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Synthetic therapeutic peptides: science and market

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The decreasing number of approved drugs produced by the pharmaceutical industry, which has been accompanied by increasing expenses for R&D, demands alternative approaches to increase pharmaceutical R&D productivity. This situation has contributed to a revival of interest in peptides as potential drug candidates. New synthetic strategies for limiting metabolism and alternative routes of administration have emerged in recent years and resulted in a large number of peptide-based drugs that are now being marketed. This review reports on the unexpected and considerable number of peptides that are currently available as drugs and the chemical strategies that were used to bring them into the market. As demonstrated here, peptide-based drug discovery could be a serious option for addressing new therapeutic challenges.

Recent pharmaceutical market evolution

The pharmaceutical market is evolving in a context of increasing economic pressure. First, public authorities are pushing for lower healthcare costs through reduced drug pricing and increasing use of generic substitution. Second, regulatory authorities are more demanding in terms of drug efficacy, quality and safety, which – combined with (bio)technological progress – has led to an increase in pharmaceutical R&D costs [1]. At the beginning of the 2000s, the Tufts Center for the Study of Drug Development estimated that the average cost of developing a new prescription drug was US$ 802 million (US$ 335 million for preclinical and US$ 467 million for clinical trials) [2,3]. More recently, these expenses have been estimated at US$ 1318 million including costs of capital and failures, the latter representing approximately 70% of the total amount [4]. In fact, 38% of the drug candidates under development are abandoned in phase I clinical trials because of toxicity, 63% of those that reach phase II clinical trials are withdrawn for lack of efficacy or poor bioavailability, 45% of the remaining drug candidates fail in phase III clinical trials, and 23% of those that satisfy the clinical trials are not authorized by the Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) [5]. Attrition owing to lack of efficacy, toxicology and clinical safety are the most common causes of failure in the development of new molecular entities (NMEs). The rate of failure during drug development is, thus, 90% in general and even greater in the case of drugs for the central nervous system (CNS) [5,6].

Third, with a decrease in R&D productivity (as shown by the low number of approvals for NMEs in recent years: 17 NMEs and 2 biologic license applications, or BLAs, approved by the FDA in 2007 [7], the lowest number recorded since 1983 and 21 NMEs and 3 BLAs in 2008 [8]) and patent expiry of blockbuster drugs in the past decade, a pipeline problem has emerged in the pharmaceutical industry. To be competitive and profitable in this high-pressure context, pharmaceutical companies need to improve strategies for anticipating and identifying crucial events in drug development as early as possible to reduce their costs [3]. Pharmaceutical companies also need to be strongly innovative to discover new drugs or technologies and to market innovative products, or at least to give a second life to their molecules through product lifecycle management or new therapeutic applications. There is a convention in the pharmaceutical industry that to recoup R&D

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investment and make a reasonable profit, a product needs to bring in peak annual sales of US$ 500 million [3].

Peptides as drugs: a revival of interest

Peptides are generally considered to be poor drug candidates because of their low oral bioavailability and propensity to be rapidly metabolized. The concept that a drug can be not 'orally available' has become more and more accepted and, as a consequence, some pharmaceutical companies have contributed in recent years to a revival of interest in peptides as potential drug candidates [9]. New synthetic strategies to improve productivity and reduce metabolism of peptides, along with alternative routes of administration, have been developed in recent years, and a large number of peptide-based drugs are now being marketed.

Therapeutic peptides traditionally have been derived from three sources: (i) natural or bioactive peptides produced by plants, animal or human (derived from naturally occurring peptide hormones or from fragments of larger proteins); (ii) peptides isolated from genetic or recombinant libraries and (iii) peptides discovered from chemical libraries [10,11].

Generally, the size of the peptide determines the most suitable technology for its production: chemical synthesis, recombinant DNA technology, cell-free expression systems, transgenic animals and plants or enzymatic synthesis. With the use of unnatural amino acids and pseudo-peptide bonds, chemical synthesis offers access to a much wider chemical diversity than peptide derivatives produced by recombinant technologies, with a diversified potential for intellectual property (in terms of patentable new chemical entities). Large-scale chemical synthesis has become a viable technology for the production of small- and medium-sized peptides ranging from approximately 5 to 50 residues, and the chemical way is now often a better technological option than the biotechnological methods of recombinant DNA or biocatalysis for the synthesis of medium-sized peptides that comprise most of the pharmaceutically relevant molecules. In particular, production of synthetic therapeutic peptides has become possible for the pharmaceutical industry with recent developments of solid-phase peptide synthesis (SPPS), initially developed by Merrifield [12] (Fig. 1). SPPS is crucial in the early steps of preclinical research and in the production of peptide-based active pharmaceutical ingredients (APIs) [13]. The main SPPS strategies are sequential synthesis, convergent synthesis and chemical ligation. Sequential synthesis involves the stepwise addition of amino acids until the desired peptide is achieved. Convergent synthesis involves the independent solid-phase synthesis of peptide sequences (fragments) that are then cleaved from the polymer without N-terminal (or C-terminal) and side-chain protecting group removal and linked by condensation in solution (mixed-phase synthesis). This solid-phase and solution-phase hybrid peptide synthesis is often the most appropriate way to synthesize peptides that contain >50 amino acid residues. Chemical ligation involves coupling of totally deprotected fragments by chemoselective reactions [14]. Several systems for the automated *t*-Boc/Bzl and Fmoc/*t*-Bu SPPS, ranging from 1.5 mg to 5 kg scale, are now available from several companies, including AAPPTec, Activotec, Applied Biosystems, CEM, CS Bio, Intavis, Peptide Scientific, Protein Technologies and ThuraMed (CreoSalus group).

Limitations to the use of peptides as drug candidates and key proteolytic enzymes involved in peptide degradation

Peptide limitations

Bioavailability and biodistribution of peptide drug candidates, which include absorption, transport, passage of biological membranes and cellular barriers, are determined by a combination of their physicochemical properties, such as aqueous solubility, lipophilicity, H-bond formation, chemical stability and metabolic stability (proteolytic and/or enzymatic degradation). With a few exceptions, peptides composed of natural amino acids are not very good drug candidates because of their intrinsic physicochemical properties and pharmacokinetic profiles. When compared with therapeutic proteins and antibodies, peptide drug candidates do have notable drawbacks: they generally have low stability in plasma, are sensitive to proteases and can be cleared from the circulation in a few minutes.

Thus, the main limitations generally attributed to therapeutic peptides [15,16] are: low oral bioavailability (injection is generally required); a short half-life because of their rapid degradation by proteolytic enzymes of the digestive system and blood plasma; rapid removal from the circulation by the liver (hepatic clearance) and kidneys (renal clearance); poor ability to cross physiological barriers because of their general hydrophilicity; high conformational flexibility, resulting sometimes in a lack of selectivity involving interactions with different receptors or targets (poor specific biodistribution), causing activation of several targets and leading to side effects; eventual risk of immunogenic effects; and high synthetic and production costs (the production cost of a 5000 Da molecular mass peptide exceeds the production cost of a 500 Da molecular mass small molecule by more than 10-fold but clearly not 100-fold) [17].

Proteolytic enzymes

As mentioned above, the proteolytic stability of natural peptides is one of the principal limitations of their use as drug candidates. Human blood is composed of 44% red blood cells, 1% white blood cells and 55% plasma. Plasma consists of 91% water, 7% proteins and 2% salts. It contains more than 120 different proteins, including albumin (HSA), immunoglobulin G (IgG), fibrinogen (factor I), alpha-2-macroglobulin (α2M), alpha-1-antitrypsin (A1AT), transferrin (siderophilin) and lipoproteins and numerous proteolytic enzymes, such as esterases and peptidases. As indicated in Table 1, according to the enzyme classification (E.C.) (http://www.biochem.ucl.ac.uk/bsm/enzymes/ec3/index.html, http://www.ebi.ac.uk/thornton-srv/databases/enzymes/), numerous human proteolytic enzymes (peptidases) are involved in peptide degradation [18,19]. The greatest threat to therapeutic peptides lies in the lumen of the small intestine, which contains gram quantities of peptidases secreted from the pancreas (e.g. α-chymotrypsin, trypsin, pancreatic elastase, carboxypeptidases A, B, D, N and U and so on), as well as cellular peptidases from mucosal cells. The second major enzymatic barrier is the brush border membrane of the epithelial cells, which contains at least 15 peptidases [20] (e.g. dipeptidyl-peptidase IV, prolyl tripeptidyl-peptidase, angiotensin-converting enzyme, leucyl-aminopeptidase, aminopeptidase M, aminopeptidase A, neprilysin and so on), that together have a broad specificity and can degrade both peptides

