Small bioactive peptides for biomaterials design and therapeutics

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Small Bioactive Peptides for Biomaterials Design and Therapeutics

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Abstract

This review aims to provide a concise yet extensive survey of key short bioactive peptide sequences for a range of applications ranging from biomaterials development through to peptides with therapeutic uses. The following are considered: cell adhesion motifs, structural peptides, cell-penetrating and tumor-homing peptides, antimicrobial peptides, peptide hormones, growth factors and matrix metalloprotease substrates, neuropeptides, amyloid peptides, antioxidant peptides, peptide affinity tags, anticancer peptides and others. This review provides a convenient resource, summarizing a broad range of important sequences with great utility both as a resource concerning small peptide drugs and also novel biofunctional peptide-based materials.

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1. Introduction

Peptides are remarkable biomolecules with a huge diversity of important roles *in vivo*. Short peptides are generally easy to synthesize by chemical routes or they can be obtained recombinantly and are thus attractive agents and targets for therapies and diagnostics and the fabrication of bionanomaterials. This review provides a summary of short bioactive peptide sequences as a useful "one-stop" reference. Since it is obviously not possible to discuss every short peptide sequence with bioactivity that has been discovered or synthesized, the focus here is on key sequences. This means sequences that have been used in research by many groups for a specific application. Most peptides considered in this review are the subject of papers with a few dozen citations, although newer key works providing important insights are also discussed. Peptides with a broad range of activities ranging from cell adhesion motifs to model amyloid peptides are considered here, but it is not possible to list every single short peptide sequence that has been studied, hence a threshold has been applied.

This review only deals with short bioactive peptides, short here referring to a peptide with approximately 18 or fewer residues. This is a somewhat arbitrary cut-off in some senses but it does correspond roughly to the length of peptide that might be considered for routine solid phase synthesis. In addition, it ensures that this review itself is reasonably compact. Longer peptides such as the peptide hormones glucagon (29 residues) or insulin (human insulin has 51 residues) are not discussed here. As a general comment, it may be noted that short native linear peptides with ca. 20-100 residues tend to adopt α-helical structures. A linear peptide must have at least a couple of heptad repeats to form an α-helical structure. In contrast, many (but by no means all) shorter peptide fragments can form β-sheet structures (or can be designed to do so), as discussed below. Also longer peptides with suitable repetitive domains can form β-sheet or other secondary structures (polyproline II for example, in the case of collagen). Cyclic peptides due to steric constraints tend to adopt turn structures.

This review covers short peptides with bioactivities as summarized in Fig.1. These include peptides with roles as cell adhesion motifs, structural peptides (typically sequences from extracellular matrix proteins), cell-penetrating and tumor-homing peptides, antimicrobial peptides, peptide hormones, growth factors and matrix metalloprotease substrates, amyloid peptides, neuropeptides, and other miscellaneous natural peptides and peptide tags. The peptides have been discovered through a variety of methods which include isolation from natural products, rational screening methods such as phage display or peptide library methods or *ab initio* design or "bioinspired" design. Recently, high throughput screening based on protein database analysis has been shown to have great scope in the identification of key sequences, for example for binding domains to particular substrates.

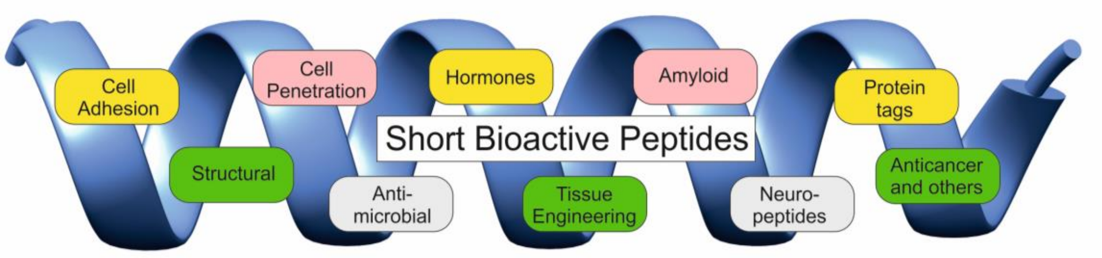


Fig.1. Classes of bioactive peptide considered in this review.

There is overlap between some sections, in one example antimicrobial peptides often show cell-penetrating properties. In another case, combinations of peptides with different functionalities may be required for a specific application. For example, tissue engineering and the development of protein/peptide-based biomaterials requires the presence of multiple motifs, including cell adhesion sequences but also structural domains, degradation domains, growth-factor stimulating motifs and others. Excellent reviews cover some of the required peptide sequences for biomaterials application in tissue engineering, wound healing and regenerative medicine.[1-3] Integrin cell adhesion motifs such as the classic RGD sequence have been reviewed.[4] Reviews are also available on cell-penetrating peptides,[5-6] antimicrobial peptides[7-12] (note though that many animal-derived peptides have sequences too long to be considered here[13-14]), peptide hormones,[15-19] amyloid,[20-28] neuropeptides,[29-32] protein tags,[33-37] and miscellaneous peptides including those with anti-cancer activity. To the best of our knowledge, there are no reviews providing a compact and up-to-date brief summary of bioactive short peptides. A recent review covers orally absorbed cyclic peptides.[38] Inevitably for such a broad topic, there will be omissions for which we apologize in advance. This review is a survey of important and widely-used small bioactive peptides, covering the literature from the initial reports on the discovery or design of these peptides up to recent examples of their applications. It is not intended to discuss every single newly synthesized or discovered small peptide in a review with the scope of this one. The intention is to provide a timely and useful summary, providing a "toolbox" of known bioactive short peptides for researchers developing new biomaterials.

In the following, peptide sequences are presented with single letter codes. D-amino acids are generally indicated with lower case letters. Peptide termini are generally not specified.

Table 1. Summary of Short Bioactive Peptides

Sequence/Name	**Source**	**Activity**	**Key references**
RGD(S)	Fibronectin	Integrin cell adhesion motif	[4, 39-44]
Eptifibatide	Derived from a snake venom peptide	Integrin cell adhesion motif and antithrmobyltic	[45-47]
PHSRN	Fibronectin	Synergy domain	[48]
REDV	Fibronectin	Integrin cell adhesion motif	[49-50]
YIGSR	Laminin	Integrin cell adhesion motif	[51-52]
IKVAV	Laminin	Integrin cell adhesion motif	[53]
DGEA	Collagen (type I)	Integrin cell adhesion motif	[54]
KRSR	Designed based on consensus repeat	Heparin binding and osteoblast adhesion	[55-57]
GFOGER/GFPGER	Collagen (type I and type IV)	Integrin cell adhesion motif	[58-61]
$(GAGA)_n$	Silk	Structural protein	[62]
$(GXY)_n$ (X,Y= residues other than G, typically P or O, hydroxyproline)	Collagen	Structural protein	[63-65]
$(VPGXG)_n$	Elastin	Structural protein	[66-67]
GGRPSDSYGAPGGGN	Resilin	Structural protein	[68-70]
GYSGGRPGGQDLG	Resilin	Structural protein	[70-71]
YGRKKRRQRRR (TAT peptide)	HIV regulatory protein	Cell-penetrating peptide	[72-78]
Penetratin	Drosophila development DNA-binding protein	Cell-penetrating peptide	[79-81]
RRWWRF	Designed	AMP	[82]
Surfactin	Bacteria	AMP	[83-85]
Bacitracin	Bacteria	AMP	[86-89]
Polymyxins	Bacteria	AMPs	[90-91]

Tachyplesins	Horseshoe crab	AMPs	[7, 13, 92]
Protegrins	Porcine leukocytes	AMPs	[13, 93-94]
Defensins	Various vertebrates and invertebrates	AMPs	[7-8, 13, 94-96]
Bactenecin	Bovine neutrophils	AMP	[97]
Indolicidin	Bovine neutrophils	AMP	[7, 11, 13, 98]
Daptomycin	Bacteria	AMP	[99-101]
LPFFD	Designed	Amyloid β fibril disruptor	[102]
Oxytocin	Natural hormone	Activities related to childbirth and social bonding	[63, 103]
Vasopressins	Natural hormones	Water retention Vasoconstriction	[103]
Angiotensins	Natural hormones	Vasoconstriction	[103-105]
Bradykinin	Natural hormone	Vasodilator	[106-108]
pGHWSYGLRPG	Natural hormone	Stimulates hormone release	[109]
PWpG	Natural hormone	Stimulates hormone release	[110-113]
Somatostatin	Natural hormone	Endocrine system regulator (growth hormone inhibitor), neurotransmitter	[114]
Octreotide	Somatostatin analogue	Growth hormone inhibitor and glucagon and insulin inhibitor	[115-116]
Lanreotide	Somatostatin analogue	Growth hormone inhibitor and glucagon and insulin inhibitor	[117-119]
Luteinizing hormone releasing hormone	Natural hormone	Sperm and testosterone production	[109, 114]
WMNF	Natural hormone	Anxiolytic	[120]
GNNQQNY	Yeast prion protein	Model Amyloid Peptide	[121-122]
VQIVYK	Tau protein	Model Amyloid Peptide	[123-125]
$(AEAEAKAK)_2$	DNA-binding protein zuotin	Model Amyloid	[126]
RADARADARADARADA	Designed	Tissue	[127-129]

	alternating peptide	engineering	
FF	Dipeptide	Simplified peptide nanostructure former	130
GPQGIAG	Collagen type I	MMP substrate	131-132
Enkephalins	Natural opioid receptor peptides	Opioid receptor peptides. Neurotransmitters	103, 133
Endomorphins	Natural opioid receptor peptides	Opiod receptor peptides.	134-135
Substance P	Neurotransmitter	Neurotransmitter and other roles	136
Dalargin	Leu-enkephalin analogue	Opioid receptor agonist	137
Glutathione	Natural in most organisms	Antioxidant	138
βAH (carnosine)	Muscle and brain tissue	Antioxidant	76, 139-140
Cyclosporin	Soil fungus	Immune supressant	141-143
Oligo(arginine)	Synthetic, recombinant	Protein fusion tag (also cell-penetrating and antimicrobial)	34, 144
Oligo(histidine)	Synthetic, recombinant	Protein fusion tag	145-146
WSHPQFEK (StrepTag II)	Synthetic, recombinant	Protein fusion tag	34, 147-148
EQKLISEEDL (myc tag)	Synthetic, recombinant	Protein fusion tag	34, 149
DYKDDDDK (FlagTag)	Designed	Protein fusion tag	33, 150
Bleomycins	Bacteria	Anti-cancer activity	151-155
Dolastatin 10	Marine organism	Anti-cancer activity	156-157
Apicidin	Fungal metabolite	Anti-cancer activity	158-160
Romidepsin	Soil bacterium	Anti-cancer activity	161-166
Largazole	Cyanobacterium	Anti-cancer activity	167-168
Aspartame (DF-OMe)	Synthetic	Artificial sweetener	169-170

AMP denotes antimicrobial peptide, pG denotes the non-canonical residue pyroglutamic acid (Fig.13b).

