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Therapeutic peptides: Historical perspectives, current development trends, and future directions

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ABSTRACT

Peptide therapeutics have played a notable role in medical practice since the advent of insulin therapy in the 1920s. Over 60 peptide drugs are approved in the United States and other major markets, and peptides continue to enter clinical development at a steady pace. Peptide drug discovery has diversified beyond its traditional focus on endogenous human peptides to include a broader range of structures identified from other natural sources or through medicinal chemistry efforts. We maintain a comprehensive dataset on peptides that have entered human clinical studies that includes over 150 peptides in active development today. Here we provide an overview of the peptide therapeutic landscape, including historical perspectives, molecular characteristics, regulatory benchmarks, and a therapeutic area breakdown.

1. Introduction: The evolution of peptide therapeutics

Peptides represent a unique class of pharmaceutical compounds, molecularly poised between small molecules and proteins, yet biochemically and therapeutically distinct from both. As intrinsic signaling molecules for many physiological functions, peptides present an opportunity for therapeutic intervention that closely mimics natural pathways. Indeed, several peptide drugs are essentially "replacement therapies" that add back or supplement peptide hormones in cases where endogenous levels are inadequate or absent. This is exemplified by the isolation and first therapeutic use of insulin in the 1920s in diabetics who did not produce sufficient quantities of the hormone.[1] The practice of isolating peptides from whole animal tissue continued with the purification of adrenocorticotrophic hormone (ACTH) from livestock pituitary glands to treat a variety of endocrine disorders in patients.[2]

The utilization of peptides as therapeutics has evolved over time and continues to evolve with changes in drug development and treatment paradigms (Table 1). Peptides isolated from natural sources, such as insulin and ACTH, provided life-saving medicines in the first half of the 20th century. When sequence elucidation and chemical synthesis of peptides became feasible in the 1950s, synthetic oxytocin and vasopressin also entered clinical use. As venoms of arthropods and cephalopods became recognized as treasure troves of bioactive peptides, isolation of natural products from exotic sources became a popular strategy for identifying new potential therapeutics. The genomic era allowed for the identification and molecular characterization of receptors for many important endogenous peptide hormones, and industry and academia began to pursue novel peptidic ligands for these receptors.

Enthusiasm for peptide therapeutics was subsequently tempered by certain limitations of native peptides, such as short plasma half-life and negligible oral bioavailability. The short half-life of many peptide hormones is explained by the presence of numerous peptidases and excretory mechanisms that inactivate and clear peptides. This lability allows the body to rapidly modulate hormone levels to maintain homeostasis but is nonetheless inconvenient for many therapeutic development projects. (These limitations of peptides have been described in detail elsewhere.[3] We will focus on the characteristics of peptides that have been nominated for human clinical development.) Investigators began to use medicinal chemistry techniques to make candidates more drug-like by improving half-life, stability under physiological conditions, and receptor selectivity. Peptide analogs of native hormones with improved pharmaceutical properties thus entered the clinic.

Another obstacle for peptidic drug development is oral bioavailability: digestive enzymes designed to break down amide bonds of ingested proteins are effective at cleaving the same bonds in peptide hormones, and the high polarity and molecular weight of peptides severely limits intestinal permeability. As oral delivery is often viewed as attractive for supporting patient compliance, the need for injection made peptides a less appealing option for indications that required chronic, outpatient therapy.

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Table 1
Source or chemical nature of early peptides.

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

Furthermore, the availability of massive combinatorial chemistry libraries and high-throughput screening (HTS) technologies swung the pendulum in a new direction, towards small molecules that target peptide receptors. Small molecules are generally more suitable for oral delivery and easier to manufacture than peptides; the challenge lies in finding a small molecule that mimics a peptide ligand's receptor binding and selective modulation. The number and diversity of scaffolds present in modern screening libraries supported the idea that lead molecules could be identified, optimized, and developed into drugs. Structural biology added another arrow to the quiver by elucidating key molecular interactions at receptor active sites that could be leveraged by any class of molecule.