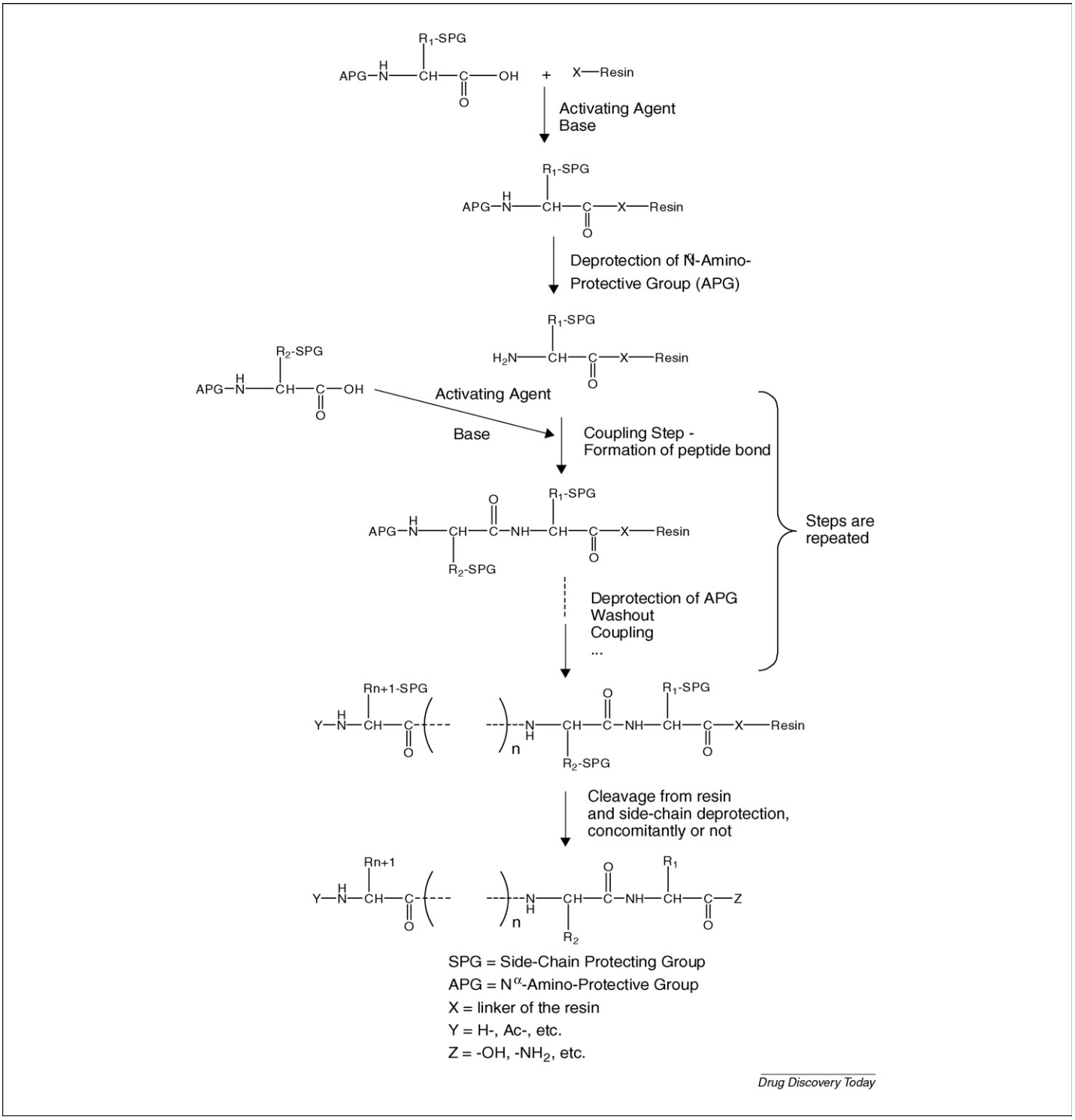

FIGURE 1

Sequential (or linear) solid-phase peptide synthesis (SPPS). This figure illustrates the repetitive stepwise process (activation, coupling, deprotection, washout and cleavage) of chemical peptide synthesis by solid-phase technique.

and proteins. Lysosomal peptidases (leukocyte elastase, cathepsins B and D and so on) will also target peptides or proteins endocytosed by epithelial or endothelial cells. In the matrix metalloproteinase family (zinc-dependant endopeptidases) known to degrade extracellular matrix proteins, interstitial collagenase (MMP-1, *E.C.3.4.24.7*) is also able to cleave specific small molecules such as peptides. Amongst proteases, carboxypeptidase C – sometimes referred to as Y (*E.C.3.4.16.5*) – is the only enzyme that exhibits both the esterase and the amidase activities typical of serine proteases [19]. Many enzymes are also present in different tissues or organs. For example, in brain micro-capillaries, which constitute part of the blood–brain barrier (BBB), gamma-glutamyl transpeptidase (transferase, *E.C.2.3.2.2*), alkaline phosphatase (hydrolase, *E.C.3.1.3.1*), monoamine oxidase (oxidoreductase, *E.C.1.4.3.4*), catechol-*O*-

TABLE 1

Most important human proteolytic enzymes involved in peptide degradation.

Enzymes	E.C. number	Cleavage sites
Endopeptidases		
Serine proteases	***E.C.3.4.21***	
α-Chymotrypsin	*E.C.3.4.21.1*	Tyr-|-Xaa, Trp-|-Xaa, Phe-|-Xaa, and also Leu-|-Xaa and Met-|-Xaa
Trypsin	*E.C.3.4.21.4*	Arg-|-Xaa and Lys-|-Xaa
Thrombin	*E.C.3.4.21.5*	Arg-|-Gly
Plasmin	*E.C.3.4.21.7*	Lys-|-Xaa > Arg-|-Xaa
Prolyl oligopeptidase, or prolyl endopeptidase[a]	*E.C.3.4.21.26*	Pro-|-Xaa >> Ala-|-Xaa
Plasma kallikrein	*E.C.3.4.21.34*	Arg-|-Xaa and Lys-|-Xaa, including Lys-|-Arg and Arg-|-Ser
Pancreatic elastase	*E.C.3.4.21.36*	Ala-|-Xaa, and also Gly-|-Xaa, Val-|-Xaa and Ser-|-Xaa
Leukocyte elastase, or neutrophil elastase, or lysosomal elastase	*E.C.3.4.21.37*	Val-|-Xaa and Ala-|-Xaa
Cysteine proteases	***E.C.3.4.22***	
Cathepsin B	*E.C.3.4.22.1*	Arg-Arg-|-Xaa, and also Leu-|-Xaa, Ala-|-Xaa, Phe-|-Xaa and Trp-|-Xaa
Clostripain, or endoproteinase Arg-C	*E.C.3.4.22.8*	Arg-|-Xaa including Arg-|-Pro, but not Lys-|-Xaa
Calpain-1, or μ-calpain	*E.C.3.4.22.52*	Met-|-Xaa, Tyr-|-Xaa and Arg-|-Xaa (with Leu or Val as the P2 residue)
Aspartic acid proteases	***E.C.3.4.23***	
Pepsin	*E.C.3.4.23.1*	Preferentially Phe-|-Xaa, Tyr-|-Xaa and also Leu-|-Xaa and Trp-|-Xaa, ideally with Xaa = Phe, Trp, or Tyr
Cathepsin D	*E.C.3.4.23.5*	Preferentially Phe-|-Xaa, Tyr-|-Xaa and Leu-|-Xaa, ideally with Xaa ≠ Ala or Val
Metalloproteases	***E.C.3.4.24***	
Neprilysin, or enkephalinase, or neutral endopeptidase[a]	*E.C.3.4.24.11*	Xaa-|-Tyr, Xaa-|-Phe, Xaa-|-Trp and Xaa-|-Leu
Thimet oligopeptidase, or endo-oligopeptidase A, or endopeptidase 24.15, or pz-peptidase[a]	*E.C.3.4.24.15*	Xaa-|-Arg, Xaa-|-Ser, Xaa-|-Ile, Xaa-|-Ala, Xaa-|-Gly
Exopeptidases		
Aminopeptidases	***E.C.3.4.11***	***N-term***
Leucyl-aminopeptidase	*E.C.3.4.11.1*	Preferentially Leu-|-Xaa, but not Arg-|-Xaa and Lys-|-Xaa
Aminopeptidase M or N, or alanyl-aminopeptidase, or membrane alanine aminopeptidase[a]	*E.C.3.4.11.2*	Preferentially Ala-|-Xaa and Tyr-|-Xaa, if Yaa-Pro-|-Xaa in N-term with Yaa = Ala, Val, Leu, Ile, Phe, Tyr or Trp then the dipeptide Yaa-Pro could be released
Aminopeptidase A, or angiotensinase, or glutamyl-aminopeptidase[a]	*E.C.3.4.11.7*	Glu-|-Xaa >> Asp-|-Xaa
Dipeptidyl-peptidases and tripeptidyl-peptidases	***E.C.3.4.14***	***N-term (di- and tripeptides)***
Dipeptidyl-peptidase I, or cathepsin C or J	*E.C.3.4.14.1*	Xaa-Yaa-|-Zaa-, if Xaa ≠ Arg or Lys, or Yaa ≠ Pro, or Zaa ≠ Pro
Dipeptidyl-peptidase IV[a]	*E.C.3.4.14.5*	Preferentially Xaa-Pro-|-Yaa- (but also Xaa-Ala-|-Yaa-) with Yaa ≠ Pro or Hyp
Prolyl tripeptyl-peptidase	*E.C.3.4.14.12*	Xaa-Yaa-Pro-|-Zaa if Zaa ≠ Pro
Peptidyl-dipeptidases	***E.C.3.4.15***	***C-term***
Peptidyl-dipeptidase A, or angiotensin-converting enzyme[a]	*E.C.3.4.15.1*	Xaa-|-Yaa-Zaa, if Yaa ≠ Pro, or Zaa ≠ Asp or Glu
Metallo-carboxypeptidases	***E.C.3.4.17***	***C-term***
Carboxypeptidase A	*E.C.3.4.17.1*	Xaa-|-Yaa if Yaa ≠ Asp, Glu, Arg, Lys or Pro
Carboxypeptidase B, or protaminase	*E.C.3.4.17.2*	Xaa-|-Arg and Xaa-|-Lys
Carboxypeptidase N, or lysine(arginine) carboxypeptidase, or kininase I[a]	*E.C.3.4.17.3*	Xaa-|-Lys >> Xaa-|-Arg
Carboxypeptidase U or R	*E.C.3.4.17.20*	Xaa-|-Arg and Xaa-|-Lys
Glutamate carboxypeptidase II, or folate hydrolase	*E.C.3.4.17.21*	Xaa-|-Glu, preferentially with Xaa = Asp or Glu