2. Cell Adhesion Peptides

The RGD peptide is the minimal unit of a cell adhesive activity domain present in adhesion proteins such as fibronectin, fibrinogen and vitronectin, which all contain integrin ligands.[4l, 39-44] RGD is also presented as an adhesion recognition sequence in other proteins including laminin and some types of collagen.[171] It is used as a canonical cell adhesion motif in a vast range of biomaterials research, interacting with the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors, and was originally identified as a key factor in angiogenesis. The tetrapeptide RGDS, which is also located at the tenth type III repeating domain of fibronectin, exhibits high cell adhesion activity via binding to the integrin cell-surface receptors.[40, 43-44, 172] This motif is, like the shorter RGD variant, widely used to encourage cell growth in synthetic biomaterials.[173-178] The tetrapeptide sequence and more especially the tripeptide RGD subunit are widely employed in the development of bionanomaterials for applications in cell growth/differentiation or tissue scaffolding.[179] The RGDS tetrapeptide has antithrombolytic activity due to the inhibition of platelet aggregation resulting from the fibrinogen recognition sequence.[180-181] The bioactive RGD and RGDS motifs have also been incorporated into peptide amphiphiles (PAs).[175, 177, 182-187] The RGDS tetrapeptide may have enhanced bioactivity compared to RGD due to the additional serine residue.[40, 188-191] The self-assembly of materials containing RGD-peptide sequences has been reviewed elsewhere.[191] Consideration has been given to why RGD is an effective cell adhesion motif, for instance whether the charge pattern anionic R and cationic D separated by neutral glycine residue). However, the properties of arginine (such as its ability to form bidentate hydrogen bonds with carboxylic acids (Fig.4) seem vital since the analogous KGD sequence is known as a “disintegrin” sequence, for example it is found in some snake venom peptide sequences,[192-193] instead of RGD which is a potent integrin receptor blocker. KGD is a more specific receptor antagonist.[192-193] Disintegrins are short proteins with activity as inhibitors of both platelet adhesion and integrin-binding, however the sequences are too long for this class of protein to be considered in this review. Actually, covalent attachment of the residues may not be essential. For example, it has been shown that co-assembly of Fmoc-dipeptides [Fmoc: fluorenylmethyloxycarbonyl] that display R and D separately, i.e. Fmoc-3F-FR and Fmoc-3F-FD [3F-F denotes triply fluorinated phenylalanine], leads to a fibril structure which is cytocompatible.[194]

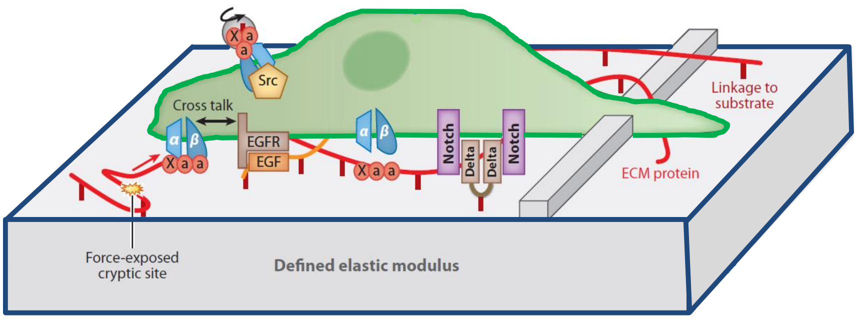


Fig.2 There are multiple cues for cell adhesion with the extracellular matrix. Adapted with permission from Ref. [195] Copyright 2010 Annual Reviews.These include integrins (labelled α, β), cell adhesion motifs Xaa (e.g. RGD), growth factors and their receptors (e.g. epidermal growth factor receptor, EGFR) and Notch transmembrane cell signaling receptors. Delta is a morphogenic biochemical factor involved in ligand clustering. Src is a mechanotransductive tyrosine kinase associated with focal adhesions.

Cyclic RGD peptides such as cyclo(RGDfV) (f: D-phenylalanine) are known to have superior activity and selectivity compared to linear analogues.[196-197] This peptide was identified through competitive $\alpha_v\beta_3$ integrin cell adhesion inhibition studies.[196] The cyclic *N*-methylated compound cyclo(RGDf[*N*-Me]V) with trade name cilengitide is under investigation for the treatment of the brain cancer glioblastoma.[17, 197-199] The related cyclic heptapeptide eptifibatide (also known as integrilin) also contains an RGD mimetic sequence Mpr-HomoArg-GDWPC-NH_2 (cyclized via disulfide bridge) [Mpr: mercaptopropionic acid, HomoArg: homoarginine].[47] It is an important antithrombolytic agent as it inhibits platelet aggregation.[46] It was derived based on a sequence from a snake venom peptide.[45, 47]

It is known that high affinity recognition by the $\alpha_5\beta_1$ integrin requires a so-called synergy peptide PHSRN, a sequence present in fibronectin.[48, 200-201] However, it has been noted that mixing (equimolar quantities of) peptide amphiphiles presenting PHSRN and GRGDSP does not lead to significant synergistic effects on $\alpha_5\beta_1$ recognition.[202-203] Instead, careful design of a peptide to present these sequences in a similar fashion to fibronectin is required (i.e. the spacing between the ligands and nature of the spacer need to be considered).[202-204]

The REDV (and lesser known LDV) sequences are also cell adhesion motifs from fibronectin. They bind to the $\alpha_4\beta_1$ integrin.[49-50] REDV sequence bears obvious sequence similarity to RGDS. It was noted that endothelial cells such as HUVECs (human umbilical vein endothelial cells) adhere to an REDV functionalized substrate but not fibroblasts or vascular smooth muscle cells.[205-206] The KQAGDV sequence also promotes smooth muscle cell adhesion.[55, 207-208]

The YIGSR peptide is a cell adhesion domain from the extracellular matrix protein laminin, present in the basement membrane.[51-52] Both poly(RGD) and poly(YIGSR) have been reported to show anticancer activity, which is enhanced compared to the corresponding oligomers, against lung tumors in mice.[209] Multimeric YIGSR also inhibits angiogenesis and tumor growth of human fibrosarcoma cells in mice.[210] The IKVAV peptide, also obtained from laminin, promotes cell attachment, spreading and neurite outgrowth.[53] A peptide amphiphile (PA) incorporating IKVAV shows promise in the treatment of spinal cord injuries in a study where cultured cells such as neurons were exposed to solutions containing PA fibrils.[211-212] A hybrid PA incorporating both laminin sequences YIGSR and IKVAV supports the survival of neurons and their morphogenesis (dendrite and axon growth) when mixed with collagen to form a fibrous scaffold.[213] Other laminin cell adhesion recognition sequences such as PDSGR (a synergy peptide for YIGSR) have been identified[171, 200, 214] but are less widely employed.

A minimal sequence DGEA from type I collagen is able to recognize the $\alpha_2\beta_1$ integrin receptor.[54] Peptides containing this sequence are able to inhibit adhesion of platelets to collagen mediated by $\alpha_2\beta_1$, but not $\alpha_v\beta_1$-mediated adhesion of platelets to fibronectin or $\alpha_6\beta_1$-mediated adhesion to laminin.[54] For breast adenocarcinoma cells which use $\alpha_2\beta_1$ as a collagen/laminin receptor, adhesion of collagen and laminin was inhibited by DGEA-containing peptides. Stem cell (human mesenchymal stem cells, hMSC) attachment was compared[215] for coatings of PAs incorporating three different cell adhesion motifs - RGDS, DGEA and KRSR. The RGDS-containing PA showed the highest initial attachment and subsequent osteogenic differentiation.[215] The latter is a heparin proteoglycan binding sequence and osteoblast adhesion promotor.[55-57]

The KRSR motif was discovered as a consensus repeat from protein database analysis of bone-related adhesion proteins.[57]

The GFOGER (O: hydroxylproline) domain, originally identified based on the sequence GFPGER within collagen I,[61] is a high affinity binding site to the integrin $\alpha_2\beta_1$ in collagens I and IV and $\alpha_1\beta_1$ in collagen 1.[60] Integrin binding sites to other collagens have also been identified.[59] Since the $\alpha_2\beta_1$ integrin receptor is involved in osteogenesis, the GFOGER domain has been incorporated into biomaterials designed to assist bone repair.[216-217]

3. Structural Peptides

Structural peptides can be large molecules, however they are included in this review since they comprise repeated short peptide sequences. One very widely studied structural peptide is silk. Silk has a semicrystalline structure with crystalline domains embedded in an amorphous matrix.[62] Silk from the *Bombyx mori* silk moth can be considered to be a multiblock copolymer. The crystalline domains contain repetitive $(GAGA)_n$ domains forming stacked β-sheets as well as GS and GT hydroxyl-containing dipeptide sequences.[62, 218-219] On the other hand, dragline spider silk contains polyalanine repeats.[62, 220]

Collagen is another structural protein based on repetitive peptide sequences. Collagen chains form a right-handed triple helical structure. The peptide contains repeating GXY triplets where X and Y are often proline and hydroxyproline respectively.[63-65] Elastin is an important extracellular matrix protein with, as its name suggests, elastic properties. It is an essential constituent of connective tissues such as skin and ligament. Elastin-like peptides (ELPs) contain $(VPGXG)_n$ repeats where X can be any amino acid except proline.[67, 221] ELPs have attracted great interest since they undergo a transition resembling a lower critical solution temperature (LCST), above which the polymer chains collapse and phase separation from water occurs.[221-222] This can be exploited in thermoresponsive release systems for example.[223]

Resilin is a structural protein found in insect wings, ligaments and other insect and arthropod organs. It has elastic properties. Bioactive sequences from the full peptide have been identified and used to create elastomeric biomaterials.[69] The first key resilin sequence identified was GGRPSDSYGAPGGGN, this being presented in repetitive form at the N terminus of a protein express by *Drosophila melanogaster*.[68-70] Another key sequence is GYSGGRPGGQDLG[70-71] and others are listed in the literature.[70] These sequences are essential in conferring elasticity. The tyrosine residues in resilin can undergo cross-linking (through radical formation) which has a significant impact on its structural and mechanical properties.[224-225]

4. Cell-Penetrating and Tumor-Homing Peptides

There are a number of mechanisms by which cell-penetrating peptides can enter cells as illustrated in Fig.3 involving direct translocation or via various endocytosis processes. This subject is reviewed extensively elsewhere.[5-6, 226-229]

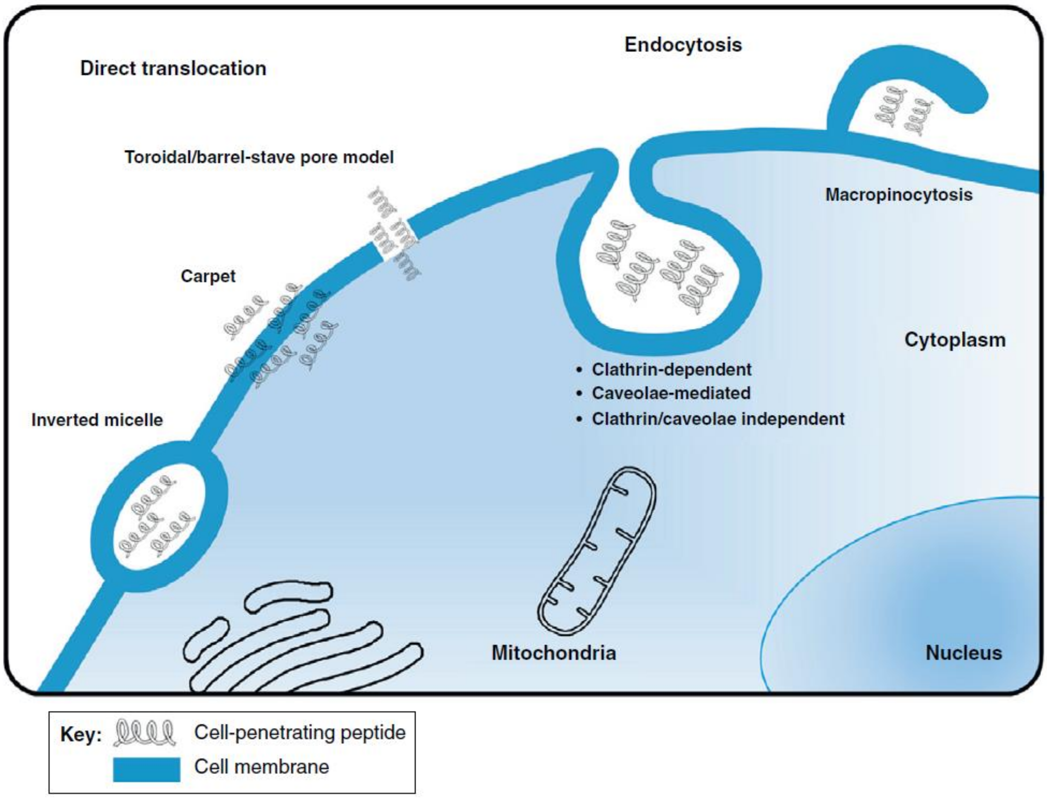


Fig.3. Mechanisms for entry of cell-penetrating peptides into a cell. Reproduced with permission from Ref. 227. Copyright 2012 Elsevier.

