond: C⁶–C¹¹) from the fish urophysis, a neuroendocrine gland located in the caudal part of the spinal cord [Y. Coulouarn et al., *Proc. Natl. Acad. Sci. USA* **1998**, 95, 15803; R. S. Ames et al., *Nature* **1999**, 401, 282; C. J. Charles et al., *Peptides* **2005**, 26, 2211; H.-P. Nothacker, S. Clark, *FEBS J.* **2005**, 272, 5694].

Ustiloxins, a family of five naturally occurring heterodetic cyclic peptides (Ustiloxin A–F) isolated from the water extracts of false smut balls on the panicles of the rice plants caused by the fungus *Ustilaginoides virens*. They share a similar 13-membered cyclic core structure characterized by an unique chiral tertiary alkyl-aryl ether linkage. A convergent total synthesis of ustiloxin D via an unprecedented ethynyl aziridine ring-opening of phenol derivatives has been described [Y. Koiso et al., *Tetrahedron Lett.* **1992**, 33, 4157; P. Li et al., *Org. Lett.* **2005**, 7, 5325].

UT, urotensin.

Uteroglobin (UG), a member of the secretoglobulin gene family. UG is a conserved progesterone-dependent protein which is

released into uterine secretions during the pre-implantation phase. Native UG consists of two identical 70 aa subunits connected in an antiparallel orientation by two disulfide bridges forming a hydrophobic cavity. The exact physiological function of this protein has not been determined. It may have potent anti-inflammatory and immunomodulatory properties. Furthermore, it has been suggested that UG may

protect the developing embryo from maternal immunological attack. The X-ray analysis of recombinant bovine UG at 1.6 Å has been described [H. M. Beier, *Ann. N. Y. Acad. Sci.* **2000**, 923, 9; Z. Zhang et al., *DNA Cell Biol.* **1997**, 16, 73; V. von der Decken et al., *Acta Crystallogr.* **2005**, F61, 499].

UV, ultraviolet.

V

V8 protease, EC 3.4.21.19, *Endoproteinase Glu-C*, *protease I*, protease type XVII-B, an extracellular endopeptidase from the V8 strain of *Staphylococcus aureus*. It cleaves peptide bonds on the C-terminal side of glutamic acid and, to a lesser extent, of aspartic acid. The X-ray crystallographic structure of V8 protease was described in 2004 [G. R. Drapeau et al., *J. Biol. Chem.* **1972**, 247, 6720; L. Prasad et al., *Acta Crystallogr.* **2004**, D60, 256].

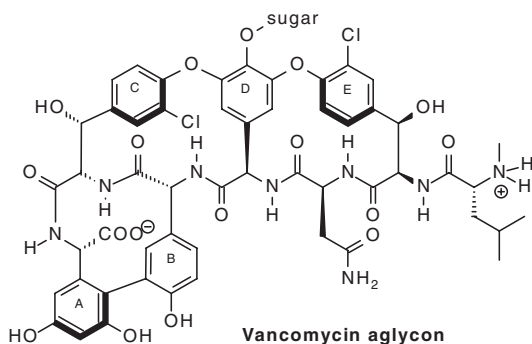
Valine (Val, V), L- α -aminoisovaleric acid, $(\text{H}_3\text{C})_2\text{CH-CH}(\text{NH}_2)\text{-COOH}$, $\text{C}_5\text{H}_{11}\text{NO}_2$, M_r 117.15 Da, a proteinogenic amino acid.

Valinomycin, cyclo-(D-ValLac-Val-D-Hiv)₃, a symmetric cyclodepsipeptide isolated from *Streptomyces fulvissimus*. This fungal antibiotic is formed by three repeating units of a sequence of D-Val, L-lactic acid (Lac), Val and D-hydroxyisovaleric acid (D-Hiv). Valinomycin acts as an ion carrier which selectively transports potassium ions across membranes. K^+ is coordinated by six Val carbonyl oxygen atoms. The amino acid side chains provide the overall hydrophobic exterior, enabling valinomycin to cross the hydrophobic core of the membrane. Within the membrane, valinomycin alternates between loaded and unloaded states through which ions are transported across the membrane. Valinomycin shows the best K^+/Na^+ selectivity of all K^+ -ionophores known to date. It is especially active against *Mycobacterium tuberculosis*. The assembly of amide and depside bonds on-resin has been overcome using a Wang-