Abbreviations: Xaa, amino acid; Hyp, hydroxyproline.

[a] Indicates peptidases present at cerebrovasculature [18].

methyl transferase (transferase, *E.C.2.1.1.6*), butyrylcholinesterase (hydrolase, *E.C.3.1.1.8*) and aromatic-L-amino acid carboxylase (or dopa-decarboxylase or aromatic-L-amino acid decarboxylase; lyase, *E.C.4.1.1.28*), are found at high levels [18,21]. Other enzymes, such as epoxidehydrolase (or epoxide hydrolase; hydrolase, *E.C.3.3.2.9*, former *E.C.3.3.2.3*), UDP-glucuronosyl-transferase (glycosyl-transferase, *E.C.2.4.1.17*), benzyloxyresorufin-*O*-deethylase (cytochrome P-450 CYP2B1; oxidoreductase, *E.C.1.14.14.1*), NADPH cytochrome P-450 reductase (oxidoreductase, *E.C.1.6.2.4*) and glutathione-*S*-transferase (transferase, *E.C.2.5.1.18*) are also found

bound to brain micro-capillaries at high levels [18,21]. The protein-disulfide reductase (oxidoreductase, *E.C.1.8.4.2*), which enables disulfide bridge cleavage by reduction in dithiol, is also abundant in the brain and can alter peptide structures stable in plasma [22,23]. Proteolytic peptide degradation, which results in short half-life (generally, a few minutes or, at best, a few hours), can be countered in various ways, in particular by using new synthetic strategies for limiting metabolism and alternative routes of administration [24]. Thus, it is usually necessary to introduce chemical modifications into peptides containing natural amino acids to adapt them for therapeutic use.

Chemical strategies to improve peptide biological activity, specificity and stability

As discussed previously, the low bioavailability of peptides is due in part to high biodegradability by gastrointestinal, plasma and tissue peptidases. Moreover, their rapid removal from the circulation can also limit their therapeutic use. Absorption, distribution, metabolism and excretion processes play a pivotal part in defining the disposition of a drug candidate and, thus, its therapeutic effect [25]. To develop a peptide as a therapeutic agent, its biological effect, pharmacokinetic profile and low immunogenicity are crucial parameters. Therefore, various chemical strategies have been developed to try and overcome the limitations of peptides to increase their *in vivo* plasma residence time. Many cyclic peptides, pseudo-peptides (modification of the peptide bond) and peptidomimetics (nonpeptide molecules) preserving the biological properties of peptides have been and are widely developed to increase their resistance to degradation and elimination, their bioavailability and their selectivity (targeting of protein–receptor interactions) to become good drug candidates. In fact, from a model peptide of interest (lead peptide), it is often necessary to optimize its chemical structure (cyclization, bioisosteric replacement of peptide bonds, changing the stereochemistry of an amino acid and so on) to obtain a compound that can be used therapeutically, even for parental administration (e.g. subcutaneous, intramuscular or intravenous injection).

The chemical optimization strategy of a therapeutic peptide is based on structure–activity relationship and/or quantitative structure–activity relationship studies of newly synthesized peptide derivatives, with the aim of improving bioavailability, reducing elimination and biodegradation and increasing selectivity or affinity to its receptor or target. As detailed in Box 1, lead peptide chemical optimization usually requires different strategies developed by peptide chemists [15,16,18,26,27]. As previously discussed, the main reasons for the low oral bioavailability of peptide drugs are pre-systemic enzymatic degradation and poor penetration of the intestinal mucosa. According to Lipinski's 'rule of five' [28–31] completed by Veber *et al.*'s analysis [32], peptides are poor candidates to move from the digestive tract to the circulatory system because of their physicochemical properties. For these reasons, until a few years ago, therapeutic peptides were generally administered by subcutaneous, intramuscular or intravenous routes (which inevitably cause discomfort for the patient) to circumvent the gut barrier. The paths of molecules in animals or humans are as follows: (i) heart (right ventricle), lungs, heart (left ventricle), then distribution to the various organs, including liver, intestine, brain, kidneys and muscles, if injected intravenously; and (ii) stomach, intestine, liver, blood, kidneys and tissues, if administered orally [33]. In the latter case, peptides have to face a strongly acidic gastric environment, high levels of intestinal proteolytic activity and a high intestinal permeability barrier [20]. Consequently, alternative routes for the administration of peptide-based drugs have been improved in recent years, and novel peptide delivery technologies have emerged, including controlled-release parenteral route (subcutaneous, intramuscular or intrave-

BOX 1

Lead peptide chemical optimization

- Search for the minimum active sequence (MAS) from N- and/or C-terminal truncated analogues (Fig. 2).
- Significance of the N- and C-terminus.
- Deletion of one or more consecutive amino acid(s) and combinatorial deletion with two or more positions omitted independently throughout the sequence (Fig. 2).
- Simplification and/or optimization of the structure after alanine scanning (Ala-scan) and/or D-scanning (D-scan) to eliminate potential sites of cleavage (notably by endopeptidases) and to determine important functional groups involved in the interaction with the target of interest (Fig. 2).
- Cyclization of the peptide sequence (between side chains or ends of the peptide sequence: head to tail, N-backbone to N-backbone, end to N-backbone, end to side chain, side chain to N-backbone, side chain to side chain) [36] through disulfide (disulfide-bond cyclization scan, Fig. 2), lanthionine, dicarba, hydrazine or lactam bridges [37] to decrease the conformational flexibility of linear peptides, to reduce hydrogen bonding, to enhance membrane permeability and, importantly, to increase their stability to proteolysis by endo- and exopeptidases.
- Substitution of a natural amino acid residue by an unnatural amino acid (D-configuration), an *N*-methyl-α-amino acid, a non-proteogenic constrained amino acid or a β-amino acid, to increase plasma stability (e.g. resistance to endopeptidases) of the peptide and/or affinity (activity) for its target.
- Isosteric, or not, amide bond replacement between two amino acids: NH-amide alkylation, the carbonyl function of the peptide bond can be replaced by CH_2 (reduced bond: –CH_2–NH–), C(=S) (endothiopeptide, –C(=S)–NH–) or PO_2H (phosphonamide, –P(=O)OH–NH–). NH-amide bond can be exchanged by O (depsipeptide, –CO–O–), S (thioester, –CO–S–) or CH_2 (ketomethylene, –CO–CH_2–). The peptide bond can also be modified: retro-inverso bond (–NH–CO–), methylene-oxy bond (–CH_2–), thiomethylene bond (–CH_2–S–), carba bond (–CH_2–CH_2–), hydroxyethylene bond (–CHOH–CH_2–) and so on, to increase plasma stability of the peptide sequence (notably towards endopeptidases).
- Blocking N- or C-terminal ends by N-acylation, *N*-pyroglutamate, C-amidation and so on, or addition of carbohydrate chains (glycosylation: glucose, xylose, hexose and so on) to increase plasma stability (notably, resistance towards exopeptidases).
- N-terminal esterification (phosphoester) or pegylation modifications to enhance plasma stability (e.g. resistance to exopeptidases) and to reduce immunogenicity. Pegylation is also designed to make the peptide larger (generally >50 kDa) to retard excretion through the kidneys (renal clearance).