The HIV-1 domain peptide TAT (Trans-Activator of Transcription) is a cell-penetrating peptide (CPP) widely used as a vehicle for transport of actives (for example to deliver peptides conjugated to TAT) into cell nuclei.[72-75, 77, 230] It was shown to enter HeLa cells when added to culture medium.[72-73] This transduction domain has high efficiency and is widely used. A shorter TAT peptide core domain RKKRRQRR has been used in several studies on cell internalization[231] and gene delivery.[232] Alternative protein transduction domains (PTDs), including those based on other viral proteins are discussed elsewhere.[75, 233] The penetratin peptide RQIKIWFQNRRMKWKK is derived from a DNA-binding protein involved in *Drosophila* fly morphogenesis.[79-81] It has an ability to translocate across neuronal membranes where it is conveyed to nuclei.[79]

The highly cationic nature of the arginine-rich sequence in TAT peptides is a key to its cell-penetration ability since mammalian cells have membranes rich in zwitterionic lipids such as phosphocholines (microbial cell membranes in constrast contain anionic lipids such as phosphoglycerols). These become polarized in the presence of cationic peptides, especially arginine-rich peptides containing guanidinium groups which form bidentate bonds with POO^- moieties (Fig.4).[78] Arginine-rich cell-penetrating peptides cause membrane pore formation due to the formation of negative Gaussian curvature in the lipid membrane upon interaction with the guanidinium group.[12, 234-235] Since natural cell-penetrating peptides are often rich in arginine residues, synthetic oligo-arginines such as octa-arginine have been investigated as vehicles for cellular transport.[230, 236] Cyclic arginine-rich peptides have also been investigated as CPPs.[237-240]

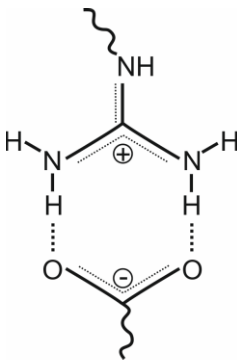


Fig.4. Bidentate binding of guanidinium groups with acidic XOO^- groups (X = C, P)

Cyclic peptides containing the ACDCRGDCFC sequence (identified from a phage display assay of RGD peptides binding to specific integrins including $\alpha_5\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_m\beta_3$[241]) are selective for α_v integrins and show "tumor-homing" properties when injected into cancerous mice.[242] Peptides containing the CNGRC sequence were identified by similar phase display assays and also exhibit tumor-homing behavior.[242-243] This peptide contains the cell-adhesive NGR sequence (present in the cell-binding region of fibronectin) located from phase display studies of binding to $\alpha_5\beta_1$ and $\alpha_v\beta_3$.[42, 244] The related peptide CGKRK also shows anti-tumor proaptotic properties, and potential in the treatment of glioblastoma.[245-246] Similarly, within the family of C-terminal R/KXXR/K sequence-containing peptides identified by Ruoslahti *et al*. as having tissue penetrating properties, the peptide CRGDK shows tumor-homing properties.[247-248] The Ruoslahti group also identified the CREKA tumor-homing peptide by phage display screening using transgenic breast cancer mice.[249]

5. Antimicrobial Peptides

There are several classes of antimicrobial peptides (AMPs). As mentioned in the Introduction, many AMPs of animal origin have longer sequences than consistent with the focus of this review. Nevertheless a variety of shorter ones are considered in this section. One class of short AMP are those rich in arginine residues. Other AMPs include those that are rich in tryptophan, proline- rich peptides, or disulfide-bridged (β-hairpin) peptides.[12] Another category, although not mutually exclusive, is microbially-derived AMPs with cylic headgroups. Some of these antimicrobial peptides are C-terminal amidated[13, 94] although this is not explicitly identified herein. Some AMPs require the presence of counterions for their activity, e.g. Ca^{2+} for Daptomycin.[250] This has led to the idea to create novel AMPs bearing organometallic moieties, a strategy to potentially overcome antimicrobial resistance since such units are not encountered in natural AMPs.[251]

AMPs act by disrupting bacterial cell membranes, usually mediated by electrostatic interactions between peptide cationic residues and anionic lipoteichoic acids and/or lipopolysaccharides which form the outer structure of the bacterial membrane. A number of detailed mechanisms, for example the “carpet” or “barrel-stave” models (Fig.3) have been proposed. In the former case, it is proposed that the peptide coats the outer membrane, whereas in the latter, transmembrane pores are formed by amphpathic α-helical peptides.[252] These comprise two faces, with one face hydrophobic and the other hydrophilic. These aggregate into pores in membranes with the hydrophilic faces on the interior of the pore.After the initial association with the membrane surface, AMPs can cause membrane pore formation, or thin the membrane or can translocate into the interior. Further details on this can be found in other reviews.[8, 10-11, 13] It is recognized that many natural AMPs are rich in the cationic residues lysine or arginine.[12, 253] As mentioned in Section 4, this is also a feature of many cell-penetrating peptides and simply reflects the ability of these peptides to induce membrane lysis. To be useful therapeutically, the lysis needs to be selective to bacterial membranes and not those of eukaryotes. The anti-microbial activity of oligo-arginine containing-peptides has been examined, although selectivity for bacterial membranes with minimal cytotoxicity in humans was not demonstrated.[254]

Tryptophan has also been identified as an important residue in several series of important AMPs including several biologically-derived peptides described in more detail below. Model sequences incorporating tryptophan include RRWWRF[82] and FRWWHR[255] (both capped at both termini). Tryptophan is weakly hydrophobic and is believed to undergo cation-π interactions with cationic species including ions or sidechains of positively charged amino acids.[12]

Short natural AMPs include surfactins, fengycins and iturins (Fig.5).[256-257] All are lipopeptides with a cyclic peptide headgroup, which enhances stability against degradation. Surfactin is a widely studied biosurfactant, and is readily available commercially.[83] This and other bioactive lipopeptides are attracting attention due to their ready production using fermentation methods.[256, 258] *Bacillus subtilis* mainly produces three families of lipopeptidic biosurfactant: the surfactins, the fengycins (or plipastatins) and the iturins (including mycosubtilin.[257] These lipopeptides provide a potentially attractive alternative to chemically synthesized surfactants and they also have potential applications due to their antimicrobial and antifungal properties.[84-85, 256-257] As well as the afore-mentioned antimicrobial and antifungal activity, these compounds also have other potential uses in biomedicine,[256, 259] for instance exhibiting anti-tumor properties. Some related natural cyclic antimicrobial and antifungal lipopeptides are discussed in a recent review on the self-assembly and bioactivity of lipopeptides.[260]

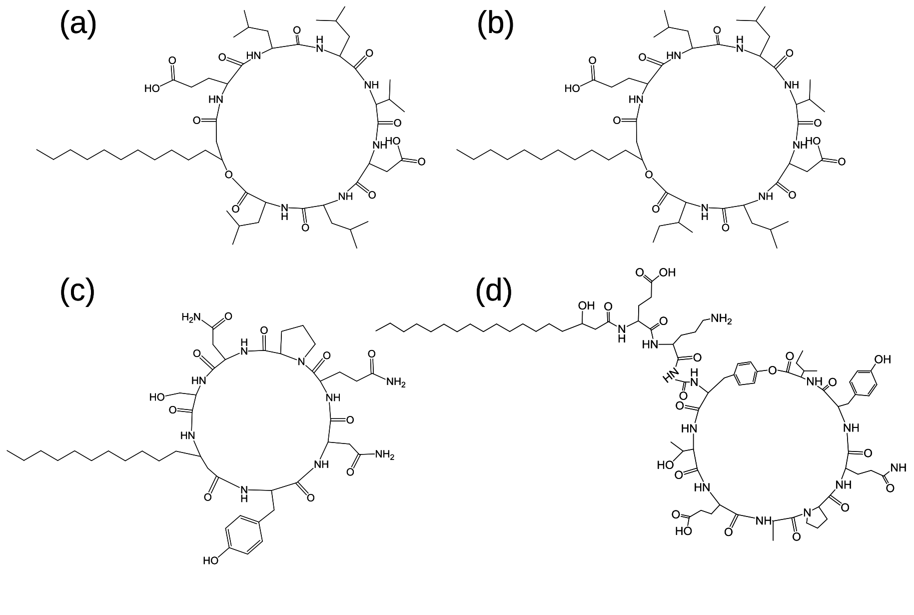


Fig.5. Structure of some lipopeptides produced by *B. subtilis*.[260] (a) Surfactin (b) Lichenysin, (c) Iturin A, (d) Fengycin/plipastatin A. Adapted with permission from Ref. [261] Copyright 2013 Royal Society of Chemistry.As detailed in ref.[257], the expressed lipopeptides actually comprise a mixture of lipid chain lengths.The bio-derived materials comprise a mixture of molecules with different lipid chain lengths.

The bacitracins are a series[86-89] of related cyclic lipopeptides (Fig.5a) with activity against Gram-positive bacteria due to their influence on the peptidoglycan synthesis in the bacterial cell wall. These compounds were originally derived from *B. subtilis* and *B. lichenformis*.[87] Lichenysins,[262-263] pumilacidins[264] and the polymyxin B peptides (Fig.6b)[91] are classes of antimicrobial molecules produced by *Bacillus licheniformis*, *Bacillus pumilus* and *Bacillus polymyxa* respectively.[260] Lichenysin A is a powerful surfactant, and antimicrobial activity against several gram positive and gram negative bacteria, although not as great as that observed for surfactin.[262] Several pumilacidins show antiviral activity against herpes simplex virus as well as anti-ulcer activity.[264] Polymyxin B (Fig.6b) and polymyxin E (colistin) show antibiotic activity against a range of gram-negative bacteria.[91] The two molecules are distinguished by the substitution of a D-leucine in colistin with a D-phenylalanine in polymyxin B.[90] The mode of action of these lipopeptides has been proposed to be membrane disruption due to interaction between the cationic polymyxin and the anionic bacterial outer membrane leading to a detergent-like activity.[91] A wide range of other cyclic depsipeptide (in which one or more amide groups are replaced by the corresponding ester goup) and N-methylated peptide (peptoid) antibiotics have been investigated.[38, 265-266]

