Review Paper

Current Advances in Therapeutic Peptides: Past and Future Trends

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Abstract

The treatment of peptides has played an important role in clinical practice since the discovery of insulin therapy in the 1920s. Over 60 peptide drugs are approved in the United States (US and other regional markets, and peptides continue to undergo drug discovery steadily. Peptide research and development has leveraged a wider range of structures known from other plant sources, via pharmacology and medicinal molecular biology, beyond its conventional focus on individual endogenous peptides. We build a comprehensive database of peptides that have met scientific studies with more than 150 constantly evolving peptides. Here we provide a simple overview of the peptide-based drug therapy environment, comprising evolutionary points of view, structural properties, operational thresholds, and explanation of the therapeutic area.

Keywords: Peptides; Clinical Practice; Drug Therapy; Therapeutic

1. Introduction

1.1 The invention of peptide therapy

Peptides constitute a special class of molecularly regulated, but biochemically and therapeutically distinct, pharmaceutical compounds. Peptides represent an opportunity for therapeutic intervention that closely imitates natural pathway as inherent signaling molecules for several physiological functions. In addition, many peptide medicines are simply "replacements" that add or substitute peptide hormones in cases of insufficient or lacking endogenous concentration. This can be demonstrated by the isolation and initial therapeutic use of insulin in diabetics in the 1920s who did not produce enough hormone [1]. Currying adrenocorticotrophic hormone (ACTH) in livestock pituitary glands to treat different endocrine conditions in patients was accompanied by insulating peptides from whole livestock tissue [2].

Peptides have evolved as therapeutics over time and continue to evolve as drug development and treatment

paradigms are evolving (Table 1). In the first half of the 20th century peptides, which were insulin-isolated and ACTH, gave life-saving medicines. In mid of 90s, synthetic oxytocin and vasopressin were also used in clinical terms, before sequence clarification and chemical syntheses of peptides became feasible. As the venom of arthropods and cephalopods have become recognized as a store of bioactive peptides, it has become a popular strategy for the isolation of natural produce from exotic sources. The genomic age allowed many important peptide hormones to be recognized and molecularly characterized by the receptors, and industry and academia started to pursue new peptide ligands for such receptors.

The enthusiasm for peptide therapy was later tempered by some native peptide limits, for example short plasma halving life and low oral bioavailability. Numerous peptidases and excretory mechanisms that inactivate or clear peptides clarify the short half-life of many peptide hormones. Such lability makes it possible for the body to modulate the hormone levels easily, but is nevertheless difficult for several clinical development projects. [These peptide limitations were described elsewhere in detail [3]. We will concentrate on peptide characteristics recommended for human clinical development]. Scientists have started using techniques of medicinal chemistry to make candidates more like medicines by improving half-life, physiological stability and the receptor selectiveness. The clinic also provided peptide analogs of native hormones with enhanced medicinal properties.

Oral bioavailability is another barrier to the production of peptide drugs: The enzymes designed to decompose amide bands of ingested proteins are effective at cleaving peptide hormones with the same interactions, and the high polarity and molecular weight of peptides severely restricts intestinal permeability. Since oral delivery is often regarded as desirable for the promotion of compliance with the patient, the need for injection decreases the appeal for evidence requiring ongoing, external care.In addition, the availability of a large combinatorial chemistry library and high percussion (HTS) technology has pendulum to small molecules aimed at peptide receptors in a new direction. The general challenge is to find a small molecule which mimics a peptide ligand's receptor binding and selective modulation; small molecules are more appropriate for oral delivery and easier to produce than peptides. In contemporary screening library, the number and variety of scaffolds support the idea that lead molecules could be detected, optimized and transformed into drugs. Structural biology applied an arrow to the carcass by delaminating main molecular interactions that could be exploited by any sort of molecule at receptor active locations.