The small molecule approach has been more successful in some cases than others. At peptidic receptors, small molecules are often less potent than peptides, and small molecules that act as antagonists are easier to identify than agonists. The large ligand-binding site of some peptidic GPCRs and specific conformational change required for signal transduction provide significant challenges for small molecule drug discovery, particularly for Class B GPCRs.[4–6] Nonetheless, orally available small molecules such as losartan and valsartan replaced the peptide saralasin (SARENIN) as angiotensin II receptor blockers for hypertension, and other small molecule drugs target Class A GPCRs for which no peptide drugs are marketed (Table 2).

While overcoming some of the challenges of peptide drugs, these small molecules retain the potential for liabilities that are infrequently associated with peptides, such as CYP inhibition leading to drug-drug interactions (DDIs) and side effects caused by off-target binding. Although a significant and important avenue of new discovery, small molecule ligands for peptidic receptors are not a complete substitute for peptide compounds.

More recently, a broader and more nuanced appreciation of the potential of peptide therapeutics has emerged. Novel synthetic strategies allow for the modulation of pharmacokinetic properties and target specificity through amino acid or backbone modification, incorporation of non-natural amino acids, and conjugation of moieties that extend half-life or improve solubility; novel formulation strategies reduce injection frequency and improve stability and other physical properties. As a result, characteristics of peptides previously viewed as liabilities are no longer as problematic: for example, injection is viewed as an acceptable route of administration for certain indications, partly due to the development of longer-acting peptides or depot formulations that reduce injection frequency. Despite the availability of multiple classes of oral medications for type 2 diabetes mellitus, the injectable GLP-1 peptide agonist market has continued to grow since the 2005 approval of exenatide, and multiple next-generation drug candidates are in development today.[9] Teriparatide, a truncated parathyroid hormone prescribed for osteoporosis, provides an anabolic mechanism of action that is distinct from oral bisphosphonates, justifying the use of a daily injectable.[10]

In addition, peptide drug candidates are being generated against a range of molecular targets that reaches beyond historically-dominant extracellular hormone receptors. Peptides that disrupt protein-protein interactions,[11,12] target receptor tyrosine kinases,[13] and inhibit intracellular targets[14] have entered the clinic. Phage display has identified new peptides as the launching point for discovery and medicinal chemistry efforts, and novel peptide scaffolds have brought new families of peptide leads into the clinic. This has subsequently culminated in a diverse and robust development landscape for therapeutic peptides.

To date, over 60 peptide drugs have been approved in the United States, Europe, and Japan; over 150 are in active clinical development, and an additional 260 have been tested in human clinical trials. Here we review the characteristics of peptide drugs and clinical candidates, therapeutic applications, and prospects for the future.

Table 2
Small molecule drugs that act on peptide receptors.[a]

Drug or drug class	Primary molecular target (s)	Action at receptor	Liabilities of small molecules[b]	Current status
Losartan and other sartans	Angiotensin II receptor 1	Antagonism	DDIs; fetal toxicity	Marketed; displaced the peptide angiotensin-receptor blocker saralasin[c]
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
Tolvaptan and other vaptans	Vasopressin V2 receptor	Antagonism	Hepatotoxicity	Marketed; no peptides are approved
Bosentan and others	Endothelin receptors	Antagonism	Hepatotoxicity; DDIs	Marketed; no peptides are approved
Aprepitant and others	Neurokinin 1 receptor	Antagonism	DDIs	Marketed; no peptides are approved
Elagolix and others	Gonadotrophin-releasing hormone receptors	Antagonism	DDIs (sufugolix)	Small molecules have entered Phase 3; multiple peptides are currently marketed

[a] Information for classes of agents with marketed drugs is derived from United States Food and Drug Administration (FDA) labels.[7]
[b] Not all agents within a given drug class display all of the liabilities outlined in the chart.
[c] In addition, saralasin acts as a partial agonist at the angiotensin II type 1 receptor and thus does not reduce blood pressure in patients with low levels of plasma angiotensin II.[8]

Table 3
Key inclusion and exclusion criteria for the peptide therapeutics database.

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

[a] Peptides developed by multiple sponsors or in multiple formulations were included once, with dates and other fields reflecting the earliest program.
[b] Only the peptidic portion of a conjugate molecule needs to meet the length limit for inclusion.

