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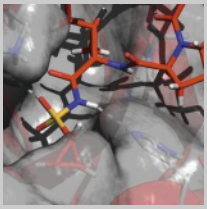

Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology
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A New Era for Peptide Therapeutics: Innovations, Challenges, and Future Directions

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Abstract: Peptide drugs are experiencing a renaissance driven by technological breakthroughs and the success of recent blockbuster drugs. A versatile peptide chemistry toolbox, modern synthesis techniques, and powerful discovery platforms are addressing many inherent roadblocks in peptide drug discovery and development allowing complex diseases to be targeted with high specificity and efficacy. As we enter a new era, peptide drugs are well suited to pursue inherently challenging, underrepresented targets and provide innovative treatment options.

Keywords: Drug discovery · Drug development · Peptide drugs · Screening technology

Introduction

The interest in peptides as drug modalities has been reignited more than a century after the first therapeutic application of the peptide hormone insulin. The rising enthusiasm has been fuelled by recent blockbuster drugs that are part of more than 40 peptide drugs approved in the last 10 years alone. Among the new drug approvals, there are structures ranging from orally bioavailable di- and tripeptides to large peptide dimers connected *via* extensive pharmacokinetic modifiers and peptide–protein conjugates. This heterogeneity is also reflected in the indications that the new peptide drugs have been approved for, which include rare genetic diseases all the way to conditions that affect millions of people worldwide. The field and its community have evolved tremendously over the last century, yielding new technologies and approaches to discover and develop future peptide therapeutics.

The Past: Insulin as the Pioneer

The history of modern peptide drugs traces back to the first use of insulin in paediatric patients for the treatment of type-1 diabetes mellitus in 1922 by Banting and Best.[1] Insulin had a transformative impact on medicine as it turned a fatal disease into a manageable condition and significantly enhanced the quality of life of patients and their families and extended their life span. The first commercial insulin products were extracted from the pancreas of cows and pigs, bearing potential for immunogenicity due to interspecies sequence differences and higher variability in product quality. The clinical success of insulin established peptides as a viable therapeutic modality and set the stage for future developments in peptide drug discovery and manufacturing (Fig. 1). The development of solid-phase peptide synthesis (SPPS) by Merrifield in 1963[2] and recombinant DNA technology leading to the first approved human insulin product from recombinant expression in 1982[3] were important breakthroughs to enable large-scale manufacturing of peptides. The ability to access high-quality products, even of longer peptides, and the chemical modification of peptide sequences to improve pharmacokinetic and pharmacodynamic properties paved the way for the commercial success of this therapeutic modality.

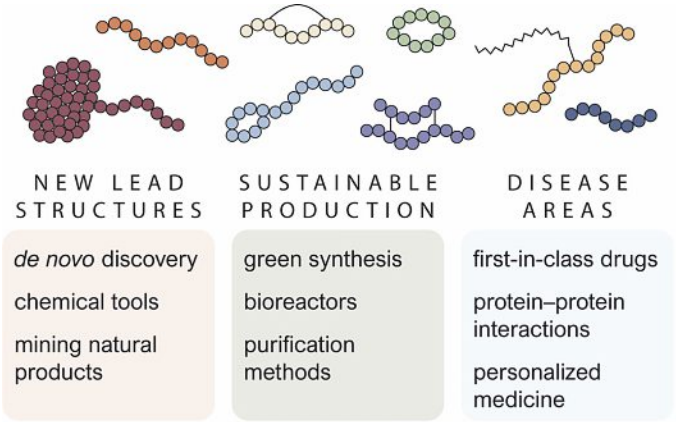

Fig. 1. The new era of peptide therapeutics builds on inventive strategies to discover novel lead structures, considers sustainable methods for manufacturing, and dives into underexplored diseases to develop the next generation of peptide drugs.