In some cases the small molecular approach has been better than in others. Small molecules are less effective than peptides in peptide receptors and small molecules that function like antagonist can be detected more easily than agonists. For small molecular drug discovery, especially in class B GPCRs, the large ligand connecting site for some peptide GP CRS and special conforming changes needed for signal transduction are significant challenges [4-7]. Nevertheless, small molecules, including losartan and valsartan available orally, substituted peptide saralasine (SARENIN) as hypertension receptor blockers and other small molecules of the class A GPCRs for which no peptide drugs are marketed Class A GPCRs (Table 2)

Although resolving some problems in peptide medicines, the potential for liabilities associated with peptides, such as CYP inhibition leading to drug / drug interactions (DDI) and side effects arising from off target binding, remains unchanged. While a major new discovery, small molecule ligands for peptide receptors are no substitute for the peptide compounds. In recent times, the potential of peptide therapeutics has been further understood and nuanced.

Novel synthetic strategies allow pharmacokinetic properties and target specificities to be modulated through amino acid or backbone changes, non-natural amino acid incorporation and mixture to extend half-life or increase solubility; new formulation strategies reduce injection frequency, and improve stability and other physical properties. Consequently, the characteristics of peptides previously seen as liabilities are no more problematic: for example, for some indications, injection is considered an acceptable route of administration partly because of production of peps or depots which reduce the injection frequency. Although several classes of oral medications for type 2 diabetes mellitus are available, the market of injectable GLP-1 peptide agonists has continued to expand since the exenatide approval in 2005 and several next generation medicines candidates are currently in development [8,9]. Teriparatide, an osteoporosis approved parathyroid truncated hormone, provides an anabolic mechanism of action that is distinct from orals and supports routine injection by oral bisphosphonates [10].

Peptide drug applicants are also produced against a variety of molecular targets beyond the historically prevailing epithelial hormone receptors. The clinic contains peptides which disturb protein-protein interactions, target the tyrosine kinasis receiver and inhibit intracellular targets [11,12]. Phage screen has recognized new peptides as the point of departure for scientific and medicinal chemical study and introduced new peptide scraffolds to the clinic [13,14]. This resulted in the production of therapeutic peptides in a complex and robust environment.

To date, in the USA, Europe and Japan, more than 60 peptide products have been approved; more than 150 are under active clinical development. We will discuss the features, therapeutic uses and prospects of peptide product and clinical candidates here.

1.2 Therapeutic peptide innovations

This dataset contains data for 484 therapeutic peptides as of March 2017, of whom 68 have been licensed in the USA, Europe and/or Japan; 8 have since been withdrawn. The list of therapeutic peptides licensed is available in additional details. The successful clinical production of 155 peptides actually includes just under half of which are in phase 2 studies (Figure1). Around 1980 and 2010, the number of peptides that reach clinical production gradually increased with an overall five-year peak at more than 22 peptides annually in 2011 (Figure2). There has been a steady increase in the total number of approved peptides with 13 peptide approvals from beginning in 2010.

2. Therapeutic peptide physical features

It is no wonder that peptides have evolved over time as a result of clinical development. The developments reflect improvements in peptide chemistry and cleaning, enhanced molecular pharmacologic methods, evolving patterns in medicinal, and the advent of competing molecular forms like monoclonal antibodies.

2.1 The length of the therapeutic peptides

Nearly all peptides that entered clinical development in the 1980s had a length of less than ten amino acids. Due to improvements in peptide synthesis and manufacturing technology, the average peptide length increased in the following decades (Figure 3) [15-17]. There has also been a wider range of popular molecular targets, including GPCRs from class B, enabled by bigger peptide ligands. Application candidates are more equally distributed over the current decade in the different length ranges up to 40 amino acids, indicating perhaps that length is no longer a significant constraint for peptide drug development.

2.3 Peptide therapeutic chemical structure

We defined the ' chemical basis ' of peptide drugs in relation to endogenous peptide molecules: natural, analog and heterologous. Even if the first native peptides were isolated from mammalian tissue, the most common native peptides on the market are produced either synthetically or by recombinant expression. Many biomedical peptides were then described from non-mammalian natural sources including toxins and venom that function on compelling molecular targets. Researchers ' motivation for creating analogs defined as modified or substituted version of native peptides with improved drug properties was the limitations of endogenous peptides. For example, desmopressin is a vasopressin analog with longer half-life and enhanced specificity for the arginine vasopressin second receptor over other vasopressin group receptors; and octreotide compared to the native somatostatin hormone, which has enhanced plasma half-life and enhanced specificity for sst2 and sst5 binding affinities [18,19].