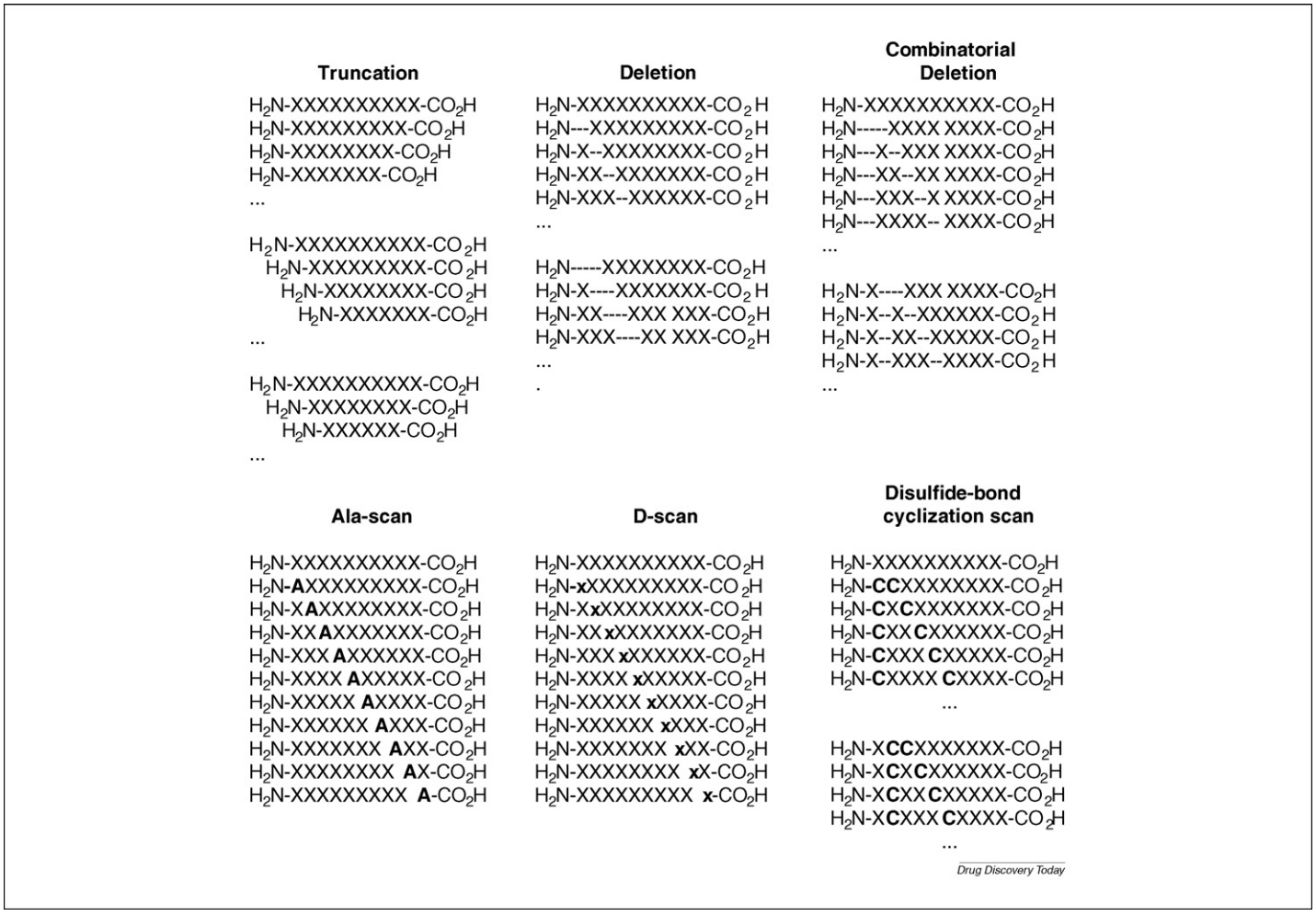

FIGURE 2

Chemical optimization strategies of peptides. This figure illustrates the main strategies developed by peptide chemists for lead peptide optimization.

nous), mucosal route (nasal spray, pulmonary delivery or sublingual delivery), oral route (penetration enhancers, protease inhibitors or carriers) and transdermal route (patches) [24]. The biodistribution study of a therapeutic peptide is essential to determine its uptake by various organs and its selectivity for its targeted site of action. Despite these recent advances in oral delivery, the bioavailability of therapeutic peptides with any of the current technologies is much lower than that obtained by injection. The speed of action and the low side effects of a peptide injection are unbeatable in case of emergency treatments [34]. In spite of some limitations and thanks to progress in chemical synthesis and routes of administration, synthetic therapeutic peptides present numerous advantages compared with their homologous compounds (proteins and antibodies) and with small organic molecules.

Advantages of peptides over other drug candidates

Compared with proteins and antibodies, peptides have the potential to penetrate further into tissues owing to their smaller size. Moreover, therapeutic peptides, even synthetic ones, are generally less immunogenic than recombinant proteins and antibodies [35]. Peptides have other advantages over proteins and antibodies as drug candidates, including lower manufacturing costs (synthetic versus recombinant production), higher activity per unit mass (15–60-fold, assuming 75 kDa for one combining site of an antibody and 10–50 amino acids for a therapeutic peptide), lower royalty stack than antibodies because of a simpler intellectual property landscape during discovery and manufacturing, greater stability (lengthy storage at room temperature acceptable), reduced potential for interaction with the immune system (assuming the peptide contains no known immune-system signalling sequence) and better organ or tumour penetration [26].

Therapeutic peptides also offer several advantages over small organic molecules that make up traditional medicines. The first advantage is that often representing the smallest functional part of a protein, they offer greater efficacy, selectivity and specificity (limited non-specific binding to molecular structures other than the desired target) [36] than small organic molecules. A second advantage is that the degradation products of peptides are amino acids, thus minimizing the risks of systemic toxicity (minimization of drug–drug interactions) [34]. Third, because of their short half-life, few peptides accumulate in tissues (reduction of risks of complications caused by their metabolites). Most therapeutic peptides, which are mainly derived from natural peptides, are receptor agonists [37]. Generally, small quantities of these peptide agonists are necessary to activate the targeted receptors [38]. Few

TABLE 2

Synthetic therapeutic peptides that have reached American, European and/or Japanese pharmaceutical markets.

INNs	Brand names	Length	Sequences	Companies	Indications
ACTH and derivatives					
corticorelin ovine triflutate, or corticorelin trifluoroacetate	Acthrel®, Stimu-ACTH®[a]	41 aa	H-Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH_2, $(trifluoroacetate)_n$ (n = 4 to 8)	Ferring Pharms	Diagnosis of ACTH-dependent Cushing's syndrome
corticorelin acetate injection[c], or hCRF	Xerecept®	41 aa	H-Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH_2, acetate	Celtic Pharma	Peritumoral brain edema (FDA orphan drug status – Phase III)
cosyntropin, or ACTH 1-24, or tetracosactide hexaacetate	Cortrosyn®, Cosyntropin, Synacthen®[a]	24 aa	H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-OH, hexaacetate	Amphastar Pharms, Sandoz-Novartis Pharma	Diagnosis of adrenocortical insufficiency
seractide acetate, or ACTH, or corticotropin	Acthar® Gel-synthetic[b]	39 aa	H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asp-Ala-Gly-Glu-Asp-Gln-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe-OH, acetate	Armour Pharm	Diagnosis of adrenocortical insufficiency
ACE inhibitors, excluding pseudo-peptides and peptidomimetics as alacepril (Cetapril®), benazepril (Cibacen®, Lotensin®), captopril (Capoten®, Capozide®, Lopirin®), cilazapril (Inhibace®, Justor®, Vascace®), delapril (Adecut®), fosinopril (Fozitec®, Monopril®), imidapril (Tanatril®), moexipril (Moex®, Perdix®, Univasc®), perindopril (Aceon®, Coversyl®), quinapril (Accupril®), ramipril (Altace®, Ramace®, Triatace®, Triatec®), spirapril (Renormax®), temocapril (Acecol®), trandolapril (Mavik®, Odrik®), zofenopril (Zofenil®)					
enalapril maleate (or 2-butanedioate)	Enalapril Maleate, Renitec®[a], Vasotec®	3 aa	(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-Ala]-Pro-OH, maleate or (Z)-2-butenedioate	Biovail Pharms, Merck Sharp & Dohme, Apothecon, Genpharm, Ivax Pharms, KRKA DD Novo Mesto, LEK Pharms, Mylan, Ranbaxy, Sandoz-Novartis Pharma, Taro, Teva, Torpharm, Watson Labs, Wockhardt	Hypertension
lisinopril	Lisinopril, Prinivil®[b], Zestril®	3 aa	(S)-1-[N^2-(1-carboxy-3-phenylpropyl)-Lys]-Pro-OH	AstraZeneca, Merck Sharp & Dohme, Actavis Elizabeth, Apotex, Aurobindo Pharma, Ivax Pharms, LEK Pharms, Lupin, Mylan, Par Pharm, Ranbaxy, Sandoz-Novartis Pharma, Teva, Vintage Pharms, Watson Labs, West Ward, Wockhardt	Hypertension, congestive heart failure
Angiotensin II receptor antagonist					
saralasin acetate	Sarenin®[b]	8 aa	H-Sar-Arg-Val-Tyr-Val-His-Pro-Ala-OH, acetate [1-Sarcosyl-8-Alanyl-angiotensin II]	Norwich-Eaton Pharms, Procter & Gamble	Hypertension
Antidiabetic agents					
exenatide	Byetta®	39 aa	H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 [Incretin mimetics (GLP-1 et GIP)]	Amylin Pharms, Eli Lilly	Glycemic control in patients with type 2 diabetes mellitus