2. The therapeutic peptides dataset

We have compiled a comprehensive set of data related to all peptides that have entered human clinical studies, subject to certain dataset inclusion criteria (Table 3 and Supplementary Information). This database includes information on chemical structures, molecular pharmacology, therapeutic indications, clinical trial initiation dates, and global regulatory status. Reports derived from an earlier version of this dataset have been published through the Peptide Therapeutics Foundation and elsewhere;[15,16] in the intervening years, we have continued to maintain and curate a proprietary version of the data at Ferring Research Institute. The analysis presented in this article only includes peptides with development activity geared toward regulatory approval in major pharmaceutical markets (the United States, Europe, and Japan) as of March 2017.

2.1. Development status of therapeutic peptides

As of March 2017, this dataset contains information on 484 therapeutic peptides. Of these, 68 have been approved in the United States, Europe, and/or Japan; eight peptides have subsequently been withdrawn. The list of approved therapeutic peptides is available in the Supplementary Information. 155 peptides are in active clinical development, just under half of which are currently in Phase 2 studies (Fig. 1).

The number of peptides entering clinical development gradually trended upward between 1980 and 2010, with the five-year trailing average peaking at over 22 peptides per year in 2011 (Fig. 2). The cumulative number of approved peptides has gradually increased as well, with 13 peptide approvals occurring from the start of 2010 through this writing.

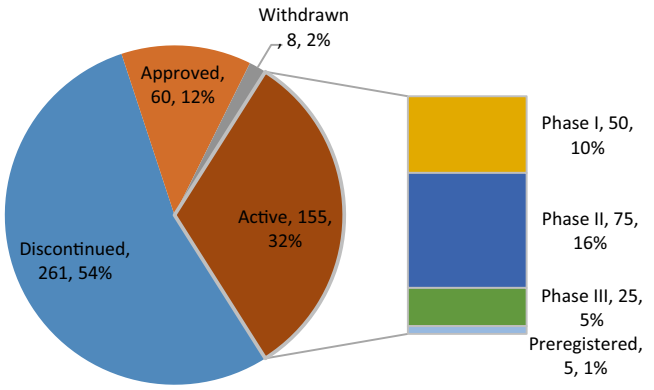

Fig. 1. Current development status of therapeutic peptides. Numbers refer to the number and percentage of all peptides in the given category. "Withdrawn" refers to previously approved products no longer on the market; "Discontinued" refers to programs terminated prior to approval, and the "Active" category encompasses all peptides in active clinical development.

2.2. Physical characteristics of therapeutic peptides

Not surprisingly, the characteristics of peptides entering clinical development have evolved over time. These changes reflect advances in peptide chemistry and purification, improved tools for molecular pharmacology, shifting healthcare trends, and the emergence of competing molecular types such as monoclonal antibodies.

2.2.1. Peptide length

In the 1980s, nearly all peptides entering clinical development were fewer than 10 amino acids long. Average peptide length has increased in each subsequent decade (Fig. 3), largely due to improvements in peptide synthesis and manufacturing technology.[17–19] A broadened range of popular molecular targets, including B class GPCRs, that are activated by larger peptide ligands has also played a role. In the current decade, development candidates are more equally distributed in the various length ranges up to 40 amino acids, suggesting perhaps that length is no longer a serious limitation for peptide drug development.

2.2.2. Chemical basis of peptide therapeutics

We characterized the "chemical basis" of peptide drugs with respect to their relationship to endogenous peptide molecules: **native**, **analog**, and **heterologous**. A **native** peptide has the same sequence as a peptide natural product. Although the first native peptides were isolated from mammalian tissues, most native peptides currently on the market are produced synthetically or through recombinant expression. Many biologically active peptides, including venoms and toxins acting on intriguing molecular targets, have subsequently been identified from non-mammalian natural sources (Supplementary Material).

The limitations of endogenous peptides provided motivation for researchers to create **analogs**, which are defined here as modified or substituted versions of native peptides with improved drug properties. For example, desmopressin is an analog of vasopressin, with longer half-life and improved selectivity for the arginine vasopressin receptor 2 over other vasopressin family receptors; and octreotide, compared with the native hormone somatostatin, which has an increased plasma half-life and increased selectivity for sst_2 and sst_5 receptor subtypes.[20,21]

Heterologous peptides were discovered independently of the natural peptide, such as through synthetic library screening, phage