Heterologous peptides have been identified independently of natural peptides, such as by means of synthetic library sampling, phage show, or other methods [20]. Examples include the peptide portion of the thrombopoietin romiplostim (AMG531), which is identified by the phage test, and the LY2510924 [21], which was discovered by screening for better results. On the market and in progress, most peptide medicines are analogous that build on native hormones intrinsic activity with enhanced medicinal proprieties (Figure 4). The possibility of native peptids as a biological precedent de-risks the analog drug discovery program in relation to target validation. Conjugation to polyethylene glycol (PEG), lipids, and proteins such as the FC fragments was used as a semiproduct extension as a clinical development since the beginning of 2010 was conjugate products (Figure 5). The strategy was to begin clinical development in late 1990s with the first such peptides. Conjugation can also be applied to transmit a cytotoxic payload or imagery to different peptide cell types. (Table 4).   For the summary of various conjugation strategies used with candidates for the production of therapeutic peptides.

3. Molecular targets of therapeutic peptides

As described above, many endogenous peptides and their analogs were known as potential medicines, so peptide hormone receptors are suitable targets for peptide medicines. The main class of drugs targets for peptides are G-protein-Coupled Receptors (GPCRs). Although this dominance has declined over time, more than 40 percent of GPCRs have been targeted since 2010. (Figure 6). Common targets are also Non-GPCR cell surface receptors including natural peptide receptors and endogenous protein ligand cytokine receptors. The majority of the remaining targets are antimicrobials, ion channels and other extracellular goals (e.g. structure proteins, adherence molecules and secreted enzymes), and a small number of intracellular goals with cell penetration strategies are being followed.

Due to the success of a first-class peptil, a number of follow-up research programs exploring the same process have rapidly increased its popularity. Due to the success of a first-class peptil, a number of follow-up research programs exploring the same process have rapidly increased its popularity. The GnRH receptor was a ' soft ' target in the 1980's and 1990's, reflecting the potential of gnRH agonists and antagonists in the treatment of a number of important conditions controlled by reproductive hormones. GnRH targeting peptides for prostate carcinoma, endometriosis, assisted reproduction and other indications have been developed in a range of delivery formats. In 2000, efforts to develop were moved towards antagonists of GnRH small molecules.

Development of peptides in the late 1990s shifted direction when GLP-1 receptor agonists from exendin four

structures entered the clinic with type 2 diabetes and subsequently obesity [22]. The development of the gastrointestinal peptide receptor associated with appetite, insulin secretion and energy balance has been driven by metabolic disease as a global health concern [23]. We have 47 peptides, of which five are approved and 16 are in active clinical development as of March 2017, which are targets for GLP-1 receptors in the clinic.

Another movement is toward multi-pharmacy, in which a single element that simultaneously operates on many receptors or a molecule that includes many functional domains is used to tackle several molecular targets. The variants of Dopastin (BIM-23A760) were related to a little molecular dopamine agonist and were engineered for two contributors to the pathology [24] for neuroendocrine cancer. Many recently entered hybrid molecules are trying to target various fronts of metabolic illness. ' Twincreeins ' are individual peptides acting as an agonist of a GLP-1 receptor [25] and a glucagon or GIP receptor and other therapeutic candidate consisted of an agonist GLP-1 peptide bound covalently with a PCSK9 antibody [26,27].

4. Application of therapeutic peptides

Peptides have also been studied throughout the clinical continuum, representing a range of possible useful indications and perhaps in accordance with the deliberate optimism of several research programmes. It is not unusual that the fields of peptide production at the increased concentration (currently) are areas of considerable interest for the drugs industry: metabolic, oncological and cardiovascular conditions (Figure7). Therefore, the clinical landscape of approved peptide drugs does not reflect the production of peptides. Therefore, the clinical landsmark of authorized peptide therapies may not reflect the production of peptides. Some oncology findings have evolved for example, but few have received approval, which may just reflect low oncology rates of success overall.