type resin with the hydroxy acids protected, e.g., as tetrahydropyranyl derivatives and coupled using DIC/DMAP. In case of the valinomycin analogue cyclo-(Val-D-Man-D-Val-L-Lac-), the linear precursor was synthesized on-resin, and then cyclized in solution using HATU (24% yield) activation at the Lac residue [R. M. Izatt et al., *Chem. Rev.* **1985**, 85, 271; B. Dietrich et al., *Macrocyclic Chemistry*, VCH, Weinheim, **1993**; W. Duax et al., *Biopolymers* **1996**, 40, 141; O. Kuisle et al., *J. Org. Chem.* **1999**, 64, 8063; J. S. Davies, *J. Peptide Sci.* **2003**, 9, 471].

Valorphin, H-Val-Val-Tyr-Pro-Trp-Thr-Gln-OH, a 6-peptide isolated from bovine hypothalamus tissue possessing opiate activity. Valorphin corresponds to the partial sequence 32–38 of the bovine hemoglobin β -chain, and may belong to the hemorphins (\rightarrow exorphins) [V. Brantl et al., *Eur. J. Pharmacol.* **1986**, 125, 309; J. Erchegyi et al., *J. Pept. Protein Res.* **1992**, 39, 477].

Vancomycin, a glycopeptide antibiotic from a fermentation broth of the actinomycete *Streptomyces orientalis*, later renamed *Nocardia orientalis* and finally reclassified as *Amycolatopsis orientalis*. It exhibits lethal properties against all tested strains of *Staphylococcus* and other Gram-positive bacteria. Despite recent incidences of bacterial resistance to vancomycin, it became almost legendary because of its performance against methicillin-resistant *S. aureus* (MRSA). Vancomycin and the closely related *teicoplanin* are typically administered parenterally to treat



severe staphylococcal infections, including MRSA. Worldwide sales of vancomycin in 1997 were US\$ 417 million. Vancomycin was discovered by Eli Lilly in 1956. The complete structure was established only in 1982, followed by elucidation of the crystal structure in 1996, and the total synthesis of vancomycin aglycone and vancomycin itself in 1999. Vancomycin consists of seven amino acids containing in total five aromatic rings. The sugar components are D-glucose and L-vancosamine. Vancomycin binds reversibly to the -Lys-D-Ala-D-Ala- sequence of the peptidoglycan monomer and prevents the transglycosidase from polymerizing the peptidoglycan monomers; this results in cell death. The biosynthesis proceeds through construction of the amino acid building blocks, formation of the linear heptapeptide according to multienzyme thiotemplate mechanism, oxidative coupling processes, and finally glycosidations [C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1982**, 104, 4293; M. Schäfer et al., *Structure* **1996**, 4, 1509; K. C. Nicolaou et al., *Angew. Chem. Int. Ed.* **1999**, 38, 2096; F. C. Tenover, L. C. McDonald, *Curr. Opin. Infect. Dis.* **2005**, 18, 300; J. L. Pace, G. Yang, *Biochem. Pharmacol.* **2006**, 71, 968].

Vanchrobactin, N-[N'-(2,3-dihydroxybenzoyl)-D-arginyl]-L-serine, a siderophore pro-

duced by the bacterial fish pathogen *Vibrio anguillarum* serotype O2. This pathogen is the causative agent of vibriosis, an fatal hemorrhagic septicemia resulting in considerable economic losses in aquaculture farming [R. G. Soengas et al., *Tetrahedron Lett.* **2007**, 48, 3021].

Vapreotide, → somatostatin.

Vasoactive intestinal contractor (VIC), a murine vasoactive peptide (VIC) and its human analogue → endothelin-2 (ET2) are vasoactive hormone composed of 21 amino acids belonging to the ET-SRTX group (→ endothelin, → sarafotoxins). The biologically active mature VIC peptide is produced from a 175-aa precursor protein (prepro-VIC) [K. Saido et al., *J. Biol. Chem.* **1989**, 264, 14613; K. Saido et al., *Genomics* **2000**, 64, 51].