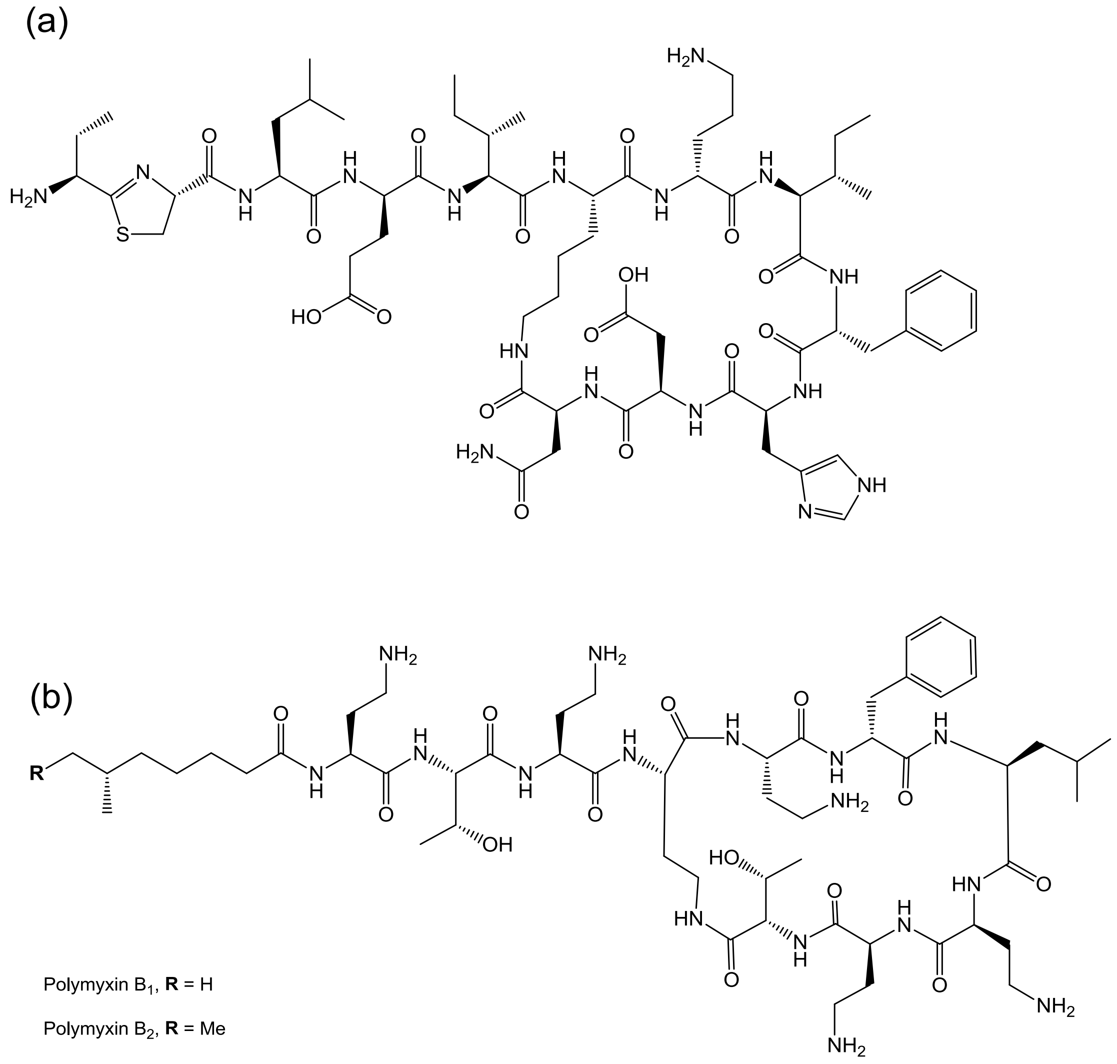
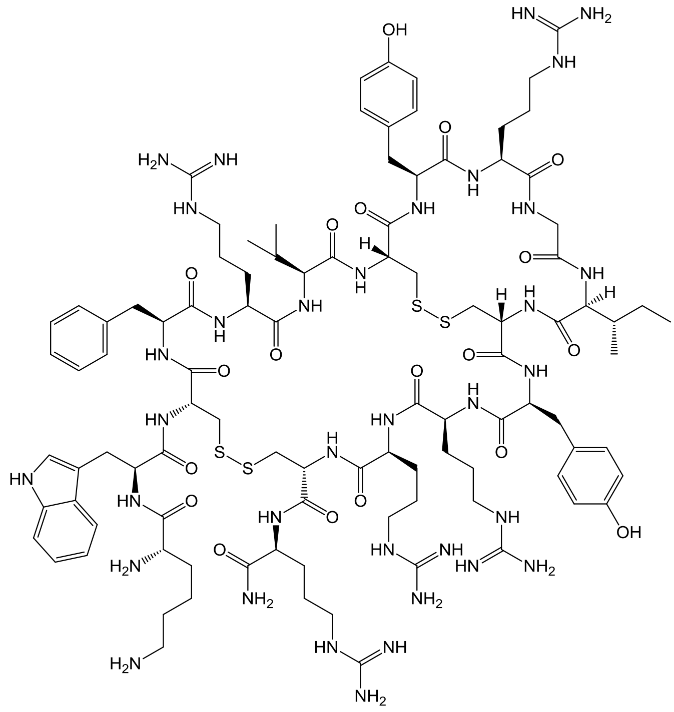


Fig.6. Molecular structures of (a) bacitracin A_1,[89] polymyxin B_1 and B_2.[38, 90]

The two tachyplesin antimicrobial peptides contain four cysteines forming two di-sulfide bridges to give a bicyclic peptide (Fig.7). These peptides, originally obtained from horseshoe crabs, are highly cationic containing five residues.[7, 13, 92] The class of protegrin peptides (from porcine leukocytes), protegrin-1 to protegrin-5, have a similar bicyclic structure, containing six arginines.[13, 93-94] Defensins are longer cysteine-rich antimicrobial peptides isolated from a variety of animals.[7-8, 13, 94-96] These peptides are too long to be considered further in this review. Bactenicin with sequence RLCRIVVIRVCR is bridged by a single disulfide bond.[7-8, 13, 97] It is obtained from bovine neutrophils and is among the shortest bio-derived cationic AMPs.[267] Many other antimicrobial peptides have been and are being discovered from natural sources such as soil (e.g. the newly discovered antibiotic teixobactin[268] as well as the gramicidins discussed below) or organisms such as amphibians (e.g. magainin[94, 269]) or spiders (e.g. gomesin[94, 270]). However, these are also not discussed in detail here, as the sequences are too long. Summaries of natural antimicrobial peptides from plants and animals are available in the literature.[8, 10, 13, 94, 271-272]

(a)



(b)

KWCFRVCYRGICYRRCR

Fig.7. (a) Molecular structure of tachyplesin 1.[92] (b) Sequence code with S-S bridge location indicated.

The gramicidins are a series of 15-residue peptides active against Gram-positive bacteria, being derived from the soil bacterial species *Bacillus brevis*. The peptides have the sequence with alternating L- and D- residues, formyl-**X**GAlAvVvWl**Y**lWlW-ethanolamine, where **X** is V or I and **Y** is W (gramicidin A),[273] F (gramicidin B)[89, 274-275] or Y (gramicidin C).[89, 274-275] Gramicidin D is a mixture of related peptides[276] and Gramicidin S is the cyclic decapeptide cyclo(VOLfP)$_2$ [O: ornithine].[7] Gramicidins are interesting antimicrobial peptides without cationic residues. They form β-helix dimers which span the lipid bilayer,[277-279] causing the formation of selective ion channels, rather than causing bacterial cell lysis due to electrostatic binding as in the case of the cationic AMPs discussed above.

Among animal-derived host defense peptides, those with short sequences include indolicidin and bactenicin. Indolicidin, which is cow-derived (from bovine neutrophils), has the sequence ILPWKWPWWPWRR[7, 11, 13, 98] and can be seen to be tryptophan-rich. Peptides rich in this residue can have antimicrobial properties as well as arginine-rich ones,[12] and in fact indolicidin is stated to be have the highest tryptophan content of any “protein”.[98, 280] A number of studies also point to anti-viral activity of indolicidin.[10] Derivatives of the wasp venom peptide mastoparan[281] with sequence INLKALAALAKKIL are being investigated as potential antimicrobial agents despite the toxicity of the parent peptide to mammalian cells.[282] The derivative mastoparan-X INWKGIAAMAKKLL has had its conformation in solution determined by NMR[283] which reveals it to be surely one of the shortest α-helix forming peptides (Fig.8).

Fig.8. Structure from solution NMR of Mastoparan-X (pdb: 2CZP).[283]

Helical peptides containing the KLAK sequence have been shown to possess selective and potent antimicrobial activity with low mammalian cytotoxicity. [284] Antimicrobial activity was demonstrated for both Gram-negative *E. coli* and Gram-positive *S. aureus*.[284] The (klakkla)$_2$ peptide (in its D-amino acid form to reduce proteolysis) was conjugated to 'tumour homing' sequences cyclo(CNGRC) or double cyclic ACDCRGDCFC to create anti-cancer peptides which showed anti-cancer activity in mice.[285]

Daptomycin is a potent AMP which is a cyclic branched 13-residue peptide produced by the Gram-positive bacterium *Streptomyces roseosporous*.[99-100] It is also known under the tradename Cubicin and is used as an antibiotic to treat serious infections caused by Gram-positive bacteria.[101, 250] It is effective against infections where antimicrobial resistance is a problem, including methicillin-resistant *Staphylococcus aureus* (MRSA)[100] and vancomycin-resistant Enterococci.[101, 286] There are two katanosin cyclic depsipeptides with antimicrobial activity. Katanosin B is also known as lysobactin (originally isolated from a strain of Lysobacter)[287-289] and katanosin A has a similar structure with a V7I substitution.[289] Both are potent AMPs with activity against Gram-positive bacteria such as Staphylococci.[287-289]

The echinocandins are a class of cyclic peptides with antifungal activity. They operate by blocking cell wall glucan synthesis.[290-292] Anidulafungin, caspofungin and micafungin are all examples of echinocandins (Fig.9).[38, 260] The most widely known is caspofungin, marketed as a drug by Merck and Co. The antifungal activity of this class of compound is due to the interaction of lipopeptide molecules with the insoluble polysaccharide component of the cell wall of fungal cells, specifically in the due to the inhibition of the synthesis of glucans.[290] The interactions of echinocandins with *Candida* fungi such as *C. albicans* has been particularly well studied.[290-291]

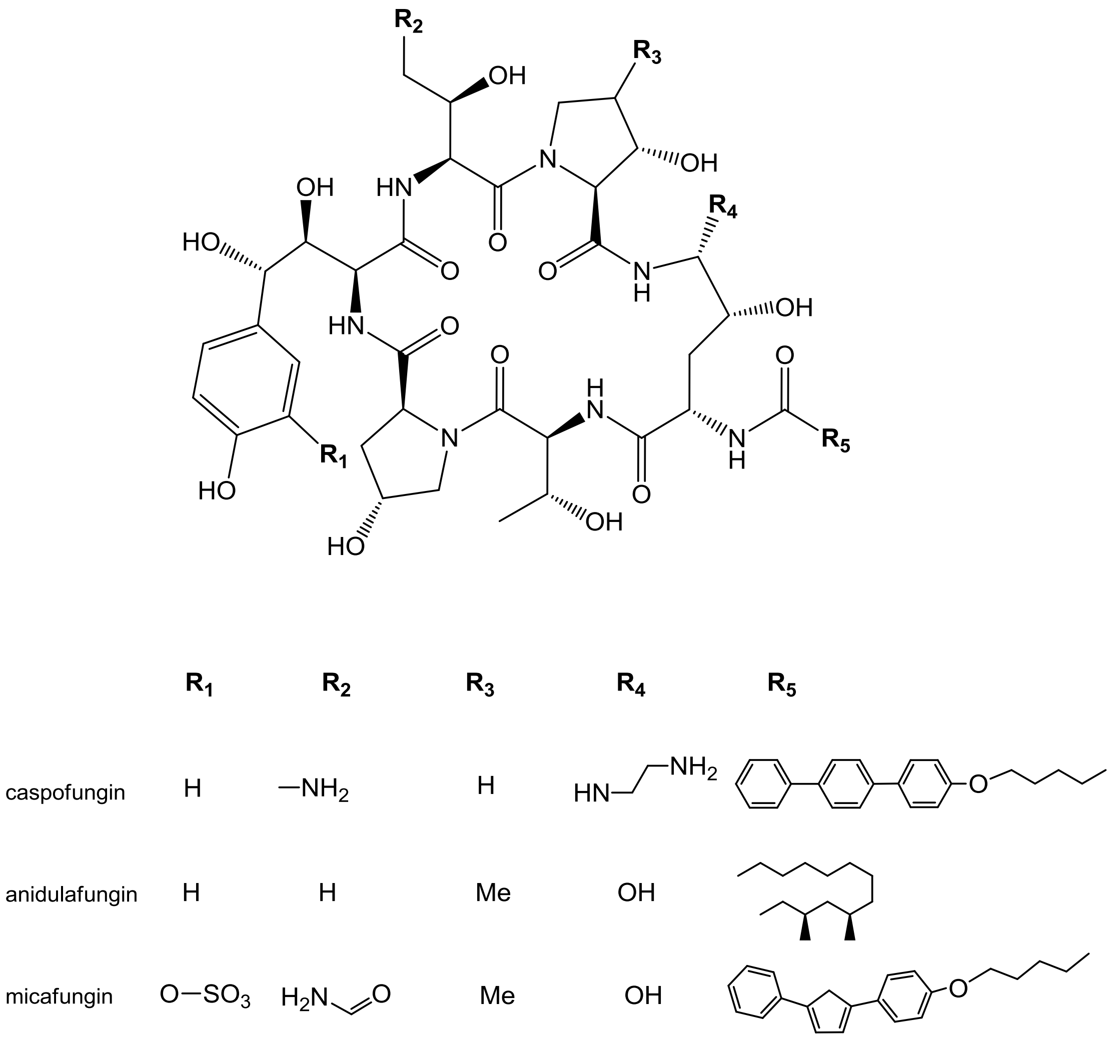


Fig.9. Structures of caspofungin, anidulafungin and micafungin. Adapted from ref.[38]