4.1 Clinical growth plans and peptide benchmarks

Since early 2010 the period of peptide clinical development for peptides authorized has differed significantly (Figure8). This peptide cohort has a mean production time of 9,4 years, significantly longer than one cycle time standard (mean 8,2 years), which takes data from mostly mid-size medicinal firms across all molecular types [3,28]. Peptides with a smaller clinical innovation duration have been generally accepted in signs with valid regulatory precedents and clearly defined clinical study endpoints: secondary hyperparathyroidism (etelcalcetide), mellitus (dulaglutide and albiglutetide) type 2 diabetes, and multiple myeloma (carfilzomib). These peptides were usually launched by major drug manufacturers via medium to late clinical trials.

In addition, we measured the likelihood of peptide production against industry-wide expectations for new botanical entities (NBEs) and noval chemical entities (NCEs). This progress measure evaluates the probability that a product in a drug discovery process will be granted regulatory approval. NPAs consist mostly of minor molecules and artificial peptides, and include poultry, antimonopolies as well as other proteins, live biological materials and drugs. NBEs mainly consist of minor molecules and artificial peptides, comprising anti-corrosion and other proteins, live bio-products, and vaccines. (The methodologies employed in recent reports by the Biotechnology innovation Research Organisation (BIO) and CMR International differ somewhat in their peptide-specific regulatory performance measurement methodologies) [27].

The peptide performance rates have dropped in the CMR International between NBEs and NCEs. (Figure 9) This might reflect the increased targets and decreased risk of peptides compared to low, early clinical development attrition rates. By comparison, peptides, including highly focused selective monoclonal antibodies and prophylactic vaccines, may be less stable and less specific than protein biologics, resulting in a stronger

attrition rate compared with NBEs.

4.2 Peptide Therapy's towards Future directions

Peptides have formed a specific therapeutic role from humble beginnings, as substances extracted from animal glands, and will remain a significant aspect in the therapeutic sector. Through expanding into new applications and therapeutic goals, using new chemical approaches to increase molecular diversity and by technologically improved medicinal properties, peptide based pharmaceuticals has kept pace with innovation and progress. We expect that work will continue to view new opportunities for peptides. Peptides are a convenient baseline for discovering drugs as the catalogue of peptide medicines used regularly in the medical practice is an endogenous ligand for peptide hormone towards targeted receptors. For the last 5 generations, first category peptides that target guanylyl cyclase C (GC-C) and melanocortin 1 receptor (MC1R) are approved by regulatory agencies: linaclotide and afamelanotide. All formulations of the native peptides are intimately related.

The future application of peptide-based drugs to new targets continues to be extended. Study. Throughout early phase, human trials or in pre-clinical models of infection a large number of peptide-added targets for which no medications have been authorised, which has shown as for the therapeutic values [29]. For instance, kisspetin trigger analogs that offer benefits to various therapeutic supports and the body weight of the patients with inherited obesity syndrome can be reduced if the agonist utilizes the melanocortin 4 receptor (MC4R) [30]. Pharmaceutical companies have submitted patent applications for endogenous peptides apelin [31,32], adrenomedullin [33] and neuromedin U [34,35] derivatives based on animal studies. The above two drug discovery projects were not examined peptide in humans, and only currently, supposed apeline version has undergone human trials [36]. Such approvals demonstrate that novel peptide therapies are still available. To control the properties of drug targeting, e.g. permeability and stability, hits are often optimized. For this purpose, an outline of the peptide chemical toolbox shows the different options. Cyclic peptides have received a special attention and modifications to achieve surface integration that bridge the gap with conventional pharmacology. Sequence motives and scaffolds, which can be used in cells, known as cell invading peptides, are especially of interest. The corresponding description, unlike most literature in this field Brock gives a realistic picture of what is expected. In addition, targeting cells, tissues, bacteria (e.g. Teixobactin) or tumors provides an additional route for groundbreaking peptide-based medicines.