Vasoactive intestinal peptide (VIP), HS DAVFTDNY¹⁰TRLRKQMAVK²⁰KYLNSIL Na, a 28-peptide amide with cardiovascular effects. It was first isolated from porcine intestine, and belongs to the → glucagon-secretin-VIP family. VIP is a potent vasodilator, a major growth stimulator, a bronchodilator, and a neuronal survival-promoting agent. VIP is widely distributed in the peripheral and central nervous systems, and acts both

as neurotransmitter and as a hormone. Thus, it is not only an intestinal peptide but, in accordance with its early given abbreviation, it is also a very important peptide. VIP is co-synthesized with \rightarrow peptide histidine isoleucine amide (PHI) on the same peptide precursor. Three major types of VIP receptor, VPAC1, and VPAC2, and PAC1, belonging to the family of G protein-coupled receptors, have been identified and molecularly cloned, and this has broadened the understanding of their mechanisms of action. VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) are the main endogenous ligands of these receptors. Because of the low VIP and PACAP concentrations in the blood, it is assumed that they act locally as autocrine/paracrine effectors. VIP-based drug design and non-invasive innovative delivery modes are promising, with the emphasis on tumor diagnosis and treatment, neuroprotection, immunomodulation, and impotence treatment. Radiolabeled VIP analogues may be used in diagnosis for imaging of lung and breast cancer. VIP receptor antagonists inhibit proliferation of lung and breast cancer cells and potentiate the apoptotic effect of chemotherapeutic agents [S. I. Said, V. Mutt, *Eur. J. Biochem.* 1972, 28, 199; T. W. Moody, I. Gozes, *Curr. Pharm. Des.* 2007, 13, 1099].

Vasopressin (VP), *antidiuretic hormone*, ADH, H-Cys-Tyr-Phe-Gln-Asn-Cys-Xaa-Gly-NH₂ (disulfide bond: Cys¹-Cys⁶), a member of the neurohypophyseal peptide hormones. VP has antidiuretic activity, and in higher doses it increases blood pressure. In bovine and other mammalian hormones Xaa = Arg (AVP), but in the porcine peptide Xaa = Lys (LVP). VP shows strong structural similarities to \rightarrow oxytocin, and has a slight oxytocin effect. VP is synthesized by the magnocellular

cells, mainly in the nucleus supraopticus, and also in the paraventricular nuclei of the hypothalamus as part of neurophysin II, a precursor protein bearing the VP sequence following the N-terminal signal sequence and in the C-terminal part the sequence of a 39-glycopeptide named \rightarrow copeptin. In this form VP is transported through the supraoptico-hypophyseal tract to the posterior pituitary, where it is stored and then released proteolytically into the blood after an adequate stimulus. VP elicits a variety of responses, both centrally and peripherally. For example, it induces water conservation by the kidney, contributing to regulation of osmotic and cardiovascular homeostasis. VP deficiency causes *diabetes insipidus*. Because of inadequate resorption by the kidneys, in this disorder up to 20 L of urine is passed per day. The biological actions of AVP are mediated by three G protein-coupled receptor subtypes: the V_{1a} (vascular), V_{1b} (V₃) (pituitary), V₂ (renal) receptors, and the oxytocin (OT) receptors. AVP V_{1a} receptors occur in many tissues, including the CNS, and mediate the vascular effects of AVP by causing vasoconstriction of the vascular smooth muscle cells. V_{1b} receptors present in the pituitary, pancreas, adrenals and CNS mediate the release of \rightarrow ACTH by AVP. Interestingly, it has been recently reported that the AVP V_{1b} receptor also regulates anxiety and depression in rats and humans. The well-known antidiuretic effects of AVP are mediated by the V₂ receptor that are present in the kidney. All receptor subtypes and OT receptors from a variety of species have been cloned. Besides their value as research tools, some V_{1a}, V₂ and OT receptor agonists and antagonists have found therapeutic application, whereas others are currently in clinical trials. Very active analogues with agonistic, dissociated, and antagonistic

properties have been synthesized which also allow for nasal application. The commercial drug [1-desamino-D-Arg⁸]VP (DDAVP) has 400 times the effect of native AVP on the kidneys, with a practically negligible effect on blood pressure. [1-desamino-penicillinamine, 2-O-methyltyrosine]AVP belongs to the widely used antagonists. Many useful analogues have been synthesized, e.g., those with increased V₁-antagonistic potency and reduced V₂ agonism (antidiuretic effects), as well as analogues with CNS activity, such as [desGly⁹-NH₂]VP. Sequence determination and the first chemical synthesis were performed by → du Vigneaud in 1953/54, together with those of oxytocin [V. du Vigneaud et al., *J. Am. Chem. Soc.* **1954**, 76, 4751; V. J. Hruby, D. Patel, in: *Peptides: Synthesis, Structures, and Applications*, E. Gutte (Ed.), p. 261, Academic Press, San Diego, **1995**; C. Barberis et al., *Drug News Perspect.* **1999**, 11, 279; M. Birnbaumer, *Trends Endocrinol. Metab.* **2000**, 10, 406; G. Griebel et al., *Proc. Natl. Acad. Sci. USA* **2002**, 99, 6370; L. L. Cheng et al., *J. Med. Chem.* **2004**, 47, 2375; G. Griebel et al., *Curr. Pharm. Des.* **2005**, 11, 1549].