Beauvericin (Fig.10) is a symmetric cylic depsipeptide (strictly, peptoid as the amides are *N*-methylated) with antifungal and insecticide properties.[293-294] It was originally isolated from a fungus,[295] and is structurally related to the enniatin family of cyclohexa-depsipeptides.[296]

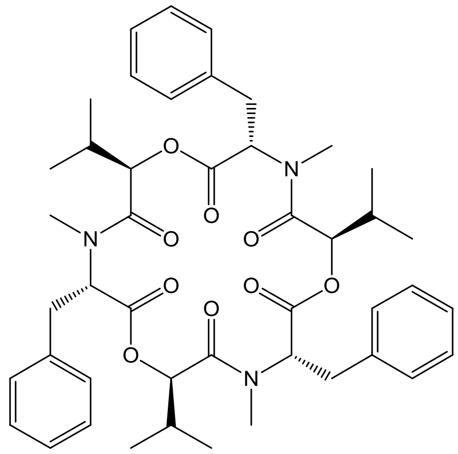


Fig.10. Molecular structure of beauvericin.[295]

6. Peptide Hormones

There are many peptide hormones with diverse biological activities in signaling and other response pathways.[15-16, 18-19] Several classes of peptide hormones have sequences too long to be considered further here but there are nonetheless several of them with short sequences and important biological functions.

Oxytocin is a member of a series of related peptide hormones which are nonapeptides with an intramolecular disulfide bond which produces a small cyclic ring (Fig.11a).[63] Oxytocin is known as the love hormone, due to putative activity in social bonding.[297-300] It is used medically to facilitate childbirth (it simulates uterine contractions)[63, 103] and milk secretion.[103] The vasopressins are a series of peptide hormones with similar structures to oxytocin, i.e. they are 9-residue peptides containing a disulfide bond which creates a cyclic region within the molecule.[63] Vasopressins act as vasoconstrictors and are thus targets for blood pressure modulation.[63] They also stimulate water resorption by the kidneys and are thus antidiuretic agents.[63] Arginine vasopressin, with sequence CYFQNCPRG stabilized by an intramolecular disulfide bridge between the two cysteine residues, is the basis for the antidiuretic (and anticoagulant) desmopressin which has the arginine vasopressin sequence but with the first C residue deamidated and with D-Arg instead of L-Arg (Fig.11b).[301]

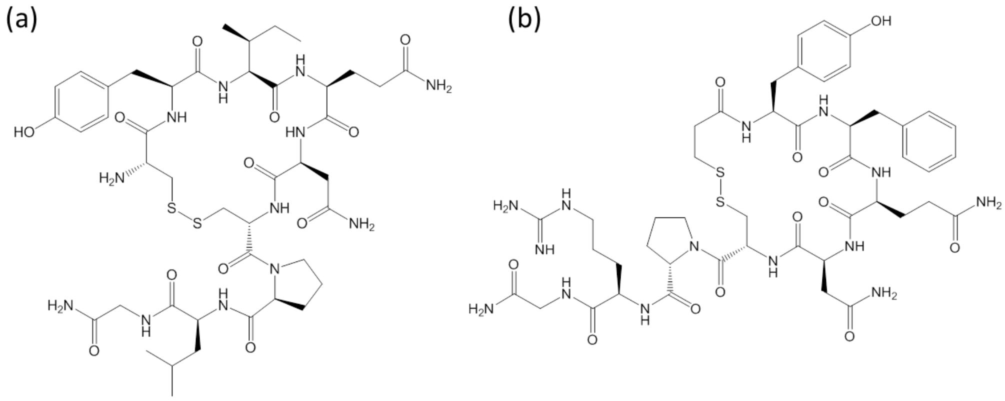


Fig.11. (a) Molecular structures of (a) Oxytocin, (b) Desmopressin.

The angiotensins are a series of four linear peptide hormones. The first, angiotensin I is obtained by cleavage of the angiotensinogen protein by renin.[103-105] Angiotensin I contains 10 residues NRVYIHPFHL, angiotensin II is derived from this by cleavage of the two C-terminal residues,[103-105, 302] angiotensin III is the heptapeptide RVYIHPF and angiotensin IV is the core hexapeptide VYIHPF.[104, 302] Angiotensin II has the important bioactivity of vasoconstriction and blood pressure increase.[104] It is produced from Angiotensin I by angiotensin-converting enzyme (ACE) and hence ACE inhibitors are therapeutic agents for blood pressure reduction and cardiovascular disease.[303-304] Angiotensin II receptor antagonists are also important therapeutic agents. Angiotensin II has an identified role in inflammation and it can regulate growth factors and cytokines.[305]

Bradykinin, with the sequence RPPGFSPFR, is a short peptide hormone with activity in blood vessel dilation (vasodilation), hence in reduction of blood pressure.[106] It is also associated with inflammatory pain.[107-108] The angiotensin converting enzyme (ACE) inhibitors increase bradykinin production.[106]

Somatostatin, also known as growth hormone-inhibiting hormone, is a 14-residue cyclic peptide (Fig.12).[306] It plays an important role in cell proliferation (via inhibition of the secretion of growth factors and cytokines) [307] and neurotransmission.[308]

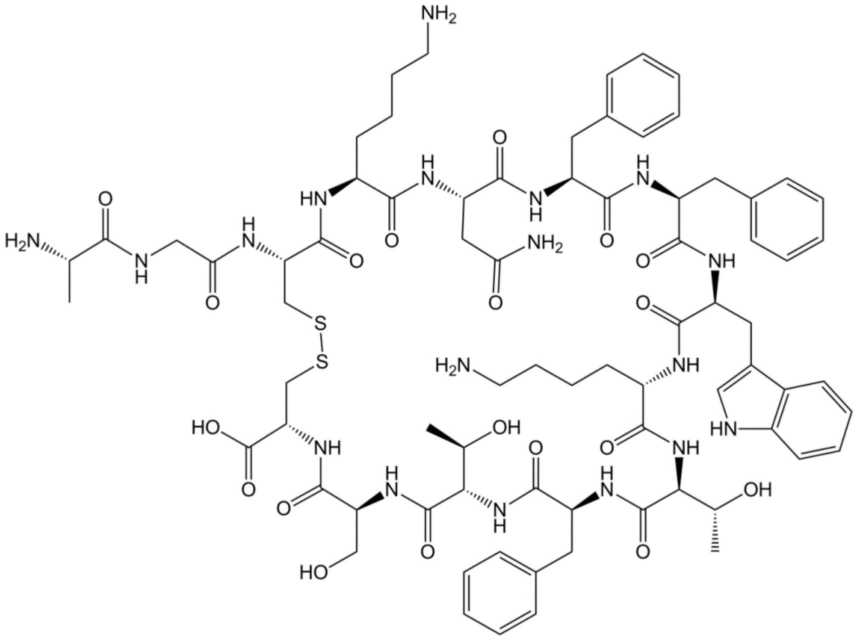


Fig.12. Molecular structure of somatostatin.

Octreotide (tradename Sandostatin) is a cyclic octapeptide (Fig.12) that mimics the activity of somatostatin.[115-116] It was designed to have enhanced in vivo stability due to the inclusion of D-amino acids as well as other modifications. The D-configuration of tryptophan fosters a bioactive conformation, based on a β-turn centered on wK.

Octreotide is a powerful growth hormone inhibitor which can be used to treat the growth hormone disorder acromegaly for example.[115, 309] Lanreotide is another long-acting analogue of somatostatin. Both octreotide and lanreotide act on the same receptors as somatostatin (G protein-coupled somatostatin receptors) and both are inhibitors of insulin and glucagon.[119] Lanreotide is a homologue of octreotide (Fig.13).[117-119] It self-assembles into nanotubes in aqueous solution.[310-313]

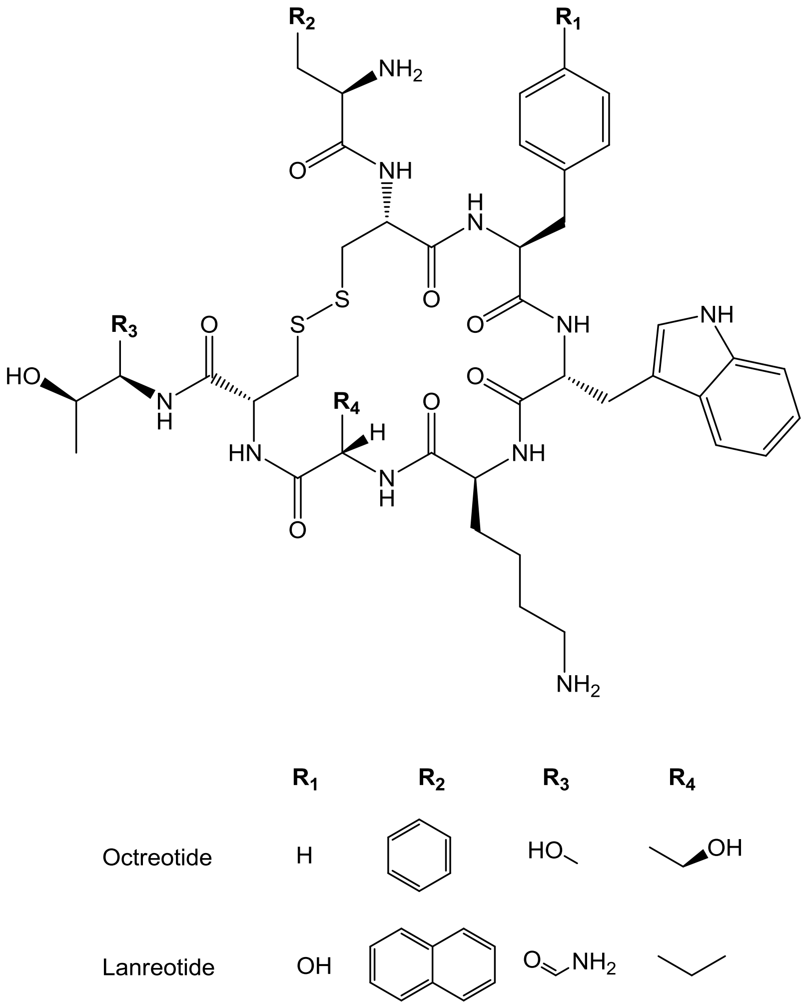


Fig.13. Molecular structures of octreotide[115] and lanreotide.[119]