liraglutide	Victoza®[a]	31 aa	H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-N^6-[N-(1-oxohexadecyl)-L-γ-Glu]-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH [GLP-1 analogue]	Novo Nordisk	Type 2 diabetes
pramlintide acetate	Symlin®	37 aa	H-Lys-c[Cys-Asn-Thr-Ala-Thr-Cys]-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2, acetate	Amylin Pharms	Both type 1 and 2 diabetes
Anti-HIV compound, excluding anti-protease pseudo-peptides and peptidomimetics as amprenavir (Agenerase®), atazanavir sulfate (Reyataz®), darunavir ethanolate (Prezista®), fosamprenavir calcium (Lexiva®/Telzir®), indinavir sulfate (Crixivan®), lopinavir (Aluvia®/Kaletra®), nelfinavir mesylate (Viracept®), ritonavir (Norvir®), saquinavir mesylate (Invirase®/Fortovase®)					
enfuvirtide	Fuzeon®	36 aa	Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2	Roche	AIDS/HIV-1 infection
Calcitonins					
salmon calcitonin	Acticalcin®[a], Cadens®[a], Calcimar®[b], Calcitonin®[b], Calsyn®[a], Caltine®[a], Forcaltonin®[a], Miacalcic®[a], Miacalcin®[b], Salco®[a]	32 aa	H-c[Cys-Ser-Asn-Leu-Ser-Thr-Cys]-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2	AstraZeneca, GNR Pharma, Lafon, Lisapharma, Pharmy II, Sandoz-Novartis Pharma, Sanofi-Aventis, TRB Pharma, Zambon France	Postmenopausal osteoporosis, Paget's disease, hypercalcaemia
elcatonin acetate	Carbocalcitonin®[a]	31 aa	c[Ser-Asn-Leu-Ser-Thr-Asu]-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2	Gelacs Innovation	Postmenopausal osteoporosis, anti-parathyroid, Paget's disease, hypercalcaemia
human calcitonin	Cibacalcin®[b]	32 aa	H-c[Cys-Gly-Asn-Leu-Ser-Thr-Cys]-Met-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH_2	Novartis Pharma	Postmenopausal osteoporosis, Paget's disease, hypercalcaemia
Cardiovascular					
bivalirudin trifluoroacetate hydrate	Angiomax®, Angiox®[a]	20 aa	H-D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-OH, trifluoroacetate hydrate	Nycomed Pharma, The Medicines Company	Anticoagulant in patients with unstable angina undergoing PTCA or PCI
eptifibatide	Integrilin®	7 aa	c[Mpa-homoArg-Gly-Asp-Trp-Pro-Cys]-NH_2	Millennium Pharms, GSK, Schering-Plough	Acute coronary syndrome, unstable angina undergoing PCI
icatibant acetate	Firazyr®[a]	10 aa	H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate	Jerini AG	Hereditary angioedema
Cholecystokinin analogues					
ceruletide diethylamine	Takus®[a], Tymtran®[b]	10 aa	Pyr-Gln-Asp-Tyr(OSO_3H)-Thr-Gly-Trp-Met-Asp-Phe-NH_2, diethylamine	Pharmacia and Upjohn, Farmitalia Carlo Erba	Diagnosis of the functional state of the gallbladder and pancreas, and stimulant of the gastric secretion

TABLE 2 (*Continued*)

INNs	Brand names	Length	Sequences	Companies	Indications
sincalide	Kinevac®	8 aa	H-Asp-Tyr(OSO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2	Bracco Diagnostics	Diagnosis of the functional state of the gallbladder and pancreas, and stimulant of the gastric secretion
CNS					
cilengitide[c], or EMD121974	///	5 aa	c[Arg-Gly-Asp-D-Phe-(N-Me)Val]	Merck-Serono	GBM (EMEA and FDA orphan drug status – Phase III)
taltirelin hydrate	Ceredist®[a]	2 aa	N-[(hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl) carbonyl]-His-Pro-NH_2, hydrate	Tanabe Seiyaku	Spinocerebellar degeneration/ataxia
ziconotide acetate	Prialt®	25 aa	[Cys^1-Cys^{16}, Cys^8-Cys^{20}, Cys^{15}-Cys^{25}]-tricyclo H-[Cys^1-Lys-Gly-Lys-Gly-Ala-Lys-Cys^8-Ser-Arg-Leu-Met-Tyr-Asp-Cys^{15}-Cys^{16}-Thr-Gly-Ser-Cys^{20}-Arg-Ser-Gly-Lys-Cys^{25}]-NH_2,acetate	Elan Pharms	Severe chronic pain
GHRH and analogue					
sermorelin acetate or GRF 1-29	Geref®[b], Groliberin®[a]	29 aa	H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate [or GRF 1-29 NH_2, acetate]	Serono Labs, Kabi, Pharmacia	Growth hormone deficiency, diagnosis evaluation of pituitary function
somatorelin acetate, or GHRH, or GHRF, or GRF	GHRH Ferring®[a], Stimu-GH®[a], Somatrel®[a]	44 aa	H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Glu-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2, acetate	Ferring Pharms	Diagnosis of somatotropic function of the anterior pituitary gland in cases of suspected growth hormone deficiency (hypophysic and hypothalamic disorders)
GnRH and analogues (agonists)					
buserelin acetate	Bigonist®[a], Suprefact®[a]	9 aa	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt (or N-ethyl-prolinamide), acetate	Sanofi-Aventis	Advanced prostate cancer
gonadorelin acetate, or GnRH, or LHRH	Factrel®[b], Kryptocur®[a], Lutrelef®[a], Lutrepulse®[b], Relefact®[a], Stimu-LH®[a]	10 aa	Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2, acetate	Baxter Healthcare, Ferring Pharms, Sanofi-Aventis, Wyeth Pharms	Stimulate the secretion of gonadotropin during disturbances fertility, and diagnosis of the functional capacity and response of the gonadotropes of the anterior pituitary
goserelin acetate	Zoladex®	10 aa	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2, acetate [or [D-Ser(OtBu)^6, $AzGly^{10}$]GnRH, acetate]	AstraZeneca	Advanced prostate cancer, breast cancer
histrelin acetate	Supprelin®[b], Supprelin LA®, Vantas®	9 aa	Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt, acetate	Endo Pharms, Roberts Pharma, Shire	Advanced prostate cancer, central precocious puberty

leuprolide acetate, or leuprorelin	Eligard®, Enantone®[a], Lucrin Depot®[a], Lupron®, Lupron Depot®, Prostap®[a], Viadur®	9 aa	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt, acetate	Abbott, Alza, Astellas Pharma, Bayer, Bedford Labs, Genzyme, Johnson & Johnson, QLT, Sanofi-Aventis, Takeda, Teva, Wyeth	Advanced prostate cancer, breast cancer, central precocious puberty
nafarelin acetate	Synarel®, Synrelina®[a]	10 aa	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2, acetate	Pfizer, Searle	Central precocious puberty, endometriosis, uterine fibroids, ovarian stimulation in ***in vitro*** fecundation
triptorelin pamoate	Decapeptyl®[a], Diphereline®[a], Gonapeptyl®[a], Pamorelin®[a], Trelstar Depot®, Trelstar LA®	10 aa	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2, pamoate	Debiopharm, Ferring Pharms, Beaufour Ipsen Pharma, Watson Labs	Advanced prostate cancer, central precocious puberty, endometriosis, uterine fibroids, ovarian stimulation in *in vitro* fecundation
GnRH antagonists					
abarelix acetate	Plenaxis™[b]	10 aa	Ac-D-2Nal-D-4-chloroPhe-D-3-(3́-pyridyl)Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-D-Ala-NH_2, acetate	Praecis Pharms, Speciality European Pharma	Advanced prostate cancer
cetrorelix acetate	Cetrotide®	10 aa	Ac-D-2Nal-D-4-chloroPhe-D-3-(3́-pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2, acetate	AEterna Zentaris, Merck-Serono	Inhibition of premature LH surges in women undergoing controlled ovarian stimulation
degarelix acetate, or FE200486	Degarelix Acetate, Firmagon®[a]	10 aa	Ac-D-2Nal-D-4-chloroPhe-D-3-(3́-pyridyl)Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carbamoyl)-Leu-isopropylLys-Pro-D-Ala-NH_2, acetate	Ferring Pharms, Astellas Pharma	Advanced prostate cancer
ganirelix acetate	Antagon®[b], Ganirelix Acetate Injection, Orgalutran®[a]	10 aa	Ac-D-2Nal-D-4-chloroPhe-D-3-(3́-pyridyl)Ala-Ser-Tyr-D-(N^9,N^{10}-diethyl)-homoArg-Leu-(N^9,N^{10}-diethyl)-homoArg-Pro-D-Ala-NH_2, acetate	Organon	Inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation
Oxytocin, antagonist and analogue					
atosiban acetate	Antocin®[a], Tractocile®[a]	9 aa	c[Mpa-Tyr(Et)-Ile-Thr-Asn-Cys]-Pro-Orn-Gly-NH_2, acetate [or [Mpa^1, D-$Tyr(Et)^2$, Thr^4, Orn^8]-oxytocin ,acetate]	Ferring Pharms	Delaying the birth in case of threat of premature birth
carbetocin acetate	Duratocin®[a], Lonactene®[a], Pabal®[a]	8 aa	c[Tyr(Me)-Ile-Gln-Asn-Cys($(CH_2)_3CO_2$-)]-Pro-Leu-Gly-NH_2, acetate	Ferring Pharms	Prevention of uterine atony, induction, and control postpartum bleeding or haemorrhage
oxytocin	Oxytocin, Pitocin®, Syntocinon®[b]	9 aa	H-c[Cys-Tyr-Ile-Gln-Asn-Cys]-Pro-Leu-Gly-NH_2	Abbott, APP Pharms, Baxter Healthcare, JHP Pharms, King Pharmas, Novartis Pharma, Teva	Initiation or improvement of uterine contractions, and control postpartum bleeding or haemorrhage
Secretin					