Vasotab, a vasoactive 56-peptide from horse fly *Hybomitra bimaculata* (Diptera, Tabanidae) salivary glands. The peptide contains six cysteine residues which form three disulfide bonds similar to the disulfide pattern of the Kazal-type protease inhibitors. In comparison to the latter, vasotab has an unique 7-amino-acid insertion between the third and fourth cysteine residues within the peptide chain. Vasotab shows positive inotropism in isolated rat hearts, vasodilatation of coronary and peripheral vessels, and Na⁺/K⁺-ATPase inhibition. Furthermore, it is capable of blocking L-type calcium channels [P. Takac et al., *J. Exp. Biol.* **2006**, 209, 343].

Vasotocin (VT), H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Arg-Gly-NH₂ (disulfide bond: Cys¹-Cys⁶), the evolutionary precursor of the → neurohypophyseal hormones. VT has been found in the pineal body of mammals and in the cerebrospinal fluid of humans. It is responsible for the regulation of water and mineral metabolism of lower vertebrates. During transition from the cyclostomata to fish, a gene duplication occurred which resulted in the formation of → oxytocin and → vasopressin. Only the replacement of Ile³ in VT by Phe led to vasopressin as the mammalian hormone. Precursors of VT (→ hydriins) have been isolated from the pars intermedia of *Rana esculenta* [F. L. Moore, C. A. Lowry, *Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol.* **1998**, 119, 251].

VCC-1, a novel → cytokine that promotes tumor growth [E. J. Weinstein et al., *Biochem. Biophys. Res. Commun.* **2006**, 350, 74].

Vessel dilator, → atrial natriuretic peptides.

VIC, vasoactive intestinal contractor.

Vinylamycin, a 14-membered cyclodepsipeptide (→ depsipeptides) isolated from the culture broth of *Streptomyces* sp. (MI982-63F1). Vinylamycin consists of D-valine, alanine, 4-amino-2,4-pentadienoic acid, and 2-hydroxy-3-(2-hydroxyethyl)-4-methyldecanoic acid. It exhibits broad and moderate antimicrobial activities against Gram-positive bacteria [M. Igarashi et al., *J. Antibiot.* **1999**, 52, 873].

Vinylogous peptides, peptides that contain α,β-unsaturated γ-amino acids (vinylogous amino acids). They are called vinylogous amino acids because they are formally extended by a vinyl group -CH=CH-. Naturally occurring vinylogous peptides such

as \rightarrow cyclotheonamide A and B have been isolated from the sponge *Theonella*. Vinylogous peptides that are composed exclusively of vinylogous amino acids have been proposed to form helical structures. *trans*-Vinylogous proline-containing peptides with *cis*-amide bonds form β -turn-like structures, while a *cis*-vinylogous residue promotes an NH to CO intramolecular H-bond, closing a nine-membered "ring" [M. Hagihara et al., *J. Am. Chem. Soc.* **1992**, 114, 6568; C. Baldauf et al., *J. Org. Chem.* **2005**, 70, 5351; C. Grison et al., *J. Org. Chem.* **2005**, 70, 10753].

Viocin, \rightarrow viomycin.

Viomycin, *viocin*, *vinactin A*, *florimycin*, a RNA-binding cyclic 5-peptide antibiotic from the culture broth of various *Streptomyces* sp. such as *S. puniceus*, *S. floridae*, and *S. vinaceus*. Viomycin inhibits prokaryotic protein synthesis and group I intron self-splicing. It enhances the activity of the ribozyme derived from the *Neurospora crassa* VS RNA, and at sub-inhibitory concentrations it induces the formation of group I intron oligomers. Viomycin is active against Gram-negative bacteria, and has found therapeutic application against *Mycobacterium tuberculosis*. *Tuberactinomycin B* (R = OH) is structurally very similar to viomycin, and is both allergenic and toxic to

kidneys [S. Noda et al., *J. Antibiot.* **1972**, 25, 427; H. Wank et al., *Orig. Life Evol. Biosph.* **1999**, 29, 391; M. G. Thomas et al., *Antimicrob. Agents Chemother.* **2003**, 47, 2823].