Luteinizing hormone releasing hormone (LHRH) also known as gonadotropin-releasing hormone (GnRH) is a decapeptide with sequence pGHWSYGLRPG (pG:

pyroglutamic acid, Fig. 14b).[114] This peptide, produced in the hypothalamus, binds to the LHRH receptor, and triggers the release of luteinizing hormone (LH) and the follicle stimulating hormone (FSH), which are responsible for the production of testosterone and sperm, respectively.[109] Another tropic (i.e. having endocrine glands as target) peptide hormone produced in the hypothalamus is TRH, thyrotropin-releasing hormone (Fig.14a).[110] This tripeptide (L-proline-L-histidyl-L-pyroglutamyl amide or 5-oxo-L-prolyl-L-histidyl-L-prolinamide) also contains the pyroglutamyl residue. It has the commercial name protirelin and is used in the diagnosis of thyroid disorders among other applications.[111-113]

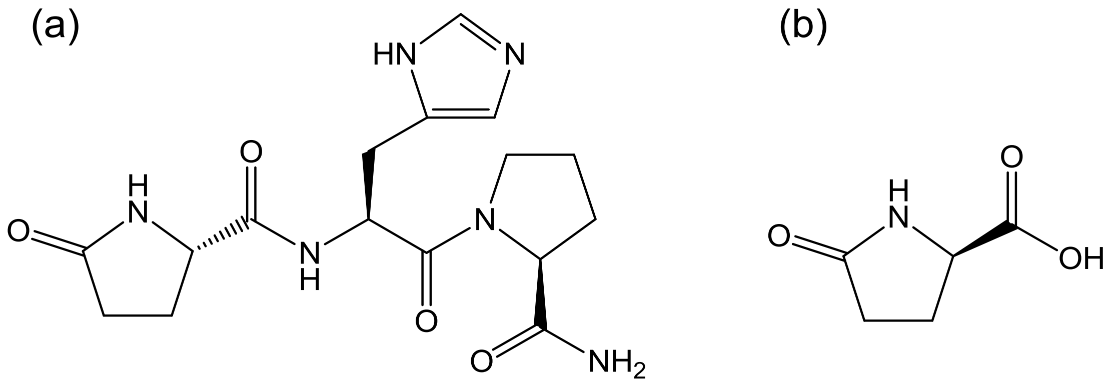


Fig.14. Molecular structure of (a) thyrotropin-releasing hormone, (b) pyroglutamic acid.

Gastrin stimulates the secretion of gastric acid in the stomach. Gastrin peptide hormones have a common C-terminal motif. There are several variants (some too long to fit within the scope of this review) such as minigastrin or gastrin-14, WLEEEEEAYGWMNF.[314] Tetragastrin (WMNF) is discussed further in Section 9.

7. Tissue Engineering and Biomaterials Development

Cell adhesion motifs which are key sequences in the design of biomaterials for tissue engineering are discussed in Section 3. Here, several additional components that are desirable in materials which can remodel in response to cellular cues are considered.

Growth factors are important in tissue engineering and wound healing. A list of growth factors involved in different processes (angiogenesis, wound healing etc) is available.[315] Growth factors are large native proteins, however short peptide substrates for growth factors have been identified. The peptide YRSRKYSSWYVALKR, taken from a sequence FGF(106-120) is an activator of the basic fibroblast growth factor (FGF-2 or bFGF) receptor.[316]

The GPQGIAG sequence is a substrate for MMP-1 and MMP-2 (which cleave between G and I) and has been used in the development of many biomaterials for tissue engineering applications.[1, 132, 317-318] An excellent review on MMP substrate sequences is available.[132] Other agents involved in tissue remodeling include the plasminogen enzymes. These degrade blood clots in the process of thrombolysis, i.e. they degrade fibril in the process of fibrinolysis. A list of tetrapeptide plasminogen activator cleavage sites is available.[2] All have N terminal arginine residues and at least one other polar residue (serine, threonine or arginine). Elastase is a protease enzyme which degrades elastin (Section 3). It acts on substrates containing oligo-alanine repeats.[319-320] The serine protease α-chymotrypsin cleaves selectively following aromatic residues,[321] e.g. in KLVFF-based peptide conjugates.[322-323] The substrate specificity for other serine proteases has been investigated.[324-325] Other substrates for degradation used in biomaterials for tissue engineering include the

APGL collagenase degradation sequence and the VRN substrate for plasmin mediated degradation.[55]

Heparin-binding peptide sequences are also an important component of biomaterials for applications in wound healing since heparin is a powerful anticoagulant. Heparin-binding peptide sequences include FAKLAARLYRKA from Antithrombin III,[2, 326] and others.[69]

The “RAD16” RADARADARADARADA peptide (and similar variants) became a commercial product (PuraMatrix) with applications in tissue engineering as hydrogels of this peptide can support the growth of various types of cell.[127-129]

8. Amyloid Peptides

Amyloid peptides form β-sheet fibril structures. Those discussed here are either simple alternating sequences or fragment peptides from disease-related amyloid peptides or proteins.

Alternating sequences such as GAGA in silk discussed above favour β-sheet formation. The presence of alternating hydrophobic and hydrophilic residues further enhances amyloid aggregation propensity. For example, the peptide EAK16 $(AEAEAKAK)_2$ was among the first to be studied which is consistent with this design rule, with the additional feature that the charge of the hydrophilic residue changes in a sequenced fashion.[126] This peptide is present in the yeast protein zuotin. The Zhang group also studied related peptides such as KFE12, FKFEFKFEFKFE, with alternating charged residues.[327-328] This peptide forms gels in suitable salt solutions.[328] As mentioned above, the "RAD16" RADARADARADARADA peptide is an amyloid former.[127-129] The structural and rheological properties of similar octapeptides (which can form β-sheet hydrogels) with alternating residues such as FEFEFKFK have been investigated.[329-332] The influence of the amino acid pattern on the self-assembly motif of this class of octapeptide has been examined.[333]

Due to the intense research interest in amyloid formation of relevance to protein misfolding diseases including Alzheimer's, Parkinson's, type II diabetes *etc*.,[25] much work has been done using model amyloid forming peptides. The following describes a few key model amyloid peptides and is not a full list since so many have been investigated. Some well-known sequences now have X-ray crystal structures determined, and a selection of the more widely used model peptides are discussed in the following.[28, 125]

One widely studied amyloid-forming peptide is GNNQQNY from the yeast prion protein Sup35. Among many studies of its amyloid properties can be highlighted fibre diffraction studies[121] and a crystal structure determination which reveals the formation of a steric zipper (Fig.15) in which the side chains are intercalated within the cross-β structure.[122, 125] Other examples of steric zippers, which exclude water from the interior of amyloid fibrils, include phenylalanine zippers.[334-335]

The VQIVYK sequence from tau (residues 306-311) forms β-sheet filaments,[123] with a cross-β structure.[124, 336] A crystal structure determination is available, which reveals a steric zipper arrangement.[125, 337]

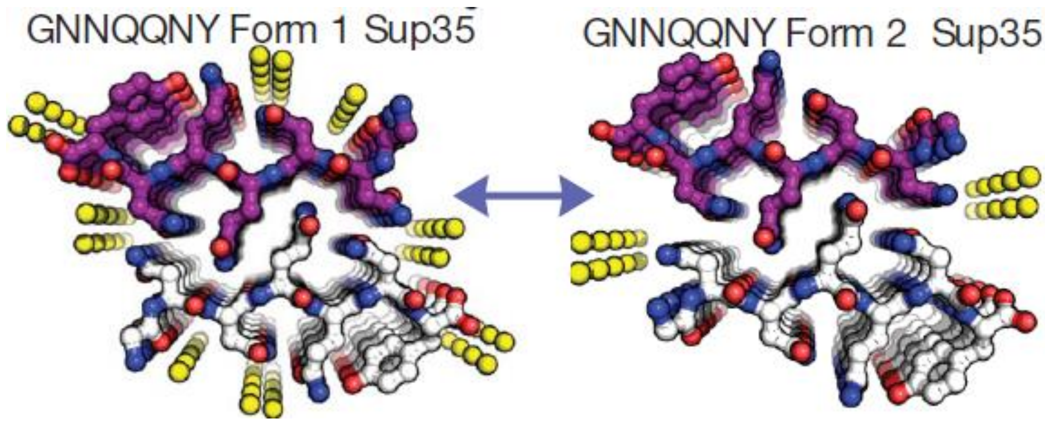


Fig. 15. Amyloid steric zipper structures from x-ray crystallography on GNNQQNY.[125] Carbon atoms are purple or white, nitrogen atoms are blue and oxygen atoms are red. The yellow circles indicate water molecules.

Deposits of human islet amyloid polypeptide (hIAPP) also known as amylin are found in the pancreas of people with type II diabetes.[338-340] The peptide NFGAIL from hIAPP has been extensively used as a model amyloid-forming peptide,[341] following its identification as a minimal β-sheet forming sequence.[342] Importantly, a crystal structure of NNFGAIL is available and this shows unusual features for an amyloid peptide, specifically a pronounced bend around the G residue and a lack of side chain interpenetration as in a typical steric zipper arrangement.[343]

The peptides KLVFF and KLVFFAE from the Amyloid β (Aβ) peptide (residues 16-20 and 16-22 respectively) are believed to be a core aggregating sequences.[344-346] Indeed, peptides incorporating this fragment can bind the full length peptide and prevent fibrillization.[347] Fragments based on KLVFF have been designed to inhibit Aβ40 and Aβ42 fibrillization. Rational design principles based on the knowledge of the pentapeptide binding sequence led to the preparation of LPFFD,[102] now known as the β-sheet breaker peptide. This peptide incorporates proline, known to hinder β-sheet aggregation and was found to reduce amyloid deposition *in vivo* (rat model) and to disassemble pre-formed fibrils *in vitro*.[102]

The FF dipeptide is a fragment of KLVFF (and of course other peptides) and it was suggested that its π-stacking has an important role in amyloid formation.[348] FF has remarkable self-assembly properties, although it does not form strictly amyloid β-sheet structures.[349-350] This peptide forms nanotubes in aqueous solution[130, 349] and in organic solvents it is possible to prepare vesicles or nanoparticles from it. Capped FF can form fibrils or nanotubes depending on the nature of the capping group,[351-352] and vertical arrays of nanotubes can be prepared from FF (with different capping groups) by spreading a film from HFIP.[353] The aggregation of peptides through aromatic stacking interactions can be enhanced by additional of bulky aromatic units such as Boc [*tert*-butoxycarbonyl] or Fmoc.[354-355] Boc-FF can form nanospheres in water as a transient in the nanotube formation process,[356] or stable nanospheres with very high stiffness in organic solvent.[357] The uncapped FF dipeptide can also form nanospheres ("quantum dots") in organic solvents.[358] Strategies other than addition of bulky aromatic substituents have been used to modulate the self-assembly of FF. One is to incorporate halogenated phenylalanine,[359-361] or other substituted phenylalanine derivatives.[361] Other approaches include changing chirality, i.e. substitution with the D-amino acid,[362] or N-terminal derivatization with other aromatic groups. [354-355, 363-364]

Computational methods have recently been used to assess the aggregation propensity of all of the $20^3 = 8000$ tripeptides.[365] After the computational screening, candidates were synthesized and assessed for hydrogelation ability based on β-sheet fibril network formation.