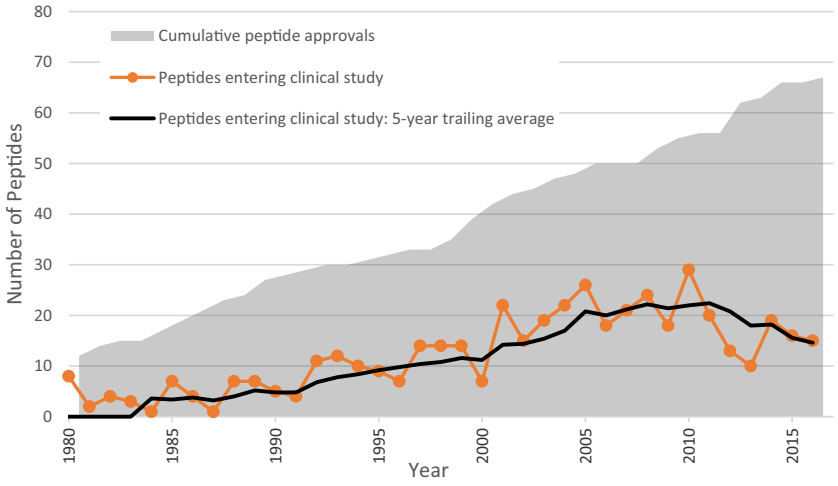

Fig. 2. Cumulative number of peptides approved in major pharmaceutical markets and the number of peptides entering clinical development. Entry into clinical development is defined as the year of the first Phase 1 or pilot human study.

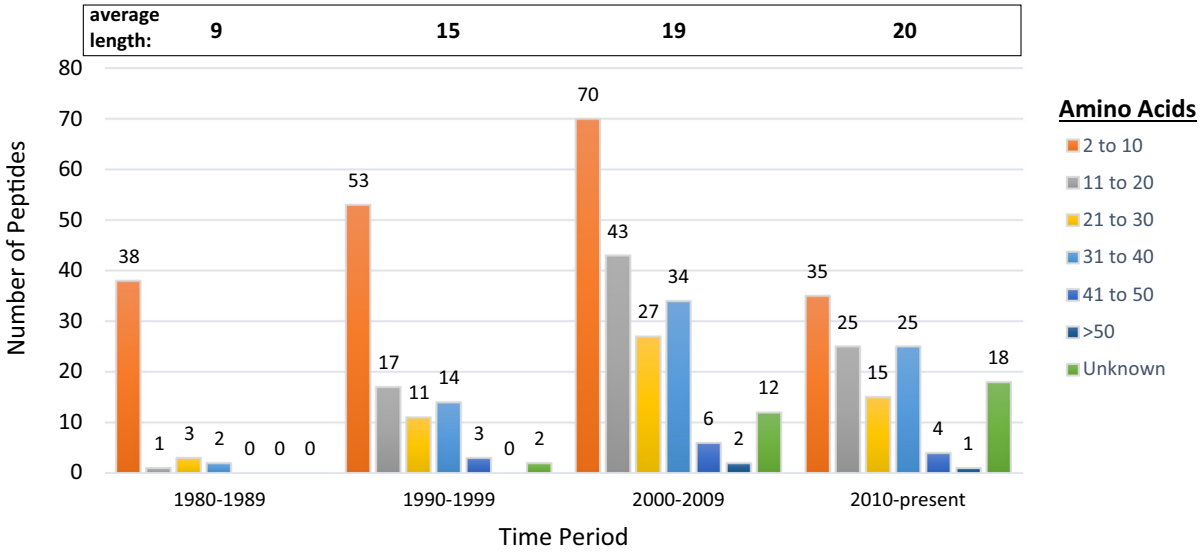

Fig. 3. Length of peptides entering clinical development, by decade. Peptides with unknown length were not included in the average length calculation.

display, or other methods. Examples include the peptidic portion of the thrombopoietin receptor agonist romiplostim (AMG531), which was discovered through phage display,[22] and the CXCR4 receptor antagonist LY-2510924, discovered via "medium-throughput" screening.[23]

The majority of peptide drugs on the market and in development are analogs that build on the intrinsic activity of native hormones with improved pharmaceutical properties (Fig. 4). An analog drug discovery program is de-risked with respect to target validation due to the availability of the native peptide as biological precedent. Methods for identifying heterologous peptide drug candidates expand target-space beyond receptors with native peptide or protein ligands, but the peptide leads may have insufficient potency or selectivity.