VIP, vasoactive intestinal peptide.

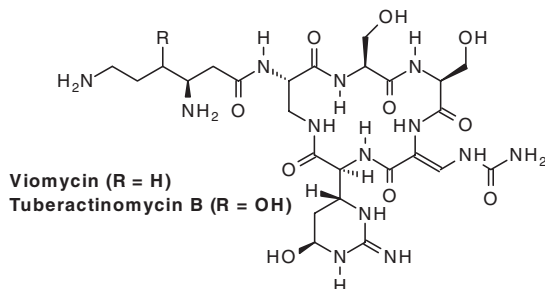
Viridogrisein, \rightarrow etamycin.

Viscosinamide, a cyclodepsipeptide (\rightarrow depsipeptides) isolated from an extract of *Pseudomonas fluorescens* DR54. It contains Leu (3), D-Glu, D-*allo*-Thr, D-Val, D-Ser (2), Ile, and β -hydroxydecanoic acid with the ester bond between D-*allo*-Thr³ and Ile⁹. Viscosinamide exhibits antifungal and surfactant properties [T. H. Nielsen et al., *J. Appl. Microbiol.* **1999**, 87, 80].

VLDL, very low-density lipoprotein.

VP, vasopressin.

Vpu, *viral protein U*, an integral membrane 81-peptide ($M_r \sim 16$ kDa) encoded by the HIV-1 genome and playing an important role in the viral life cycle. Vpu both enhances virion release from human cells and the degradation of CD4, the cellular surface receptor of HIV-1. The oligomeric N-terminal transmembrane domain forms a cation-specific ion channel which is responsible for the enhanced release of mature virus particles from the cell surface. In



addition, Vpu mediates degradation of the CD4 receptor in the ER by interactions of the cytoplasmic domain with both the cytoplasmic tail of CD4 and the β TrCP component of the SCF ^{β TrCP}E3 ubiquitin ligase complex. Structure and dynamics of the transmembrane domain were investigated by solid-state NMR with magic-angle spinning [E. A. Cohen et al., *Nature* **1988**, 334, 532; S. Bour, K. Strebel, *Microbes Infect.* **2003**, 5, 1029; S. Sharpe et al., *Biochemistry* **2006**, 45, 918].

W

Wang resin, 4-benzyloxybenzyl alcohol resin, a resin routinely used for the Fmoc/Bu^t approach for the synthesis of free peptide acids. Wang resin can be easily obtained from → Merrifield resin by esterification with methyl 4-hydroxybenzoate, followed by reduction of the methyl ester with LiAlH₄ [S. S. Wang, *J. Am. Chem. Soc.* **1973**, 95, 1328].

Water-soluble carbodiimide (WSCDI), 1-ethyl-3-(3'-dimethylamino)carbodiimide HCl salt (EDC) or WSC (HCl), a carbodiimide-type coupling reagent that is soluble both in organic and aqueous solvents. EDC can be employed for the modification, conjugation, or immobilization of native peptides and proteins. The urea derivative formed during coupling with EDC can be removed by acid-base extraction from organic media because of the tertiary amino group.

Wieland, Theodor (1913–1995), Professor of Organic Chemistry (1951–1968) at Frankfurt/Main (Germany), and director of the department of natural product chemistry at the Max Planck Institute for medical research at Heidelberg (1968–1981). Besides other important contributions in natural science and peptide research, he made the → mixed anhydride method available for modern peptide synthesis, and as early as 1953 described the basic principle of

→ native chemical ligation. He wrote a monograph on the “Peptides of Poisonous Amanita Mushrooms” (Springer, 1986), in which his pioneering work on the elucidation of the analytical, structural, synthetic chemistry of the toxic *Amanita* fungi as well as many structurally related analogues, including their molecular–biological effects, is well documented. Theodor Wieland was a great natural scientist, one of the pioneers of modern peptide chemistry, and particularly a humanitarian with unlimited patience and personal modesty; notably, he was admired for his sparkling spirit and warm humor [B. Witkop, M. Eigen, *Theodor, Hermann, Felix Wieland (5 June 1913–24 November 1995)*, *Proc. Am. Phil. Soc.* **1998**, 142, 316].