TABLE 2 (*Continued*)

INNs	Brand names	Length	Sequences	Companies	Indications
secretin (human)	ChiRhoStim®	27 aa	H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2	ChiRhoClin	Diagnosis of pancreatic exocrine dysfunction, and gastrinoma, Zollinger-Ellison syndrome
secretin (porcine)	SecreFlo™[b]	27 aa	H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2	ChiRhoClin	Diagnosis of pancreatic exocrine dysfunction, and gastrinoma, Zollinger-Ellison syndrome
Somatostatin (GHIH or SRIF) and analogues (agonists)					
depreotide trifluoroacetate (plus sodium pertechnetate)	NeoTect™[b], NeoSpect®[a]	10 aa	Technetium (^{99m}Tc) c[homoCys-(N-Me)Phe-Tyr-D-Trp-Lys-Val], (1→1)-sulfide with 2-mercaptoacetyl-β-Dap-Lys-Cys-Lys-NH_2, trifluoroacetate	Amersham Health, Berlex Labs, CIS bio International, Nycomed Imaging	Diagnosis (scintigraphic imaging) of lung tumours
edotreotide (plus yttrium-90)[c]	Onalta®	7 aa	***N***-[[4,7,10-Tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-D-Phe-c[Cys-Tyr-D-Trp-Lys-Thr-Cys]-NH-[*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]] or (DOTA D-Phe^1,Tyr^3)octreotide	Molecular Insight Pharms	Gastro-entero-pancreatic neuroendocrine tumours (FDA orphan drug status – Phase II)
lanreotide acetate	Somatuline Autogel®[a], Somatuline Depot®	8 aa	H-2Nal-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH_2, acetate	Beaufour Ipsen Pharma, Globopharm, Tercica	Acromegaly, carcinoid syndrome
octreotide acetate	Octreotide Acetate, Sandostatin®, Sandostatin LAR®	8 aa	H-D-Phe-c[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thol, acetate	Abraxis Pharma, Bedford Labs, Sandoz-Novartis Pharma, Sun Pharma, Teva	Acromegaly, carcinoid syndrome
pentetreotide (plus indium-111)	OctreoScan®	8 aa	[N-(diethylenetriamine-N,N,N′,N″-tetraacetic acid-N″-acetyl)-D-Phe-c[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thol [octreotide DTPA]	Mallinckrodt, Bristol-Myers Squibb	Diagnosis (scintigraphic imaging) of primary and metastatic neuroendocrine tumours
somatostatin acetate	Stilamin®[a]	14 aa	H-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH, acetate	Merck-Serono	Acute variceal bleeding
vapreotide acetate	Octastatin®[a], Sanvar®[a]	8 aa	H-D-Phe-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH_2, acetate	Debiopharm, H3 Pharma	BOV
Vasopressin analogues					
argipressin	Pitressin®[a]	9 aa	H-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Arg-Gly-NH_2 [or 8-L-argininevasopressine]	Monarch/King Pharms	Central diabetes insipidus, and BOV
desmopressin acetate	DDAVP®[b], Defirin®[a], Desmopressin Acetate, Minirin®, Minirinmelt®[a], Octim®[a], Stimate®	9 aa	c[Mpa-Tyr-Phe-Gln-Asn-Cys]-Pro-D-Arg-Gly-NH_2, monoacetate trihydrate [or 1-(3-mercaptopropionic acid)-8-D-argininevasopressine monoacetate trihydrate]	Apotex, Bausch & Lomb Pharms, Barr Labs, Behring, Ferring Pharms, Hospira, Pharmaceutique Noroit, Sanofi-Aventis, Teva	Central diabetes insipidus, nocturnal enuresis, nocturia, and stoppage of bleeding or haemorrhage in haemophilia A patients
lypressin	Diapid®[b]	9 aa	H-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH_2 [or 8-L-lysinevasopressine]	Sandoz-Novartis Pharma	Central diabetes insipidus, Cushing's syndrome
phenypressin	Felypressin®[a]	9 aa	H-c[Cys-Phe-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH_2 [or 2-L-phenylalanine-8-L-lysinevasopressine]	Globopharm	Stomatitis, pharyngitis

terlipressin acetate	Glypressin®[a]	12 aa	H-Gly-Gly-Gly-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH_2, acetate [or triglycyl-8-L-lysinevasopressine]	Ferring Pharms	BOV
Miscellaneous					
ADH-1[c]	Exherin™	5 aa	Ac-c[Cys-His-Ala-Val-Cys]-NH_2	Adherex Technologies	Malignant melanoma (FDA orphan drug status – Phase II)
afamelanotide[c], or melanotan-1, or CUV1647	///	13 aa	Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 or [Nle^4, D-Phe^7]-α-MSH	Clinuvel Pharms	Erythropoietic porphyries (EMEA and FDA orphan drug status – Phase III)
bortezomib	Velcade®	2 aa	Pyz-Phe-boroLeu-$(OH)_2$	Janssen-Cilag, Millennium Pharms	Multiple myeloma, and refractory, mantle cell lymphoma
glatiramer acetate	Copaxone®, Copolymer1®[a]	random mixture	H-(Glu, Ala, Lys, Tyr)n-OH, acetate	Teva	Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis
glutathion	Agifutol®[a], Glutathiol®[a], Tathion®[a],	3 aa	H-γ-Glu-Cys-Gly-OH	ProThera	Hepatic insufficiency, wound healing, inflammation of respiratory tract, asthenia
IM862, or oglufanide disodium[c]	Thymogen[a]	2 aa	H-Glu-Trp-OH, disodium	Altika, Cytran, Implicit Bioscience	Immune system related diseases (FDA orphan drug status for ovarian cancer – Phase II)
MALP-2S[c], or macrophage-activating lipopeptide-2 synthetic	///	13 aa	S-[2,3-bispalmitoyloxy-(2R)-propyl]-cysteinyl-Gly-Asn-Asn-Asp-Glu-Ser-Asn-Ile-Ser-Phe-Lys-Glu-Lys	Mbiotec	Pancreatic cancer (EMEA orphan drug status – Phase II)
pentagastrin	Pentagastrin Injection BP®[a], Peptavlon®[b]	5 aa	((1,1-dimethylethoxy)carbonyl)-bAla-Trp-Met-Asp-Phe-NH_2	Cambridge Labs, SERB Labs, Wyeth-Ayerst Labs	Diagnosis of the gastric secretion
protirelin, or thyroliberin, or TRH, or TRF	Thypinone®[b], Thyrel TRH®[b], Stimu TSH®	3 aa	Pyr-His-Pro-NH_2	Abbott, Ferring Pharms	Diagnostic assessment of thyroid function
sinapultide, or KL4 in lucinactant	Surfaxin®[a]	21 aa	H-Lys-Leu-Leu-Leu-Leu-Lys-Leu-Leu-Leu-Leu-Lys-Leu-Leu-Leu-Leu-Lys-Leu-Leu-Leu-Leu-Lys-OH	Discovery Labs	Prevention of RDS in premature infants, and meconium aspiration syndrome
spaglumat magnesium (or sodium) salt	Rhinaaxia®[a], Naaxia®[a]	2 aa	Ac-Asp-Glu-OH, magnesium or sodium salt	Laboratoire Thea	Allergic rhinitis and conjunctivitis
teduglutide[c]	Gattex®	33 aa	H-His-Gly-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Met-Asn-Thr-Ile-Leu-Asp-Asn-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-LysIle-Thr-Asp-OH	NPS Pharms, Nycomed	Short Bowel Syndrome (EMEA and FDA orphan drug status – Phase III)
Vx-001[c], or $TERT_{572Y}$	///	9 aa	Tyr-Leu-Phe-Phe-Tyr-Arg-Lys-Ser-Val	Vaxon Biotech	NSCLC (EMEA and FDA orphan drug status – Phase II)