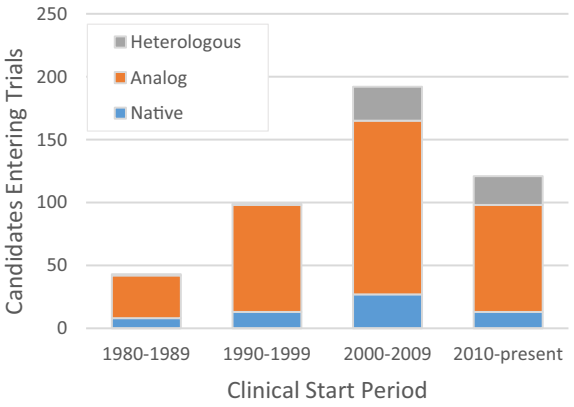

Fig. 4. Chemical basis of peptides entering clinical development.

2.2.3. The rise of peptide conjugates

Conjugation has emerged as a popular mechanism to alter or enhance the properties of peptide and protein drug candidates. The proportion of conjugated peptides and the variety of conjugated moieties has increased over time; 30% of peptides that entered clinical development since the start of 2010 are conjugates (Fig. 5). Conjugation to polyethylene glycol (PEG), lipids, and proteins such as Fc fragments has been used as a half-life extension

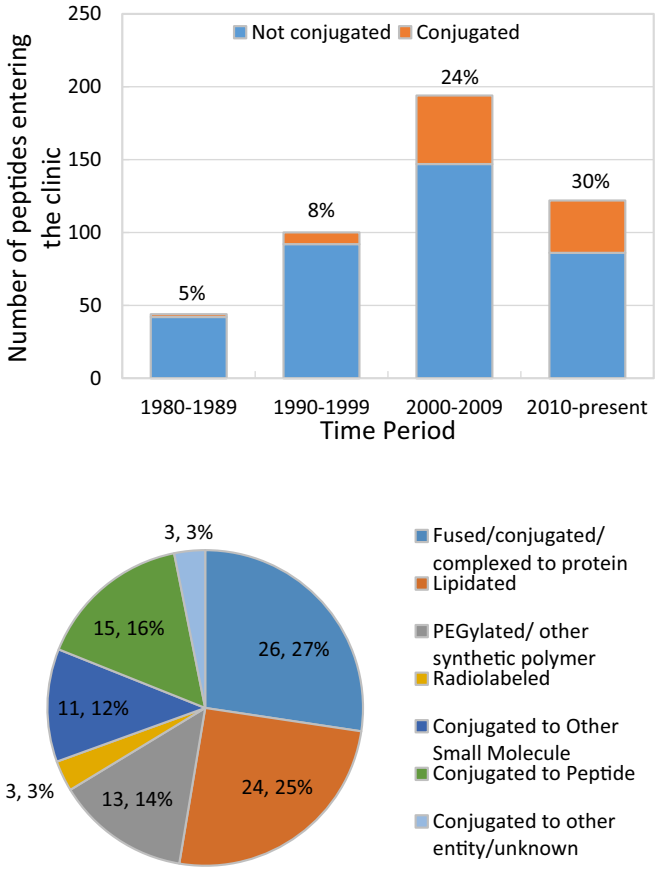

Fig. 5. Number and percentage of conjugated peptides entering clinical development (top) and distribution of all conjugated moieties in the peptide database (bottom).

strategy, with the first such peptides entering clinical development in the late-1990s. Conjugation can also be used to deliver a cytotoxic payload or imaging agent to specific cell types targeted by the peptide. See Table 4 for a description of various conjugation strategies deployed with therapeutic peptide development candidates.

2.3. Molecular targets of therapeutic peptides

As noted above, many endogenous peptides and analogs thereof have been developed as potential therapeutics; thus, peptide hormone receptors are logical targets for peptide drugs. G-protein coupled receptors (GPCRs) represent the largest class of drug targets for peptides. Although this dominance has shrunk over time, greater than 40% of peptides that entered the clinic since 2010 have targeted GPCRs (Fig. 6). Non-GPCR cell surface receptors, including natriuretic peptide receptors and cytokine receptors with endogenous protein ligands, are also popular targets. Antimicrobials, ion channels, and other extracellular targets (e.g. structural proteins, adhesion molecules, and secreted enzymes) make up the majority of the remaining targets, while a small number of intracellular targets are being pursued with the help of cell penetrating strategies.