WSCDI, water-soluble carbodiimide.

WWamides, biologically active 7-peptide amides originally isolated from ganglia of the African snail *Achatina fulica*. The name is related to the both terminal Trp(W) residues. *WWamide-1*, H-Trp-Lys-Glu-Met-Ser-Val-Trp-NH₂, shows inhibitory activity on a central neuron of the snail. Furthermore, it exhibits peripheral modulatory effects on muscular contractions in various tissues of the snail and other mollusks. *WWamide-2* corresponds to [Arg²]*WWamide-1* and *WWamide-3* to [Gln³]*WWamide-1*, respectively [H. Minakata et al., *FEBS Lett.* **1993**, 323, 104].

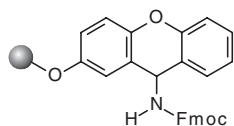
X

Xaa, unknown or unspecific amino acid (also Aaa).

XAL handle, 5-(9-aminoxanthen-2-oxy)valeric acid, a handle for Fmoc/Bu^t SPPS of peptide amides. It is a promising alternative to the → PAL handle due to its higher acid lability [Y. Han et al., *J. Org. Chem.* **1996**, 61, 6326].

Xan, 9H-xanthen-9-yl, 9-xanthidryl.

Xanthenyl resin, a highly acid-labile resin suitable for SPPS of protected peptide amide segments [P. Sieber, *Tetrahedron Lett.* **1987**, 28, 2107].



Xanthenyl resin

Xenin 25, MLTKFQTKSA¹⁰RVKGLSFH PK²⁰RPWIL, a 25-peptide from the human gastric mucosa. It is structurally related to → neurotensin. The C-terminal sequence 19–25 is in common with amphibian → xenopsin. Xenin 25 inhibits pentagastrin-stimulated secretion of acid, to induce exocrine pancreatic secretion and to affect intestinal motility. It represents the N-terminus of a cytosolic coat protein (alpha-COP) from which it can be cleaved via the 35-aa proxenin by aspartic proteases. Furthermore, it has been reported that xenin is a peptide marker to neuroendocrine tumors of the duodenum [G. F. Feurle et al., *Gastroenterology* **2002**, 123, 1616].

Xenopsin, pGlu-Gly-Lys-Arg-Pro-Trp-Ile-Leu-OH, an 8-peptide from the skin extract of the South African frog *Xenopus laevis*. It shows sequence homology with both the C-terminal parts of → xenin 25 and → neurotensin, respectively. Xenopsin shares a number of its biological activities with neurotensin [K. Araki et al., *Chem. Pharm. Bull.* **1973**, 21, 2801; G. E. Feurle et al., *Cell. Mol. Life Sci.* **1982**, 38, 679].

Xenopsin-related peptides (XRP), two peptides from the avian gastric extracts with a C-terminal hexapeptide sequence in common with → xenopsin. **XRP 1**, [His¹,Pro²] xenopsin, and **XRP 2**, H-Phe-[His¹,Pro²] xenopsin show xenopsin-like activities on gastric regulation [R. E. Carraway et al., *Peptides* **1991**, 12, 107].

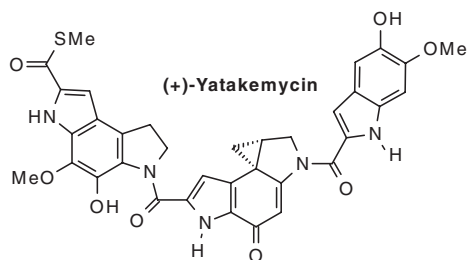
Xfin, a *Xenopus* zinc finger protein expressed in the cytoplasm of the oocyte. Xfin is a phosphoprotein showing the ability to bind an unusually large stretch (185 bases) of DNA. It has been reported that Xfin is expressed during cone differentiation in the retina of the frog *Xenopus laevis*. Xfin is a Cys2-His2 → zinc finger protein in which the Zn²⁺ ions are tetrahedrally coordinated by the His and Cys residues. According to the first NMR structure of a zinc finger, it forms a compact globule containing a two-stranded antiparallel β-sheet and an α-helix that are stabilized by the Zn²⁺ ion [D. Rhodes, A. Klug, *Cell* **1986**, 46, 123; S. De Lucchini et al., *Mech. Dev.* **1991**, 36, 31; F. M. Rijli et al., *Int. J. Dev. Biol.* **1993**, 37, 311].