9. Neuropeptides, Antioxidants and Immune-Related Peptides

There are two enkephalin peptides Met-enkephalin YGGFM and Leu-enkephalin YGGFL which are endogenous ligands for μ-opioid receptors in the brain.[103, 133] Dalargin with sequence YaGFLR (a: D-alanine) is a Leu-enkephalin analogue with specificity for μ opioid receptors.[366] Dalargin is usually excluded from the brain however lipidation leads to a self-assembled fibril structure, which is reported to both reduce degradation in plasma and enables transport across the blood-brain barrier.[367] The endomorphin tetrapeptides have high selectivity and affinity for the μ-opioid receptors.[134] Two endomorphin peptides were isolated from brain extracts. Endomorphin-1 has the sequence YPWF and endomorphin-2 has the sequence YPFF. These peptides are of interest for the further development of pain relief therapies. However, it has to be noted that the direct application of these peptides in analgesia was demonstrated in a rodent model by i.c.v. (intracerebroventricular) administration. [135] Peripheral administration of these peptides is ineffective as they are too easily degraded, appropriately modified versions may be designed to circumvent this.

Substance P is the undecapeptide RPKPQQFFGLM which acts as a neurotransmitter and is involved in pain and analgesia.[368-369] It is a member of the tachykinin family of neuropeptides which have the common C-terminus FXGLM[136] where X is a hydrophobic residue.

Another class of neuroactive peptides are the tryptophan-containing non-ionizable opioid peptides such as the naturally occurring (fungus derived) tetrapeptide cyclo[Phe-D-Pro-Phe-Trp], known as CJ-15208.[38, 370] This peptide is an orally-available antinociceptive (it blocks pain stimuli by sensory neurons). It is able to cross the blood-brain barrier and reach opioid receptors.[370]

A series of fragments of the cholecysotokinin peptide are found naturally. Cholecystokinin is a gastric peptide, identified as a 33-residue peptide in porcine intestine extracts.[371] It causes the release of digestive enzymes and acts as a satiety signal.[372-373] Cholecystokinin octapeptide (CCK-8) has the sequence NY(SO_3H)MGWMNF (i.e. it contains a sulfated tyrosine residue).[371] Cholecystokinin tetrapeptide (CCK-4), also known as tetragastrin, is a peptide fragment derived from the larger peptide hormone cholecystokin and has the sequence WMNF. It is an anxiolytic and is used to induce panic attacks in studies of anxiety.[120] The C terminal sequence in these peptides is common to the gastrin peptide hormones as mentioned in Section 6.

Glutathione is tripeptide (L-γ-glutamyl-L-cysteinylglycine, H-isoGlu-Cys-Gly-OH) denoted GSH, in which there is a gamma peptide link between the glutamic acid side chain and cysteine. It is an antioxidant, the thiol group serving as a reducing agent *in vivo*, disrupting disulfide bonds in proteins to yield free cysteine groups.[138, 374] It is involved in many biological processes including metabolism, protein and DNA synthesis and protection of cells.[138]

The dipeptide L-carnosine (β-alanine-histidine, βAH) has a range of biological activities.[76, 140, 375-376] In particular it has antioxidant properties for carbohydrates (anti-glycation)[377-378] and lipids (anti-lipoxidation).[139] The presence of the β–alanine (βAH) residue is implicated in these roles, since it can react directly with oxidized carbohydrates and lipids.[379] The histidine (H) residue is able to bind to transition metal ions. Histidine-containing dipeptides such as L-carnosine are present in the mammalian brain within neuroglia and certain types of neurons.[380] Carnosine is present in muscle and nerve tissue, as well as the brain.[76, 140, 375-376] Carnosine has been proposed as a treatment for Alzheimer's disease,[380] and it has also been shown to delay senescence of cultured cells,[381] which has been ascribed to the antioxidant properties of the peptide.[378]

Thymopentin, also known as TP-5, is a pentapeptide fragment (RLNVY) corresponding to residues 32 to 36 of human thymopoetin (a.k.a. lamina-associated polypeptide 2).[382-383] Thymopentin is an immunostimulant, used for example in the treatment of dermatitis.[383] Many other medical applications involving immunomodulation have been summarized.[384] Splenopentin with sequence RLGVY is a related immunomodulation peptide.[384] Cycloinopeptide is a cyclic nonapeptide cyclo-(Pro-Pro-Phe-Phe-Leu-Ile-Ile-Leu-Val) extracted from linseed oil[385] with activity as an immunosuppressant.[386]

Cyclosporin or cyclosporine (Fig.16) is a cyclic 11-residue peptide/peptoid hybrid with sequence cyclo[AbuSar(N(Me)L)V(N(Me)L)Aa(N(Me)L)(N(Me)L)(N(Me)V)-(N(Me)Bmt(E))].[143, 387] Peptoids are *N*-substituted analogues of peptides, and here Sar denotes sarcosine, *N*-methylglycine, Abu denotes aminobutric acid and Bmt(E) denotes (E)-but-2-enyl threonine. Cyclosporin is a powerful immunosuppressant, working on T-lymphocytes.[141-142, 387] It also displays antifungal and anti-inflammatory properties. It is an extract from soil fungus and is synthesized by a nonribosomal synthetase.[142]

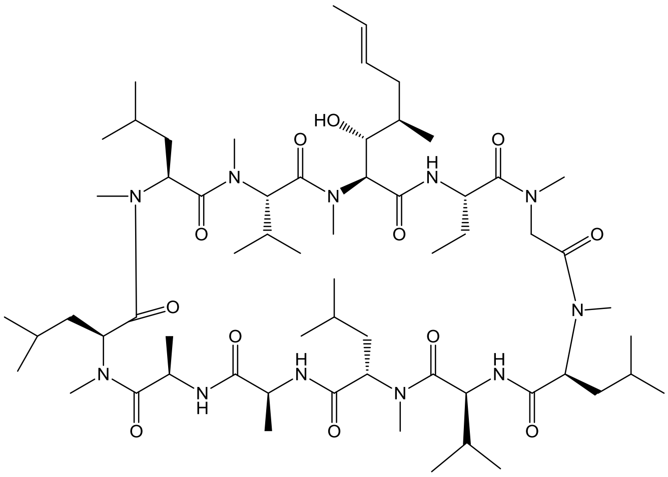


Fig.16. Molecular structure of cyclosporin.

10. Protein Tags

Recombinant production of proteins is becoming a ubiquitous technology. Peptide tags enable isolation via affinity chromatography of expressed proteins cleaved at defined positions (Fig.17). Short peptide cleavage sequences have advantages compared to longer tags in minimizing the effect on the processing and conformation of the expressed protein.

(a) (b)

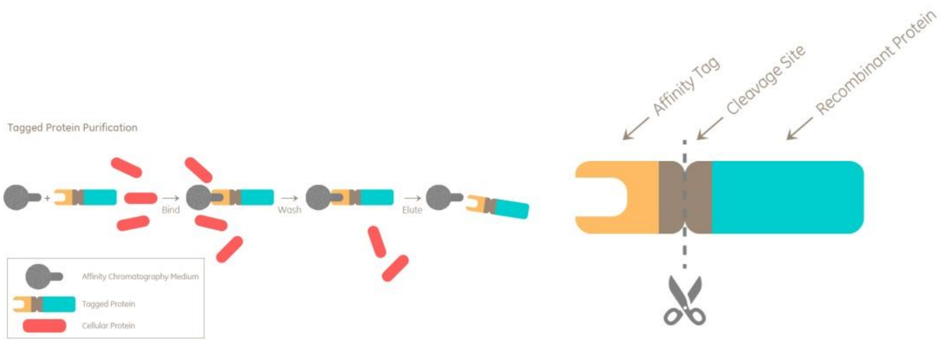


Fig.17. (a) Affinity chromatography purification of recombinant proteins tagged with an affinity peptide domain. (b) Cleavage done on column or after elution.[388]

The oligo-or poly-histidine tag (e.g. hexa-histidine), developed by researchers at Roche,[145-146] is widely used in the affinity purification of expressed recombinant proteins.[389] The protein to be labelled is engineered to incorporate N- or C-terminal histidine repeats. A common system employs a hexahistidine tag along with a metal chelate among which the nitrilotriacetic acid (NTA)/Ni^{2+} system is widely used. Since nickel ions are hexa-coordinated and four electrons are used in binding to NTA, two electrons are available to bind hexahistidine tags. This interaction has high affinity and selectivity.[390-392] Other oligopeptides including oligo(arginine) (developed in 1984[144]), oligo(aspartic acid) and oligo(phenylalanine) have also been used as fusion tags.[33] Some of these sequences can adversely influence the tertiary structure of proteins to which they are attached.[34]

The Strep-tag II peptide (WSHPQFEK) is an affinity sequence for use in streptavidin or modified streptavidin columns.[34, 147-148] The myc or c-myc tag (derived from a transcription factor regulator gene) corresponds to peptide EQKLISEEDL.[34, 149] Use of this tag is based on a known anti-c-*myc* antibody used as an immunochemical agent in cell biology.[393]

A range of other peptide tags, including commercially licensed technologies, has been developed including FlagTag (sequence DYKDDDDK) which incorporates a cleavage site for enterokinases (a class of digestive enzyme).[33, 150] It is used in immunoaffinity chromatography. The Spytag peptide with sequence

AHIVMVDAYKPTK[394] is designed to bind to the Spycatcher protein via amide bond formation.[395]

Derivatives of the cyclic peptide phalloidin (Fig.18) are used as fluorescent tags. Phalloidin is a bicyclic heptapeptide, originally isolated from the death cap mushroom.[396] It is used in fluorescent stains in cell viability studies because it binds to (and stabilizes) actin (in its filamentous form),[396-397] which is an essential component of the cytoskeleton.

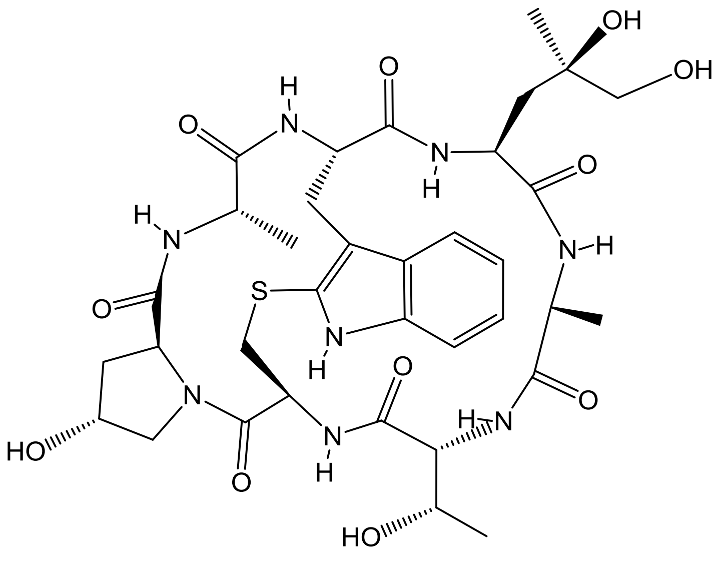


Fig.18. Molecular structure of phalloidin.

Lists of other fusion tags for recombinant protein production are available with detail on the purification systems and the advantages and disadvantages of particular systems.[33-35, 37]

11. Anti-Cancer Peptides

Anticancer “tumor-homing” peptides have been discussed in Section 4. Here several types of cyclic peptide with anticancer activity are discussed.