Certain targets have rapidly increased in popularity due to the success of a first-in-class peptide, resulting in numerous follow-on research programs pursuing the same mechanism. During the 1980s and 1990s, the gonadotropin-releasing hormone (GnRH) receptor was a "hot" target, reflecting the promise of GnRH agonists and antagonists in treating a variety of important conditions regulated by reproductive hormones. GnRH-targeting peptides were formulated into a range of delivery formats and approved for prostate cancer, endometriosis, assisted reproduction, and other indications. Development efforts shifted towards small molecule GnRH antagonists in the 2000s.

Peptide development changed focus in the late-1990s when GLP-1 receptor agonists derived from the exendin-4 structures hit the clinic for the treatment of type 2 diabetes and, eventually, obesity.[24] The emergence of metabolic disease as a major worldwide health concern has driven development of agents that target gastrointestinal peptide receptors associated with appetite, insulin secretion, and energy balance.[25] By our count, 47 peptides that target GLP-1 receptor have entered the clinic, of which five are approved and 16 are in active clinical development as of March 2017.

Another trend is towards polypharmacy, wherein multiple molecular targets are addressed by a single molecule that simultaneously acts on multiple receptors or by a molecule that contains multiple functional domains. Dopastatin (BIM-23A760) was a hybrid of a peptidic somatostatin receptor agonist linked to a small molecule dopamine agonist, designed to address two contributors to neuroendocrine tumor disease pathology.[26] Several hybrid molecules that have recently entered clinical development attempt to target metabolic disease on different fronts. "Twincretins" are single peptides that act as agonists of the GLP-1 receptor and the glucagon or GIP receptors,[27] and another drug candidate consists of a GLP-1 agonist peptide covalently tethered to a PCSK9-inhibiting antibody.[28]

2.4. Therapeutic uses of peptides

Peptides have been investigated across the therapeutic spectrum, reflecting the potential utility across a wide range of indications and perhaps coupled with the cautious optimism that accompanies many development programs. Not surprisingly, the areas of highest concentration for peptide development (at present) are areas of high interest to the pharmaceutical industry: metabolic disease, oncology, and cardiovascular disease (Fig. 7).

Interestingly, the therapeutic landscape of approved peptide drugs does not mirror that of peptides in development. For example, many peptides have entered development in oncology indications but few have received approval, which may simply reflect poor success rates in oncology as a whole.[29,30]

Table 4
Examples of peptide conjugates.

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

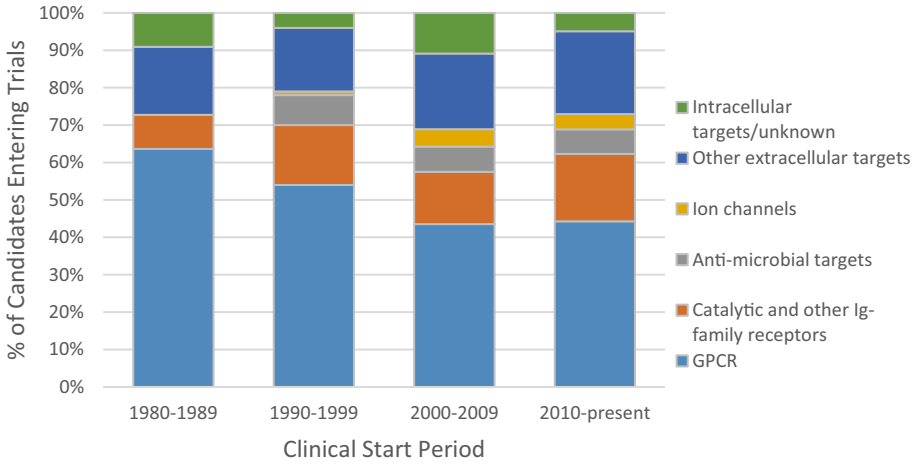

Fig. 6. Molecular targets of peptides entering clinical development.