Y

Yatakemycin, an exceptionally potent, naturally occurring antitumor agent isolated from a culture broth of *Streptomyces* sp. TP-A0356 in 2003. (+)-Yatakemycin contains a characteristic dienone cyclopropane ring system which also occurs in other antitumor compounds that possess remarkable antitumor activity via a sequence-selective DNA alkylation at the activated cyclopropane [Y. Igarashi et al., *J. Antibiot. (Tokyo)* **2003**, 56, 107; M. S. Tichenor et al., *J. Am. Chem. Soc.* **2004**, 126, 8396; K. Okano et al., *J. Am. Chem. Soc.* **2006**, 128, 7136].

Yeast mating factor α , α -factor, pheromone α -factor, WHWLQLKPGQ¹⁰PMY, a 13-peptide acting as a pheromone of mating type a cells of *S. cerevisiae*. It inhibits DNA synthesis, thereby preventing cell division of mating type a cells [D. Stoetzler et al., *Eur. J. Biochem.* **1976**, 69, 397; F. Naider, J. M. Becker, *CRC Crit. Rev. Biochem.* **1986**, 21, 225].

Yunnanin F, a cyclic 8-peptide showing anthelmintic activity and moderate anti-inflammatory activity [B. Poojary, S. L. Belagali, *Eur. J. Med. Chem.* **2005**, 40, 407].



Z

Z, benzyloxycarbonyl.

Zeamatin, a 27-peptide produced by *Zea mays* seeds with antifungal activity. Zeamatin causes probably by permeabilizing the fungal plasma membrane the release of cytoplasmic material from *C. albicans* and *Neurospora crassa*, which results in hyphal rupture. Peptides similar to zeamatin also occur in *Sorghum bicolor*, *Triticum aestivum*, and *Avena sativa* seeds [W. K. Roberts, C. P. Selitrennikoff, *J. Gen. Microbiol.* **1990**, *136*, 1771; A. J. Vigers et al., *Mol. Plant-Microbe Interact.* **1991**, *4*, 315].

ZEBRA protein, *BZLF1*, *Zta*, *Z* or *EB1*, a 245 aa protein belonging to the bZIP family of transcription factors. It shows sequence similarity to other basic region leucine zipper proteins such as yeast GCN4 and the human c-Fos and c-Jun. Members of this family bind DNA through their ~60-aa bZIP domain. This domain comprises an N-terminal basic region that contacts the DNA and a C-terminal leucine zipper which dimerizes by forming a \rightarrow coiled coil. However, the bZIP domain (sequence region ~175–220) of ZEBRA is unusual due to the lacking of the canonical leucine-zipper motif. It has been suggested that ZEBRA dimerizes and binds DNA differently from the other bZIP proteins, though the mechanism remains unclear. ZEBRA acts as the Epstein–Barr virus (EBV) immediate-early transcription factor, triggering the switch from latent to lytic infection by EBV [P. J. Farrell et al., *EMBO J.* **1989**, *8*, 127; T. Kouzarides et al., *Oncogene*

1991, *6*, 195; P. Morand et al., *Acta Crystallogr.* **2006**, *F62*, 210].

Zeins, the major storage proteins of maize belonging to the \rightarrow prolamins. In maize, the ethanol-soluble or protamine fraction consists of the zeins ($M_r \sim 10$ –22 kDa) that constitutes as much as half of the total protein of the endosperm. They are characterized by a high content of Glu (23%) and Leu (19%). The amino acid sequence of a representative of the zeins has been derived from the nucleotide sequence of a zein cDNA clone [D. Geraghty et al., *Nucleic Acids Res.* **1981**, *9*, 5163].