Bleomycins are important anti-cancer agents. The molecules are peptide derivatives (Fig.19), being glycosylated peptide-polyketides containing two thiazolines resulting from cyclization of cysteine residues.[151-155] The bleomycins are non-ribosomal peptides produced by the bacterium *Streptomyces verticillus*.[151] They act by cleaving DNA strands.[154, 398] Bleomycins have been classed as “metalloantibiotics” because they were originally discovered to be antibiotics and their activity (binding and cleaving DNA molecules) depends on the presence of ions (especially Fe^{2+}).[89]

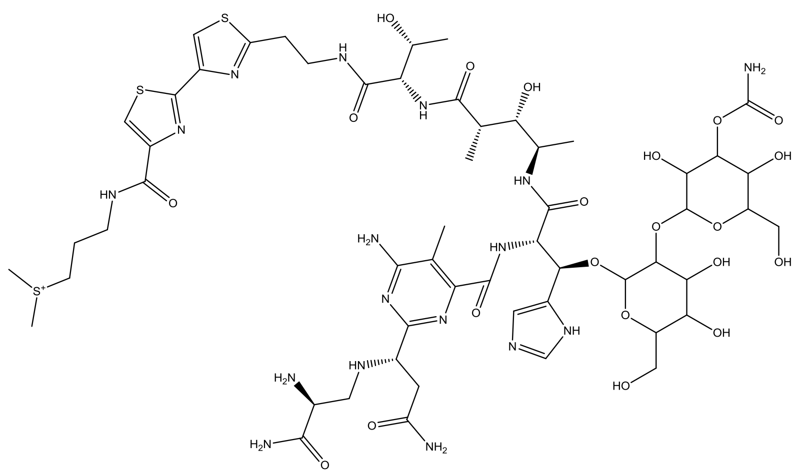


Fig.19. Molecular structure of bleomycin A_2.[154]

Dolastatin 10 (Fig.20) is a short peptide containing five residues with an interesting selection of non-proteogenic amino acids.[156-157] This peptide, originally isolated from a marine mollusk, has potential anticancer activity, as it has an antimitotic activity, inhibiting tubulin polymerization.[157] Dolastatin 10 is one example from a diverse range of marine natural products with anti-cancer properties resulting from microtubule growth inhibition,[17, 399-400] such as hemiasterlins which are short linear peptide derivatives obtained from a marine sponge.[401]

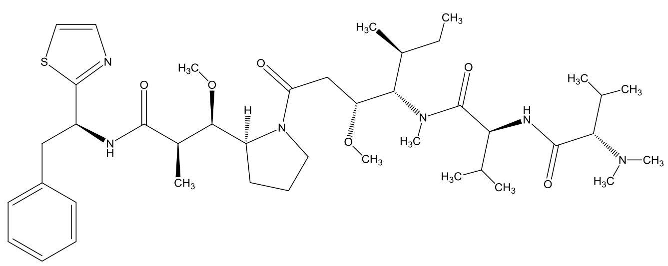


Fig.20. Molecular structure of dolastatin 10.

Apicidin (Fig.21a) is a cyclic tetrapeptide which is a histone deacetylase inhibitor (HDAC).[158-160] It was isolated as a fungal metabolite.[402] It has potential anticancer activity[158-160] and acts against protozoan parasites such as Plasmodium (malaria infective agent),[402] among other applications. Chlamydocin is a related cyclic tetrapeptide[403] obtained from origins as a fungal natural product.[38, 404] It is reported to inhibit the growth of tumor cells.[405-406] Romidepsin (Fig.21b) is a bicyclic depsipeptide (isolated from a soil bacterium[161]) which is also a histone deacetylase inhibitor with pronounced anticancer activity against several types of lymphoma.[162-166] Largazole (Fig.20c) also belongs to the class of cyclic depsipeptide natural products with HDAC anticancer activity.[167-168] A variety of other, less well studied cyclic peptides with anticancer activity are covered in a recent review.[38]

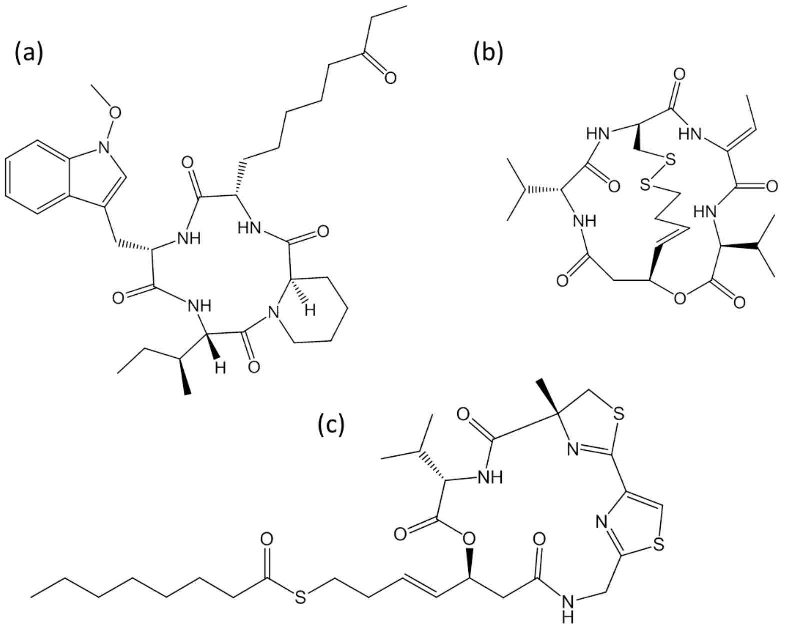


Fig.21. Molecular structures of (a) apicidin,[402-403] (b) romidepsin,[38, 161] (c) largazole.[168, 407]

12. Miscellaneous Peptides

Protein-protein interactions can occur through recognition of short peptide sequences. This has been particularly extensively studied for signaling protein complexes such as the Src-homology domains SH2 and SH3.[408-409] SH2 and SH3 domains regulate the activity of Src tyrosine kinases. SH2 domains recognize phosphorylated tyrosines in specific sequences (see e.g. ref.[410]). SH3 is a proline-recognition domain which has affinity for particular proline sequences such as the consensus motif PXXP.[410-412] Peptides have also been designed to inhibit protein interactions.[413] As these proteins involve recognition of sequences within larger proteins, and not short peptides *per se*, this fascinating subject is not considered further here.

The artificial sweetener aspartame is the dipeptide ester DF-OMe.[169, 414] Since it contains phenylalanine, products containing this peptide are labelled as such to alert those suffering from the inherited condition phenylketonuria in which phenylalanine metabolism is disrupted. For this and other reasons, the safety of aspartame has been investigated in considerable detail.[170, 415]

A range of peptides have been obtained by screening methods that bind to specific inorganic materials, nanoparticles, metals and metal oxides etc. The peptides are of interest for peptide functionalization of nanoparticles (for diagnostic or therapeutic applications for example), heavy metal remediation, templated synthesis etc. These sequences tend to be rather specific to individual studies or a particular application, and are not considered further here. Metal ions are also proposed to play important roles in the progression of amyloidosis for example of Amyloid β.[345] Peptides may be designed to mimic larger metalloproteins.[416] Reviews on the topic of peptides binding to inorganic materials/peptide immobilization on inorganic materials are available.[417-418]

Another important area where small peptides have promise is the field of artificial enzyme where the aim is to create an active hydrophobic pocket mimicking that of a folded protein, but using a short peptide. Short histidine-bearing peptides have attracted particular attention in the development of peptide-based catalysis. For example, the tripeptide Hff is a thermoreversible hydrogelator which is able to catalyse the hydrolysis of an ester.[419] Similarly, Fmoc-FFH self-assembles into nanotubes and is able to catalyse ester hydrolysis.[420] An FF peptide with N-terminal ferrocene unit is able to form oil-in-water nanoemulsions and has redox activity.[421] In another example, the tripeptide glutathione (section 9) is able to form iron-sulfur clusters in the presence of UV light, this mimicking the active site of ferrodoxins.[422] The self-assembly of small peptides into defined nanostructures may itself lead to enhanced activity in catalysis, since the peptide is presented at high density. In one example, $(EF)_n$ and $(FE)_n$ lipopeptides capped with N-terminal proline are able to catalyse an aldol reaction when aggregated (as fibrils) but this does not occur with unaggreated homologues (with much shorter C-terminal alkyl units).[423]

13. Conclusions and Discussion

Combining different functionalities into a peptide sequence is not as straightforward as just linking peptide sequences in a linear fashion due to the multiplicity of intermolecular interactions at play including electrostatic forces, van der Waals forces, hydrogen bonding, aromatic stacking interactions etc. This is exemplified by the discussion in Section 3 about RGD and the synergy PHSRN domain. A defined spacing (of amino acids non-functional for integrin binding in this case) between these two motifs is needed as a minimal element of a functional conjugate. In other cases the design may need more than control of just spacing, or it may simply not be possible to create a conjugate when the functional domains are incompatible or antagonistic. Lipidation is a strategy to create assemblies of a hydrophilic peptide domain presented at high density on the surface of nanofibrils, which can exhibit enhanced bioactivity compared to the unconjugated peptide.[424]

Computational screening (e.g. the impressive first analysis of aggregation propensity of all tripeptides[365]) is a powerful method which could be developed to screen other properties of di- and tri-peptides but it is of limited use for larger peptides where unfortunately as yet, *ad hoc* design rules, serendipity or bioinspiration are required to discover novel short peptides with interesting functionality. This review has given an overview of some examples. Unfortunately an overarching set of principles able to account for why a particular peptide has optimal or excellent desired activity are unlikely ever to be available since the parameter space is so vast (not just due to the 20^n hypothetical sequences from the 20 proteinogenic amino acids but all the other variables associated with aggregation including solution conditions etc) and the number of applications is so large. This is, in part, what makes this such a fascinating research field. In particular cases, design rules are available. For instance it is now well established that lysis-causing antimicrobial peptides require cationic arginine residues in their sequence, whilst ion channel forming cyclic peptides have an alternating D/L amino acid design.[425] In other cases, such as amyloid peptides, tools based on (peptide/amino acid) property databases are available (e.g. WALTZ, Zyggregator[426] or TANGO[427-428] aggregation predictors) to predict aggregation propensity however this often only provides *post hoc* rationalization.

There are many promising directions in the application of novel peptides in fields such as tissue engineering and biomaterials development, and the creation of enzyme mimics. Some examples of research to date in these fields have been provided but there is great scope for further development. Of course, there is also immense interest in small peptide, peptide-based and peptide-inspired therapeutics for a range of conditions and this field is likely to see exciting discoveries in the near future.

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Biography

Professor Ian W. Hamley is Diamond Professor of Physical Chemistry at the University of Reading (UK). He obtained his PhD at the University of Southampton (UK) and undertook postdoc positions in Amsterdam, The Netherlands (AMOLF) and the University of Minnesota, USA. He returned to the UK in 1993 to take up a lectureship at the University of Durham (1993-5) then moved to the University of Leeds (1995-2005) where he was promoted in 2003 to Professor. He moved to the University of Reading in 2005 to take up a joint appointment with Diamond Light Source, the UK synchrotron facility (2005-2010). He has more than 20 years' experience of research on different types of soft materials, including peptides, polymers, liquid crystals and surfactants. He received a Royal Society-Wolfson Research Merit Award in 2011, the Royal Society of Chemistry Peter Day Award for Materials Chemistry (2016) and the MacroGroup UK Medal (2017). His research programme focuses on the self-assembly of peptide materials and its relationship to bioactivity. He has supervised more than forty postdoctoral and postgraduate researchers and has published over 370 papers and several edited and authored books.

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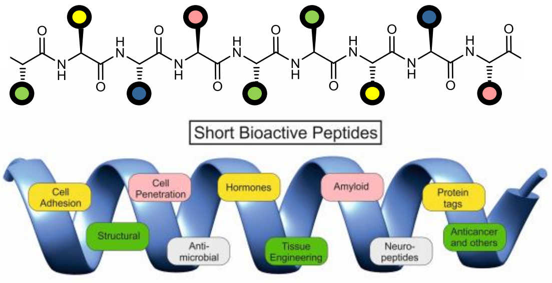
TOC Entry



Short Bioactive Peptides
Cell Adhesion
Cell Penetration
Hormones
Amyloid
Protein tags
Structural
Anti-microbial
Tissue Engineering
Neuro-peptides
Anticancer and others