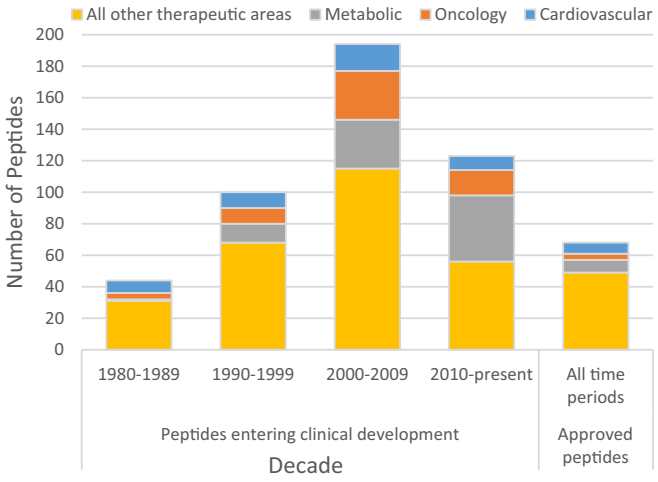

Fig. 7. Primary therapeutic area for peptides by time period of clinical initiation, compared with the primary therapeutic area for approved peptides across all time periods (including pre-1980). This figure highlights peptides in the three most popular therapeutic areas (at present). See the Supplementary Information for therapeutic area definitions.

3. Clinical development timelines and benchmarks for peptides

The duration of peptide clinical development has varied widely for the peptides approved since the beginning of 2010 (Fig. 8). The median development time for this cohort of peptides was 9.4 years, which is slightly longer than one benchmark for cycle times (median of 8.1 years) that captures data from a group of primarily mid-to-large-sized pharmaceutical companies across all molecule types.[31] In general, peptides with a shorter length of clinical development were approved in indications for which clear regulatory precedent and well-defined clinical trial endpoints exist: secondary hyperparathyroidism (etelcalcetide), type 2 diabetes mellitus (dulaglutide and albiglutide), and multiple myeloma (carfilzomib). These peptides were also typically ushered through mid-to-late-stage clinical trials by larger drug sponsors.

We also performed a comparison of the probability of success for peptides compared to industry-wide benchmarks for new biological entities (NBEs) and new chemical entities (NCEs). This success metric looks at the likelihood that a drug candidate will

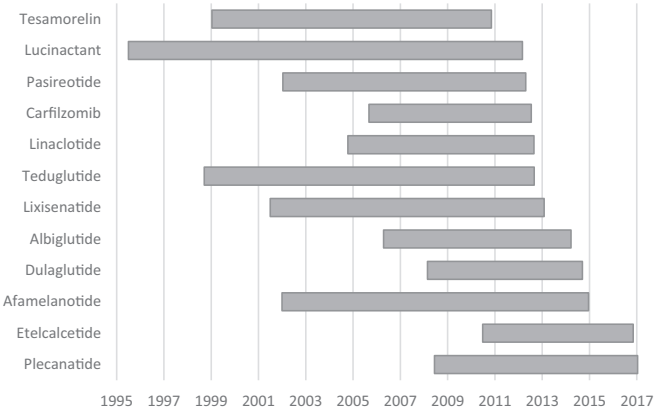

Fig. 8. Duration of clinical development for peptides approved since 2010. The left side of each bar represents initiation of the first clinical trial; the right side of each bar represents the peptide's first approval in a major market.