Refinements in peptide analyzing and computational engineering will continue supporting drug development. Screening toxins and other plant products of natural ingredients metabolomically, proteomically and genomically could recognize bioactive Peptides that include specific structure characteristics produced by unusual post-translation synthesis [37-40]. Improved understanding of the molecular basis for human genetic disorders will produce novel possible therapy leads, and de-orphanizing poorly defined peptide targets will promote research programs for new membrane-ligand pairing [41]. In addition, new methods to the development, production and development of peptide drugs will therefore expand the versatility of the unique class of molecules. Initiatives will be under way to boost the oral disponibility of peptide clinical applications via increased drug stabilization in the gastrointestinal tract and peptide-formulation by enhancing the absorption of the central nervous system through combining them with transporter molecules or nanotubes. We will refer you to other chapters in this topic for further information on developments in peptide chemistry and conjugation. Another elegant solution to peptides is the integration of diagnostic imaging with immediate therapy steps. Following a summary of the improvements with reference to insulin-like peptides, papers exemplifying the use of vaccines for cancer immunotherapy, as antibiotics, for the treatment of CNS-like diseases [42,43], for the control

of gastrointestinal-disorders, and for the therapy)of obesity and diabetes clearly show the effect of peptides throughout disease areas [44-46] (Table 5). The final sequence of mini-examinations complements this set well by providing insights into halves of life extension, formula considerations and changes necessary to produce the new peptide generation

5. Conclusion

Finally, the scope of this particular class of molecules will be strengthened by modern peptide therapeutics, design, and half-life enhancement strategies. Initiatives have been undertaken to increase the oral availability of peptide therapeutics by growing the stabilization of drugs in the intestinal system and by implementing peptides with permeability enhancers and enhancing the availability of peptides in the CNS by conjugating or delivering peptides through nanoparticles via carrier molecules.

Author Contributions

The manuscript was written in detail and sectioned for specialized discussion with the respective authors in the field of research.　　Drafting the Review manuscript (Therapeutic peptides: Past perspectives, current development pattern, and future trends), Visualization, Conceptualization – R.C., DHO; Data collection, Data analysis and interpretation –RC., EBD, FE., SJY.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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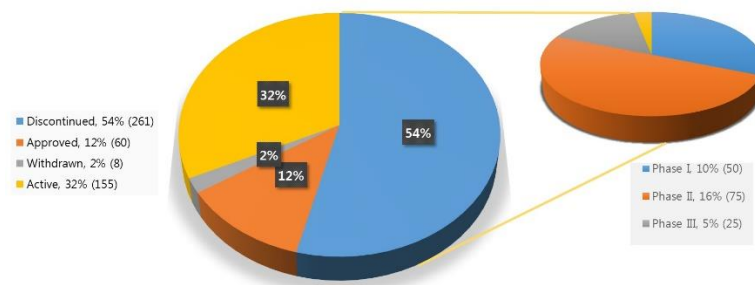
Figures:

Figure 1. Present status of therapeutic peptides production. "Withdrawn" refers to goods already licensed that are not on the market anymore; "Discontinued" refers to services terminated before acceptancel, and the "Active" The category includes all active drug development peptides.
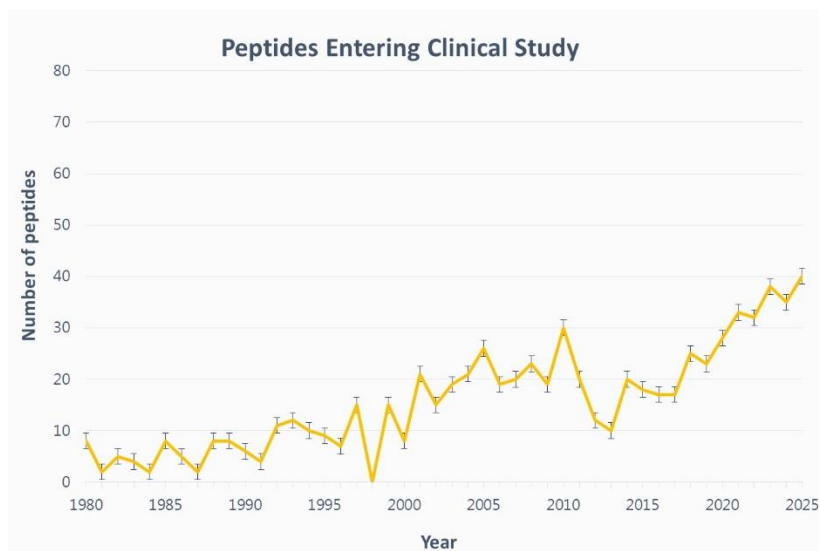