TABLE 2 (*Continued*)

INNs	Brand names	Length	Sequences	Companies	Indications
thymalfasin, or thymosin α-1	Zadaxin®[a]	28 aa	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH	SciClone Pharms International	Chronic hepatitis B, chronic hepatitis C
thymopentin	Mepentil®[a], Sintomodulina®[a], Timunox®[a]	5 aa	H-Arg-Lys-Asp-Val-Tyr-OH	Recordari, Italofarmaco, Johnson & Johnson	Primary and secondary immune deficiencies, autoimmunity, infections, cancer
vasoactive intestinal peptide acetate[c]	Aviptadil®	28 aa	H-His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2, acetate	MondoBiotech Labs, Biogen	Sarcoidosis and acute lung injury (EMEA and FDA orphan drug status – Phase II)

Abbreviations: aa, amino acid; ACTH, adrenocorticotropic hormone; AIDS, acquired immunodeficiency syndrome, Asu, 2-aminosuberic acid or 2-aminooctanoic acid; AzGly, azaglycine; bAla, β-alanine; boroLeu, boronic acid analogue of leucine; BOV, bleeding oesophageal varices; c, cyclo; Cit, citrulline; Dap or Dpr, 2,3-diaminopropanoic acid; GBM, glioblastoma multiforme; GHIH, growth-hormone-inhibiting hormone; GHRF or GRF, growth-hormone-releasing factor; GHRH, growth-hormone-releasing hormone; GnRH, gonadotropin releasing hormone; hCRF, human corticotrophin-releasing factor; Hyp, hydroxyproline; INNs, international nonproprietary names; LH, luteinizing hormone; LHRH, luteinizing-hormone-releasing hormone; Mpa, 3-mercaptopropionic acid or 3-mercaptopropanoic acid; MSH, α-melanocyte stimulating hormone; 2Nal, 3-(2-naphthyl)-alanine; Nle, norleucine; NSCLC, non-small cell lung cancer; Oic, (2S, 3aS, 7aS)-octahydroindole-2-carboxlic acid; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; Pyr, pyroglutamic acid; Pyz, 2,5-pyrazinecarboxylic acid; RDS, respiratory distress syndrome; Sar, sarcosine; SRIF, somatotropin release-inhibiting factor; Thi, 3-(2-thienyl)-alanine, Thol, threoninol, Tic, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; TRF, thyrotropin-releasing factor; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

[a] Products or brands marketed either on European or on Japanese pharmaceutical markets but not on the American pharmaceutical market.

[b] Products or brands discontinued from the American pharmaceutical market; some of them are generics, and others are withdrawn.

[c] Orphan drug status.

peptide antagonists, inhibiting ligand–receptor interactions, have reached the market so far [26]. As a general rule, antagonists must occupy more than 50% of the receptor population to be effective, in contrast to agonists, which require lower levels of receptor occupancy to be effective (normally between 5% and 20%) [6].

Since the advent of SPPS [12], chemical synthesis of therapeutic peptides can be considered as the most mature technology available [39]. Compared with synthetic therapeutic peptides, the quality and/or purity of recombinant molecules is not always optimal and peptides produced by enzymatic routes have low productivity [14]. The system of choice can be dictated by the cost of production or the modifications of the peptide sequence (for example, glycosylation, phosphorylation or proteolytic cleavage) that are required for biological activity [40]. Production systems for recombinant peptides or proteins include bacteria, yeast, insect cells, mammalian cells and transgenic animals and plants. Inability to incorporate unnatural amino acids or C-terminal amidation is another drawback of genetic engineering during the synthesis of therapeutic peptides. Moreover, the application of recombinant DNA technology typically requires a long and expensive R&D phase. Despite the technological advances in peptide synthesis by biocatalysis, the low productivity, the low yield and the high cost of enzymes could hamper competitiveness in a broad spectrum of cases. SPPS is especially suited for medium-sized peptides (up to 100 amino acid residues) that comprise most of the peptides of therapeutic relevance. Moreover, a key advantage of the chemical synthesis by SPPS is that the peptide product can be easily separated from impurities and side products. In addition, synthetic therapeutic peptides are now less expensive to produce than peptides or proteins obtained by recombinant technology (applicable only for peptide sequences including natural amino acids) or enzymatic route. As an example, even if it takes six to eight months and 106 steps to chemically synthesize at a multi-tonne per year scale the 36-mer anti-HIV peptide Fuzeon® (enfuvirtide, the first fusion inhibitor on the market for HIV treatment), its development has helped reduce costs of large-scale good manufacturing practices peptide synthesis to less than US$ 1 per gram per amino acid residue [17].

Market for synthetic therapeutic peptides

The market for synthetic therapeutic peptides rose from €5.3 billion in 2003 to €8 billion in 2005. It has been estimated that it will reach €11.5 billion in 2013 [16]. This excludes peptides, proteins and antibodies extracted from natural sources or produced by recombinant DNA technology, cell-free expression systems, transgenic animals and plants and enzyme technology.

As described in Table 2, more than 60 synthetic therapeutic peptides (comprising those used for medical diagnostics or imaging), with a size <50 amino acids, have reached the American, European and/or Japanese pharmaceutical markets through a marketing authorization as APIs, even if some of them are generics or discontinued (http://www.biam2.org/, http://www.docu-med.ch, http://www.fda.gov/, http://www.fdaapproveddrugs.us, http://www.rxlist.com and http://www.vidal.fr) [14,17,34,41].

Peptides and their homologous compounds (proteins and antibodies) can be used in multiple pathologies, including allergy and asthma, arthritis, baldness, cardiovascular diseases (coronary syndrome and angina), diabetes, gastrointestinal dysfunction,

TABLE 3

Marketed peptide derivatives, proteins and antibodies produced otherwise (recombinant DNA, and so on) than by chemical synthesis.

INNs	Brand-names	INNs	Brand-names	INNs	Brand-names
Peptides					
anidulafungin	Eraxis®, Ecalta®	bacitracin	Bacitracin®, Cortisporin®, Neosporin®	bleomycin	Blenoxane®
caspofungin	Cancidas®	colistin	Colomycin®, Coly-Mycin®, Promixin®	cyclosporine	Gengraf®, Neoral®, Pulminiq®, Restasis®, Sandimmune®
dactinomycin	Cosmegen®	daptomycin	Cubicin®	desirudin	Revasc®
gramidicin	Tyrothricine®	lepirudin or r-hirudin	Refludan®	micafungin	Mycamine®
nesiritide	Natrecor®	polymyxin B	Cortisporin®, Maxytrol®, Neosporin®, Pediotic®, Polymyxin®, Poly-Pred®	salmon calcitonin	Fortical®
quinupristin and dalfopristin	Synercid®	teicoplanin	Targocid®	teriparatide	Forteo™, Forsteo™
vancomycin	Vancocin®				
Proteins					
abatacept	Orencia®	aldesleukin	Proleukin®	alefacept	Amevive®
agalsidase beta	Fabrazyme®	alfa-1-proteinase inhibitor	Aralast™, Prolastin®, Zemaira™	alglucerase	Ceredase®
alglucosidase alfa	Myozyme®	alteplase	Activase®	anakinra	Kineret®
anistreplase	Eminase®	antihemophilic factor or factor VIII	Bioclate™, Helixate® FS, Kogenate® FS, Recombinate™, ReFacto®, Xyntha™	antithrombin III	Thrombate III®
antithymocyte globulin	Thymoglobulin®	aprotinin	Trasylol®	asparaginase	Elspar®
becaplermin	Regranex®	botulinum toxin type A	Azzalure®, Botox®, Dysport™, Vistabel®	botulinum toxin type B	Myobloc®
choriogonadotropin alfa	Ovidrel®, Ovitrelle®	chorionic gonadotrophin	Choragon®, Pregnyl®, Profasi®	coagulation factor IX	BeneFIX®
coagulation Factor VIIa	NovoSeven®	collagenase	Santyl®	darbepoetin alfa	Aranesp®
denileukin diftitox	Ontak®	dibotermin alfa	InductOs®, InFuse®	dornase alfa	Pulmozyme®
drotrecogin alfa	Xigris®	epoetin alfa	Epogen®, Eprex®, Erypo®, Procrit®	eptotermin alfa, or bone morphogenic protein-7	Osigraft®, Osteogenic protein-1™
etanercept	Enbrel®	filgrastim	Neupogen®	follitropin alfa	Gonal-F®
follitropin beta	Follistim™, Puregon®	galsufase	Naglazyme™	glucagon	GlucaGen®
human albumin	Albumarc®, Albuminar®, AlbuRx™, Albutein®, Buminate®, Flexbumin®, Plasbumin®	human insulin	Exubera®, Velosulin®	hyaluronidase	Amphadase™, Hylenex®, Hydase™, Vitrase®
idursulfase	Elaprase™	imiglucerase	Cerezyme®	immunoglobulins	Gammagard®, Octagam®
insulin	Humulin®, Novolin®	insulin aspart	NovoLog®, NovoRapaid®	insulin detemir	Levemir®
insulin glargine	Lantus®	insulin glulisine	Apidra®	insulin lispro	Humalog®
insulin zinc extended	Novolin Lente®, Novolin Ultralente™	interferon alfa-2a	Roferon A®	interferon alfa-2b	IntronA®
interferon alfa-n3	AlferonN Injection®	interferon alfacon-1	Infergen®	interferon beta-1a	Avonex®, Rebif®
interferon beta-1b	Betaseron®	interferon gamma-1b	Actimmune®	isophane insulin NPH	Humulin N®
lactase	Lactaid®	laronidase	Aldurazyme®	lutropin alfa	Luveris®
mecasermin	Increlex®	mecasermin rinfabate	Iplex®	menotropins	Menogon®, Menopur®, Repronex®
methoxy poly-ethylene glycol-epoetin beta	Micera®	oprelvekin	Neumega®	palifermin	Kepivance®