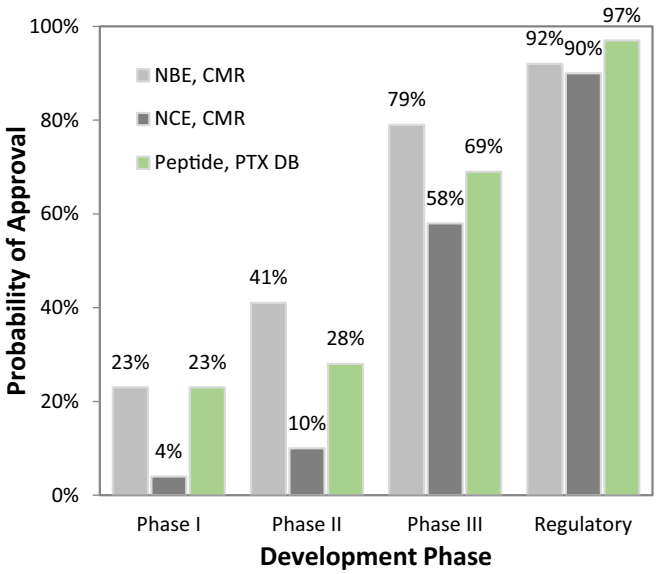

Fig. 9. Probability of success for agents at various stages of clinical development. NBE: new biological entity; NCE: new chemical entity; "Regulatory" refers to the approval rate of marketing applications by regulatory bodies (i.e. FDA, EMA). Success rates for NBE and NCE drugs are taken from the 2015 CMR International Pharmaceutical R&D Factbook, an annual report on industry trends. Peptide success rates are taken from the authors' peptide therapeutics database (PTX DB). See the Supplementary Information for a comparison of these methodologies, which differ slightly in their classifications of clinical development phases and their timeframes for data inclusion.

eventually receive regulatory approval at a given phase of development. NBEs comprise antibodies and other proteins, live biologic products, and vaccines, while NCEs primarily comprise small molecules and synthetic peptides. (The peptide-specific regulatory success calculation methodology differed somewhat from the methodologies used in recent reports by CMR International and the Biotechnology Innovation Organization (BIO);[29] see the Supplementary Information).

The peptide rates of success fell between those of NBEs and NCEs (Fig. 9) as described by CMR International. This may reflect the increased target specificity and reduced toxicity of peptides compared to small molecules, which have high attrition rates in early clinical development. In contrast, peptides may be less stable and less specific than protein biologics, including highly-target-selective monoclonal antibodies and prophylactic vaccines, resulting in increased attrition rates compared to NBEs.

4. The future of peptide therapeutics

From humble beginnings as substances isolated from livestock glands, peptides have established a unique therapeutic niche and will continue to be an important element in the pharmaceutical landscape. Peptide therapeutics have kept pace with scientific innovation by expanding into new indications and molecular targets, by exploiting novel chemistry strategies to broaden molecular diversity, and by engineering enhanced pharmaceutical properties.

We believe that research will continue to identify new peptide opportunities. As endogenous ligands for peptide hormone receptors, peptides are a natural starting point for drug discovery, as exemplified by the list of peptide drugs routinely used in medical practice. In the last five years, regulatory agencies have approved first-in-class peptides that target guanylyl cyclase C (GC-C) and the melanocortin 1 receptor (MC1R): linaclotide and afamelanotide, respectively, both of which are close analogs of native peptides. Such approvals exemplify the continuing opportunity for novel peptide therapeutics.

Research continues to expand the potential range of peptide-based pharmaceuticals to new targets. A large number of peptide-addressable targets for which no drugs are yet approved have shown therapeutic promise in early-stage clinical trials or in preclinical models of disease. For example, analogs of kisspeptin that target GPR54 may offer benefits to existing agents used for assisted reproduction,[32] and a melanocortin 4 receptor (MC4R) agonist may reduce the body weight of patients with genetic obesity syndromes.[33] Pharmaceutical companies have filed patent applications for derivatives of the endogenous peptides apelin,[34,35] adrenomedullin,[36] and neuromedin U[37,38] based on results from animal studies. Peptides from the latter two drug discovery programs have not been tested in humans to our knowledge, and a putative apelin derivative has only recently entered clinical trials.[39]

Improvements in peptide screening and computational biology will continue to support peptide drug discovery. Metabolomic, proteomic, and genomic screening of toxins and other sources of natural products can identify bioactive peptides that may contain unique structural features generated by uncommon post-translational modifications or non-ribosomal synthesis.[40–42] An improved understanding of the molecular basis for human genetic disorders can generate new potential therapeutic leads,[43] and the de-orphanization of poorly-characterized peptide receptors can stimulate research efforts for new receptor-ligand pairs.[44]

Finally, new peptide drug delivery, formulation, and half-life extension approaches will further the reach of this unique class of molecules. Efforts are underway to improve the oral availability of peptide therapeutics by increasing drug stability in the GI tract and formulating peptides with permeability enhancers,[45,46] and improving the CNS availability of peptides through conjugation to carrier molecules or delivery in nanoparticles.[47,48] *For further thoughts on trends in peptide chemistry and conjugation, we refer the reader to other chapters in this issue.*

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2017.06.052.

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