Figure 2. Cumulative number of approved peptides and number of entry into the clinical development of the major pharmaceutical markets.
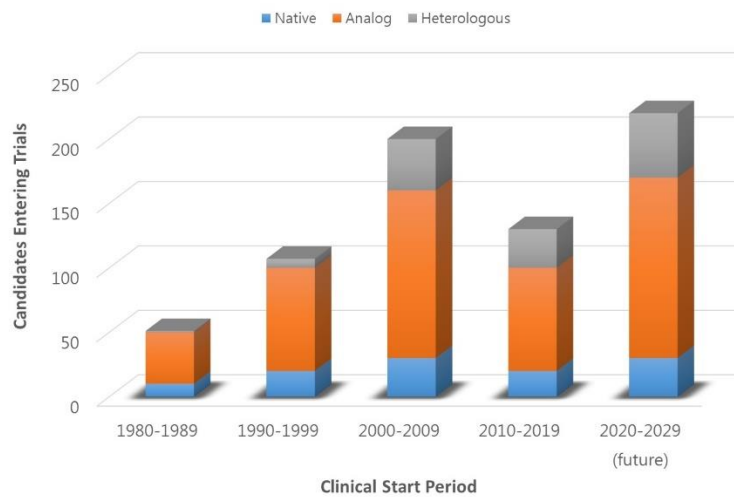
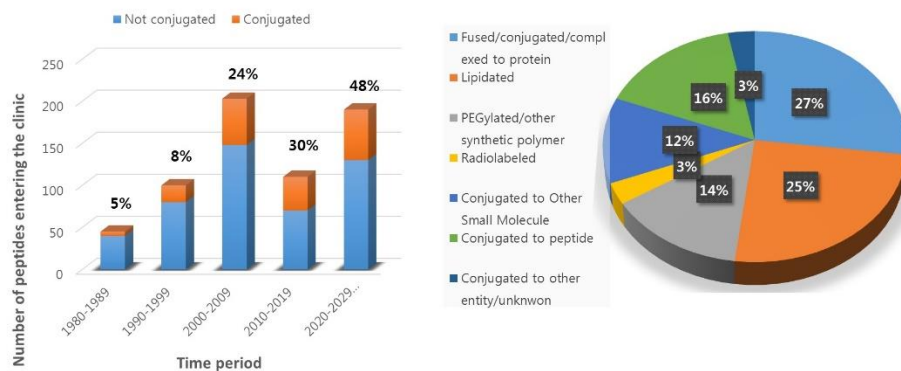Figure 3. Duration per ten years of peptides entering clinical growth.