TABLE 3 (*Continued*)

INNs	Brand-names	INNs	Brand-names	INNs	Brand-names
pancreatic enzymes (lipase, amylase, protease)	Arco-Lase®, Cotazym®, Creon®, Donnazyme®, Pancrease®, Viokase®, Zymase®	papain	Accuzyme®, Panafil®	parathyroid hormone	Preos®, Preotact™
pegademase	Adagen®	pegaspargase or PEG-L-asparaginase	Oncaspar®	egfilgrastim	Neulasta®
peginterferon alfa-2a	Pegasys®	peginterferon alfa-2b	PegIntron®	pegvisomant	Somavert®
protein C concentrate	Ceprotin®	rasburicase	Elitek®, Fasturtek®	repository corticotropin	Acthar® Gel
reteplase	Retavase®	rilonacept	Arcalyst®	romiplostim	Nplate™
sacrosidase	Sucraid®	sargramostim	Leukine®	somatropin, somatotropin, growth hormone	Accretropin™, Genotropin®, Humatrope®, Norditropin®, Nutropin®, Omnitrope®, Protropin®, Saizen®, Serostim®, Tev-Tropin®, Valtropin®, Zomacton®, Zorbtive®
streptokinase	Streptase®	tenecteplase	TNKase™	thyrotropin alfa	Thyrogen®
trypsin	Granulex®	tuberculin purified protein derivative (PPD)	Aplisol®, Aplitest®, Tuberculin PPD tine test®, Tubersol®	urofollitropin	Bravelle®, Fertinex™, Metrodin®
urokinase	Abbokinase®, Kinlytic™				
Antibodies					
abciximab	ReoPro®	adalimumab	Humira®	alemtuzumab	Campath®, Mabcampath™
apcitide Tc-99m	AcuTect™	arcitumomab Tc-99m	CEA-scan®	basiliximab	Simulect®
bevacizumab	Avastin®	canakinumab	Ilaris®	capromab pendetide In-111	ProtaScint®
catumaxomab	Removab®	certolizumab pegol	Cimzia®	cetuximab	Erbitux®
crotalidae polyvalent immune Fab	CroFab®	daclizumab	Zenapax®	digoxin immune serum Fab	Digifab™, Digibind™
eculizumab	Soliris™	efalizumab	Raptiva®	fanolesomab Tc-99m	NeutroSpec®
gemtuzumab Ozogamicin	Mylotarg®	golimumab	Simponi®	ibritumomab tiuxetan	Zevalin®
imciromab pentetate In-111	Myoscint®	infliximab	Remicade®	muromonab-CD3	Orthoclone OKT3®
natalizumab	Tysabri®	nofetumomab merpentan Tc-99m	Verluma®	ofatumumab	Arzerra®
omalizumab	Xolair®	palivizumab	Synagis®	panitumumab	Vectibix®
ranibizumab	Lucentis™	rituximab	Mabthera®, Rituxan®	satumomab pendetide In-111	OncoScint®
sulesomab Tc-99m	LeukoScan®	tocilizumab	Actemra®	tositumomab, ^{131}I-tositumomab	Bexxar®, Bexxar I-131®
trastuzumab	Herceptin®	ustekinumab	Stelara®	zanolimumab	HuMax-CD4®

Abbreviation: INNs, international nonproprietary names.

growth problem, haemostasis, immunity disease, impotence, incontinence, infective diseases (bacterial, fungal and viral), inflammation, obesity, oncology (cancer and tumour imaging), osteoporosis (calcium metabolism dysfunction), pain, vaccines and so on [34,41], which represent important markets. In this context, the CNS is certainly a paradox: it is a major therapeutic area with unmet medical needs, for which the therapeutic peptide market potential is immense. To achieve therapeutic efficacy, a potential CNS drug has to cross the BBB by one of two transcellular mechanisms: passive diffusion or active (catalyzed) transport. Passive diffusion comprises mechanisms such as transcellular lipophilic diffusion, which requires no energy. Carrier-mediated transport (CMT) and receptor-mediated transport or transcytosis (RMT) are active transport mechanisms, which require energy. Unfortunately, most small molecules and virtually all peptide and protein therapeutics are generally excluded from passive transport because of their high hydrophilicity and/or high molecular mass, even if some commercial synthetic therapeutic peptides (thyrotropin-releasing hormone, argipressin, luteinizing-hormone-releasing hormone and so on) have been demonstrated to cross the BBB by saturable transport mechanisms [42]. Peptides will probably be used intensively in the near future for various applications in the treatment of CNS diseases, notably in the design of peptide regulators of protein activity, if they are able

to cross the BBB. Peptide-based vectors (cationic or cationized peptides or proteins, which cross the BBB by adsorptive-mediated transport [43,44], and CMT- or RMT-based peptides [45–49]) developed for CNS drug targeting will certainly contribute to the development of peptide-based prodrugs with facilitated access to the CNS.

In 2004, more than 20% of drugs belonging to the top 200 sales were based on peptides, proteins or antibodies, with sales reaching US$ 40 billion and, hence, approximately 10% of the overall figure for the pharmaceutical industry [50]. According to the review of Leader *et al.* [40], which gives an interesting new functional classification of protein therapeutics, we provide herein in Table 3 a list of peptide derivatives or homologous compounds (proteins or antibodies) used for therapeutic applications, medical diagnostics or imaging, produced by other means (recombinant DNA and so on) than chemical synthesis, and having reached the American, European and/or Japanese pharmaceutical markets (some of them are generics or discontinued) (http://www.biam2.org/, http://www.documed.ch, http://www.fda.gov/, http://www.fdaapproveddrugs.us, http://www.rxlist.com and http://www.vidal.fr) [51]. As described here, more than 200 peptide drugs and homologous compounds (proteins or antibodies) containing peptide bonds are marketed now (or have been marketed) in the same pharmaceutical markets.

Concluding remarks

As stated by Loffet [34], peptides (or proteins) still suffer from a deficit in image because they (generally) have to be injected, but erythropoietin and insulin are blockbusters even though they cannot be taken orally. We are convinced that chronic treatment with new formulations or routes of administration will give a new impetus to the therapeutic peptide field [52]. The majority of marketed peptide products and homologous compounds (proteins and antibodies) are peptide hormones or peptide derivatives that simulate the action of hormones. Peptides that are agonists or antagonists for receptors implicated in oncology and inflammation, peptides as antibiotics, or peptides that act as enzyme inhibitors in a variety of therapeutic indications are increasingly being tested for efficacy at the discovery and preclinical stages, suggesting that this class of drugs might soon occupy a larger niche in the marketplace. In France, the 2008 MEDEC prize of the year (recognizing the provision of innovative molecules by pharmaceutical companies for physicians and their patients) was awarded to a synthetic therapeutic peptide: the new antidiabetic drug Byetta® (exenatide, 39 amino acids) of Eli Lilly (http://www.gazettelabo.fr/2002breves/0608/medec.htm and http://www.lemedec.com/website-medec-web/prix-medec.do). Other therapeutic peptides, such as antimicrobial peptides, with broad-spectrum antimicrobial activity against bacteria, viruses and fungi, are promised a great future, especially in counteracting the loss of efficiency of conventional antibiotics [53–55].

The decreasing number of approved drugs produced by the pharmaceutical industry, accompanied by expanding expenses for R&D, demand alternative approaches to improve pharmaceutical R&D productivity. As discussed here, peptide-based drug discovery could be a serious option for addressing as yet unresolved problems. To date, hundreds of synthetic therapeutic peptides are in clinical development, and even more are in advanced stages of preclinical development in the pipeline of biotechnology and pharmaceutical companies. This augurs a promising future for the marketing of innovative synthetic therapeutic peptides in the coming years.

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