The early generation of peptide drugs consisted primarily of endogenous peptide hormones and derivatives thereof as they represent potent signalling molecules and regulate various physiological processes such as metabolism, growth, and immune response.[4] Therapeutics based on insulin, gonadotropin-releasing hormone, oxytocin, vasopressin, somatostatin, and other hormones have become essential drugs in modern medicine. Bioactive peptide natural products, found across all kingdoms of life, have been the second important source of lead compounds due to their diverse structures and exceptional biological activities.[5–7] Their high specificity and potency forged by evolution allowed the development of novel therapeutics targeting a wide range of conditions and diseases, from pain to immunosuppression. Few peptide therapeutics have also been discovered by serendipity, including important immunomodulatory compounds for the treatment of autoimmune diseases. Despite the innovative breakthroughs and their significance for human medicine, by the end of the last century, stakeholders considered peptide drugs a niche modality.

Overcoming the Challenges of Peptide Drugs

Three intrinsic features of peptides led to hesitations with their pursuit in early drug discovery campaigns. Firstly, with over

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600 proteases encoded in the human genome, peptides are prone to undergo rapid enzymatic degradation once administered, typically *via* intravenous or subcutaneous injection.[8] The abundance and activity of proteolytic enzymes in the gastrointestinal tract present an additional challenge for oral administration routes only few therapeutic peptides have managed to overcome.[9] Secondly, peptides and their metabolites are rapidly cleared from blood circulation by renal elimination as their size is generally below the glomerular filtration barrier, and they lack specific retention mechanisms.[10] Together, the rapid degradation and elimination lead to short *in vivo* half-lives which prevent accumulation of therapeutic doses in the targeted cells or organs and, as a result, limit the clinical effect of the drug candidates. Thirdly, most peptides fail to overcome cell membranes and reach intracellular targets, which restricts their therapeutic potential to targeting of extra- and transcellular proteins.[11]

Researchers in academia and pharmaceutical industry pursued numerous strategies to address these limitations: The substitution of natural amino acids with non-natural residues such as D-, β-, or *N*-methylated amino acids and backbone isosteres has been used to optimize binding properties and increase the metabolic stability of lead compounds as these structures are less likely to be recognized by proteases.[12] Furthermore, the formation of peptide macrocycles by chemically connecting the backbone or side chains has proven to be a promising strategy to improve the enzymatic resistance against proteases, mitigate poor membrane permeability, and improve target binding.[13] To reduce elimination rates and prolong the *in vivo* circulation times of peptide drugs, their molecular weight can be increased by fusion to larger proteins or polymers such as polyethylene glycol chains.[14,15] Alternatively, conjugation to small molecules with high binding to plasma proteins (*e.g.* lipids, sugars) emerged as useful solutions to address the rapid renal clearance. Collectively, these chemical tools enabled peptide chemists to overcome inherent limitations and develop potent therapeutics.

The Present: Blockbuster Drugs

A century after the first therapeutic administration of a peptide, more than 110 peptide drugs have been approved by regulatory authorities around the globe with an estimated market value of over 30 billion CHF in 2024, which is projected to grow beyond 60 billion CHF by 2030.[16,17] Hundreds of candidates are under clinical evaluation and in preclinical stages, underlining the growing relevance and investment in this therapeutic modality.[18] Recent blockbuster drugs, such as GLP-1 receptor agonists, initially approved for the treatment of type-2 diabetes mellitus and obesity and currently studied for indications beyond metabolic disorders, have demonstrated the vast clinical and commercial potential of peptides.[19] Their success provides strong incentives to drive further innovation in the field and explore their application in disease areas that currently lack satisfying treatment options. However, as new lead structures from natural products and peptide hormones appear to become scarce, developing methods for the discovery of novel peptide candidates is critical to sustain the momentum and expand therapeutic possibilities.

De Novo Discovery of Peptide Leads

Methods for *de novo* peptide discovery, which do not rely on existing natural templates to identify and develop new lead compounds, have become a vital alternative to traditional approaches. Conceptually, *de novo* discovery involves the screening of large, unbiased compound collections for the desired properties, *such as* binding affinity toward a protein of interest.[20] *De novo* approaches span the areas of molecular biology, proteomics, and computational chemistry.