Figure 5. Number and proportion of peptides that reach clinical production (left) and distribution in the peptide pool of all conjugated moieties (right).
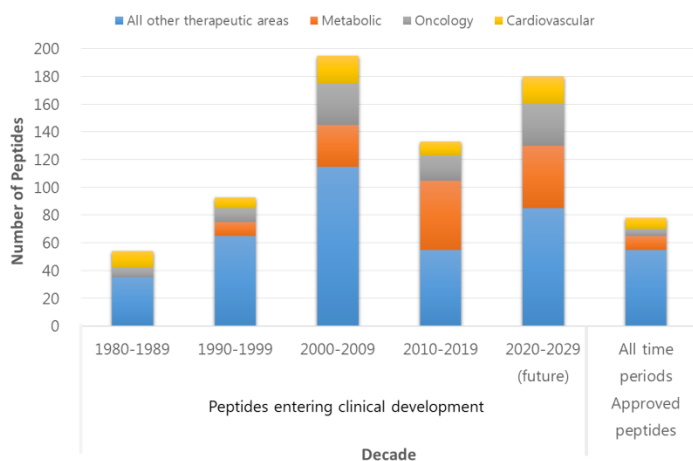
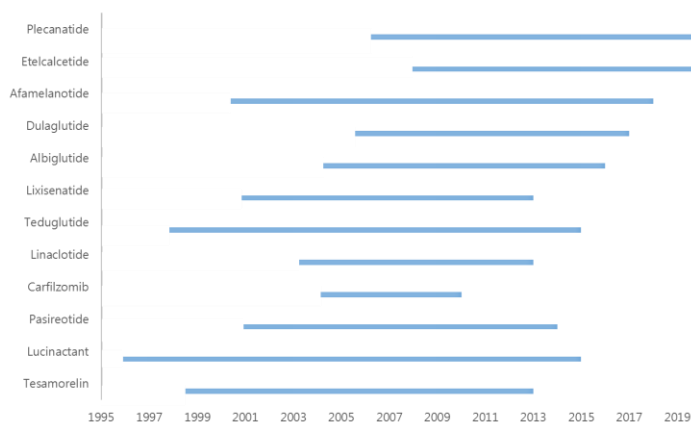Figure 4. Peptide chemistry that enters clinical development.

Figure 6. Peptide molecular targets reach clinical practice.

Figure 7. Key peptide clinical area, relative to the primary therapy zone for approving peptides over all periods, by time of clinical initiation (including pre-1980).

Figure 8. Clinical treatment period for peptides approved since 2010. The left side of each bar represents the first clinical trial is initiated; the right side of each bar represents first approval of peptide in an important market.

Figure 8. Probability of effectiveness in different phases of clinical development for agent. NBE: new biological entity; NCE: new chemical entity; "Regulatory" refers to Favorable rating by regulatory authorities of the marketing applications (i.e. FDA, EMA).

Tables:

Table 1. Early peptides ' origins or chemical structure.

Peptide	Source	Introduction to the clinic	Sequence description	Reference
Insulin	Isolated from canine and bovine pancreata	1920s	Native	
Vasopressin	Synthetic	1962	Native	
Calcitonin	Isolated from salmon ulti-mobranchial gland	1971	Native	
Oxytocin	Synthetic	1962	Native	[3]
Adrenocorticotropic hormone (ACTH)	Isolated from bovine and porcine pituitary glands	1950s	Native	
Leuprorelin	Synthetic analog of gonadorelin	1984	Nonapeptide analog of decapaptide gonaddorelin	
Octreotide	Synthetic analog of somato-statin	1988	Cyclic octapeptide analog of somatostatin-14	

Table **2.** Small molecule drugs that act on peptide receptors. [4-6]

Drug or drug class	Primary molecular targets	Action at receptor	Liabilities of small molecules	Current status
Bosentan and others	Endothelin receptors	Antagonism	Hepatotoxicity;DDIs	Marketed; no peptides are approved in major markets
Tolvaptan and other vaptans	Vasopressin V2 receptor	Antagonism	Hepatotoxicity	Marketed; no peptides are approved in major markets
Small-molecule opioids (natural, synthetic, and semi-synthetic)	Opioid receptors	Agonism	Multiple effects caused by lack of receptor subtype specificity	Marketed; no peptides are approved in major markets
Losartan and other sartans	Angiotensin II receptor 1	Antagonism	DDIs; fetal toxicity	Marketed; displaced the peptide angiotensin receptor blocker saralasin
Elagolix and others	Gonadotrophin-releasing hormone receptors	Antagonism	DDIs (sufugoix)	Small molecules have entered Phase 3; multiple peptides are currently marketed
Aprepitant and others	Neurokinin 1 receptor	Antagonism	DDIs	Marketed; no peptides are approved in major markets