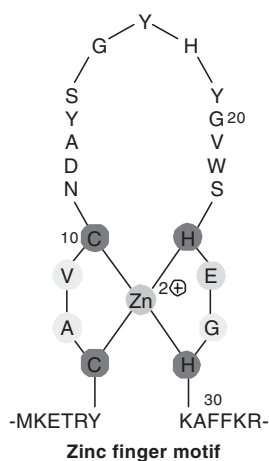
Zervas, Leonidas (1902–1980), a renowned Greek chemist and pioneer of peptide research. He started his scientific career as junior associate in the laboratory of Max \rightarrow Bergmann in Dresden (Germany). Already in 1932, the publication of a paper by Bergmann and Zervas on the introduction of the “carbobenzoxy” group (\rightarrow benzyloxycarbonyl group) described a new general method for peptide synthesis. This discovery greatly broadened the scope of peptide chemistry, and in honor of his achievement the benzyloxycarbonyl group later was given the abbreviation “Z”. In 1934, Bergmann had secured a Rockefeller Foundation fellowship for Zervas. In 1937, he became Professor of Organic Chemistry and Biochemistry at the University of Thessaloniki (Greece), and two years later accepted a full professorship of organic chemistry at University of Athens. Zervas was founder and chairman of the National Hellenic Research Foundation (NHRF), an honorary

member of the American Chemical Society, and a foreign member of the Russian Academy of Sciences [P. Katsoyannis (Ed.), *The Chemistry of Polypeptides – Essays in Honor of Leonidas Zervas*, Plenum Press, New York, 1973].

Ziconotide, a novel non-opioid, non-local anesthetic, developed for the treatment of severe chronic pain. Ziconotide CK GKGAKCSR¹⁰LMYDCCTGSC²⁰RSKGKCa (disulfide bonds: C¹–C¹⁶, C⁸–C²⁰, C¹⁵–C²⁵) also previously referred to as Prialt[®], CI 1009, or SNX-111, is the synthetic equivalent of the cone snail peptide ω -conotoxin M-VII-A (\rightarrow conotoxins), a neuron-specific N-type calcium channel blocker with an analgesic activity about 800-fold stronger than that of morphine [Z. Xia et al., *BioDrugs* 2006, 20, 275].

Zinc finger proteins, proteins containing Cys2-His2 zinc fingers as DNA-binding domains. More than 500 zinc finger proteins are known which collectively contain about 5000 of these domains in the human genome. The single domain, called a “finger”, consists of about 30 aa with a simple $\beta\beta\alpha$ fold which is stabilized by hydrophobic interactions and the Cys2-His2 motif. These domains occur in covalent tandem arrays of up to 37 repeats, and facilitate the recognition of extended DNA sequences. The characteristic nature of zinc finger proteins distinguished them from other DNA-binding motifs that typically form homo- or hetero-dimers. The first DNA-binding motif was discovered in the 344-aa *Xenopus* transcription factor IIIA (TFIIIA) during the late 1980s. The first elucidated NMR structure of a single zinc finger was the \rightarrow Xfin protein. The relatively simple structure and binding mode of zinc finger proteins have led to the engineering of custom DNA-binding proteins. A designed

six-finger peptide, bound to DNA, is \rightarrow Aart. Interestingly, the production of artificial transcription factors and targeted endonucleases is currently in progress [A. Klug, D. Rhodes, *Trends Biochem. Sci.* 1987, 12, 464; D. Rhodes, A. Klug, *Sci. Am.* 1993, 268, 56; J. C. Venter et al., *Science* 2001, 291, 1304; P. Blancafort et al., *Mol. Pharmacol.* 2004, 66, 1361; K. Beumer et al., *Genetics* 2006, 172, 2391].



Zymogens, *proenzymes*, inactive precursors of enzymes, usually proteases. Zymogens are converted into active proteases by limited proteolysis. Examples of these proteins include the zymogens of digestive enzymes, e.g., pepsinogen, trypsinogen, chymotrypsinogens, proelastase and procarboxypeptidases, and the blood coagulation enzymes (\rightarrow plasminogen and \rightarrow prothrombin). The zymogens of trypsin, chymotrypsin, and elastase, for example, have all their catalytic residues, but their active sites are distorted. Their very low enzymatic activity arises from their reduced ability to bind substrates productively and to stabilize the tetrahedral intermediate. However, during the 1990s it was shown that zymogens could be used as biocatalysts for practically irreversible peptide

bond formation (→ enzymatic peptide synthesis). Biosynthetically formed zymogens can be normally stored at their site of synthesis, without danger of causing the self-digestion of cells or tissues. Pancreatic zymogens are stored in zymogen granules; these are intracellular vesicles the membra-

nous walls of which are thought to be resistant to enzymatic degradation. However, the painful condition of acute pancreatitis is characterized by the premature activation of digestive proenzymes which are synthesized in this gland [R. M. Stroud et al., *Annu. Rev. Biophys. Bioeng.* **1977**, 6, 177].