Effective technologies have been developed based on biosynthetic methods, such as phage display and mRNA display, wherein the translational machinery is exploited to generate large libraries of peptides encoded by unique oligonucleotide tags.[21] These platforms allow for the rapid screening of peptide libraries with 10^8–10^{15} members. After affinity-based selections against the target of interest, the oligonucleotide tag attached to the peptide binder (encapsuled in the phage or in the form of conjugated mRNA) is sequenced to reveal the identity of putative binders. Chemical post-translational modifications of the peptide libraries and genetic code expansion enable the screening of macrocyclic structures, peptide–pharmacophore conjugates, and peptides bearing non-natural amino acids.[22,23] These tools greatly expand the chemical space and have resulted in the discovery of lead structures for several peptide drugs approved in the last two decades and multiple candidates in clinical evaluation.

Other *de novo* strategies rely strictly on chemical synthesis for library preparation. Adapting well-established procedures for SPPS and combinatorial chemistry permits the facile incorporation of non-natural amino acids to discover peptide candidates with highly desirable properties.[24] While initial approaches screened the resulting peptides tethered to solid support (one-bead-one-compound libraries) or individually by high-throughput methods,[25] current efforts benefit from technological breakthroughs in the field of proteomics to perform affinity-based selections with libraries of over 10^8 members. Putative binders are identified by mass spectrometry and peptide sequencing.[26] This eliminates the need for appending an additional tag for identification, which could interfere with target binding by steric hindrance. As mass spectrometers become more advanced and protocols for screening and data analysis are refined, the full potential and boundaries of this technology are yet to be determined.

Computational methods have provided additional sources of *de novo* peptide candidates for further development. The use of *in silico* docking simulations allow the rapid screening of virtual, chemically diverse libraries of peptides and peptidomimetics for experimental validation.[27] Emerging methods using machine learning and artificial intelligence have been successfully applied to mine large data sets and generate novel sequences for evaluation of their bioactive potential.[28,29]

Together, these technologies accelerate the discovery of new lead compounds, particularly for targets which are currently underrepresented in clinical pipelines such as protein–protein interactions.[30] As peptides derived from *de novo* discovery campaigns are entering clinical trials and receiving regulatory approval, they highlight the value of unbiased screening approaches.

The Future: Tackling the Challenges Ahead

The outstanding potential of peptide drugs is the reason for their recent clinical and commercial success and an important driver for the future of this modality. The combination of traditional lead discovery strategies exploiting nature's rich repertoire of peptide natural products and breakthroughs in *de novo* discovery are bound to yield novel candidates targeting current and emerging health issues. To fully benefit from the clinical potential of peptides, several challenges need to be addressed: The high process mass intensity (PMI) of peptide manufacturing, *i.e.* the amount of raw material needed to prepare a specified amount of product, represents a major concern.[31] Peptide synthesis and purification, which require large quantities of hazardous solvents and reagents, have significant impact on the environment and the production costs of peptide drugs. As the demand for peptide therapeutics grows, especially for the treatment of diseases with millions of patients affected globally, there is an urgent need to develop sustainable and efficient manufacturing processes. This includes the implementation of green chemistry and biotechnological methods to reduce the PMI of peptide therapeutics and improve their scalability. Along the same lines, improving production processes can address critical drug shortages, often caused by

complex workflows and supply chain constraints. As drug shortages can jeopardize the health of patients by increasing the risk of adverse events and mortality, robust manufacturing strategies are crucial to ensure stable product supply.[32] Finally, further advances in peptide engineering are required to improve the pharmacokinetic and pharmacodynamic properties of peptides, ideally already in the early discovery phase. Addressing these challenges will be essential for the continued growth and success of peptides in medicine.

Peptide therapeutics are entering a new era, characterized by the interplay of technological advancements, scientific insights, and clinical success stories. From their impactful beginnings in the 1920s, peptides have evolved into a versatile and powerful class of drugs with the potential to address the challenging diseases of our time. As the field continues to evolve, peptide drugs are likely to play an increasingly important role in personalized medicine by offering precise, effective, and safe treatment options. The vibrant peptide community in Switzerland with members in academia, pharmaceutical industry, and emerging start-ups has an important part in driving future innovation in peptide drug discovery, advancing novel therapeutic approaches, and contributing to sustainable peptide manufacturing processes.

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