Table 3. Key inclusion and exclusion criteria for the peptide therapeutics database.[3,47]

Criteria	Example of an included peptide	Example of an excluded peptide
Epitope-specific peptide vaccines are excluded	glatiramer (COPAXONE)	rindopep-imut
Peptides exclusively derived from non-recombinant bacterial fermentation are excluded; semi-synthetic peptides are included	voclosporin	daptomycin (CUBICIN)
Peptides conjugated to other molecules are included, s long as the drug candidate contains a discrete, functional peptidic domain that otherwise meets the inclusion criteria	dulaglutide (TRULICITY)	trebananib
Diagonostics are excluded, but peptides developed as both therapeutics and dianostics are included	lutetium DO-TATATE	annexin V-128
Lower length limit: two amino acids linked by an amide bond	carfilzomib (KYPROLIS)	bortexomib (VELCADE)
Upper length limit: recombinantly-expressed peptides less than 50 amino acids in length, or synthetic peptides of any length	lixisenatide (LYXUMIA)	insulin (all products)
Each molecular entity was included only once in the database	exenatide (BYETTA)	ex-enatide(BYDUREON)

Table 4. Peptide conjugates examples .

Peptide name	Rationale for conjugation	Conjugated moiety	Current Status
Liraglutide	Half-life extension	hexadecanoic acid	Approved
Peginesatide	Half-life extension	PEG	Approved, then withdrawn
Romiplostim	Half-life extension	Fc immunoglobulin	Approved
Zoptarelin doxorubicin	Cytotoxic agent (peptide-drug conjugate)	doxorubicin	Phase 3
Lutetium-DOTA-TATE	Radiopharmaceutical	lutetium-DOTA	Phase 3
NA-1	cell-penetrating peptide	HIV-TAT peptide	Phase 3

Table 5. Inhibitors of peptidase summary: modified from Bernkop-Schnurch et al.2007 [46]

Type of enzyme inhibitors	Inhibitor name	Availability of pharmacopeial monographs	Current Status
Not based on amino acids	Camostat mesilate, DFP, PMSF, APMSF, AEBSF, phenyl 1,2,3,4,-tetrahydro-1-naphthoate methanesulfonate), FK-448 (4-(4-isopropylpiperadinocarbonyl)		Camostat mesilate but as a drug
Amino acids and modified amino acids	N-acetylcysteine, Amino acids having hydrophobic side chains such as L-phenylalanine, boro-leucine, boro-valine, and boro-alanine		N-acetylcysteine, but as a drug
Peptides and modified peptides	Bacitracin, phosphinate inhibitor VI, Pepstatin, benzyloxycarbonyl-Pro-Phe-CHO, antipain, leupeptin, chymostatin, and elastatinal, phosphoramidon, bestatin, puromycin, and amastatin		Bacitracin, but as a drug
Polypeptides	Aprotinin, Bowman-Birk inhibitor, Kunitz trypsin inhibitor, chicken egg white trypsin inhibitor, Soy bean trypsin inhibitor	Oramed Entera Bio	Aprotinin but as a drug
Complexing agents	EDTA, EGTA, 1,10-phenanthroline, hydroxychinolin	Oramed	EDTA, as excipient and food additive
Multifunctional polymers	Poly(acrylates), polycarbophil-cysteine, carbopol (974P)-cysteine, carboxymethylcellulose–BBI, and carboxymethylcellulose–elastatinal, PCP–tetramethylenediamine–chymostatin, PCP–poly(ethylene glycol))–chymostatin conjugate, PCP–tetramethylenediamine–antipain, and PCP–tetramethylenediamine–elastatinal, chitosan–BBI	Thiomatrix	Not for modified polymers

	and chitosan–elastatina, chitosan–pepstatin, chitosan–aprotinin		
Local pH modulator	Citric acid	Enteris Pharma Tarsa	Yes, as excipient and food additive
Essential trace elements	Copper, Zinc	Cyprumed	Yes, as excipient and food additive