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Review Article

Peptide Therapeutics 2.0: AI-Driven Design, Sustainable Synthesis, and Next-Generation Medicine

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Abstract

Peptides are fundamental biological molecules that mediate diverse physiological processes, making them increasingly attractive as therapeutic agents due to their high specificity, potent bioactivity, and favorable safety profiles. Despite these advantages, current peptide synthesis methodologies face significant limitations, including lengthy production times, extensive use of hazardous solvents, and challenges in scalability. These factors contribute to substantial environmental burdens and elevated manufacturing costs, limiting broader access and application. Recent advances in artificial intelligence (AI) and machine learning (ML) offer transformative potential to overcome these hurdles by enabling predictive sequence design, real-time process optimization, and autonomous synthesis platforms. The integration of AI-driven approaches promises enhanced efficiency, reduced waste, and improved reproducibility in the manufacturing process, catalyzing the development of next-generation peptide therapeutics. This review highlights the intersection of peptide biology, synthetic challenges, and computational innovation, emphasizing implications for therapeutic development, research tools, and industrial-scale peptide production.

Keywords: Peptides, AI, Machine learning, Safety profiles, Synthetic challenges

Introduction

Peptides are biologically active short chains of amino acids, typically ranging from 2 to 50 residues, and serve critical physiological functions across virtually every tissue in the human body [1]. Leveraging their intrinsic roles as hormones, neurotransmitters, growth factors, and immune mediators, peptides have emerged as critical targets and tools in therapeutic development. Endogenous peptides regulate essential physiological processes including: glucose homeostasis (e.g., insulin, GLP-1), appetite and satiety (e.g., ghrelin, leptin), inflammation (e.g., bradykinin, α-MSH), and cellular signaling cascades involved in development, angiogenesis, and tissue repair [1-3]. Their ability to selectively bind to cell-surface or intracellular receptors enables high target specificity and poten-

cy, often surpassing the pharmacodynamic precision of small-molecule drugs [4,5]. Additionally, advances in peptide engineering (peptidomimentics) have improved stability and bioavailability, broadening their clinical applicability across metabolic, cardiovascular, neurologic, and autoimmune diseases [6].

The unique physiological attributes position peptides as a cornerstone of precision medicine, offering therapeutic advantages over traditional small molecule drugs. Although peptides have been used for decades in the treatment of endocrine, cardiovascular, and infectious diseases, recent advances in peptide engineering, formulation methods, and delivery systems have significantly expanded their therapeutic scope and clinical viability. Among the most notable examples of this progress are synthetic analogs of natural peptides, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which have revolutionized the treatment landscape for type 1 and type 2 diabetes, as well as obesity and nonalcoholic steatohepatitis (NASH) [7-9]; these agents exemplify the success of peptide-based drugs in achieving both metabolic regulation and disease modification, and they represent one of the fastest-growing classes of therapeutics globally [10,11].

In addition to pharmaceuticals, peptides are also widely used in cosmeceuticals and supplements to enhance skin repair, collagen synthesis, and anti-aging effects [12]. In biomedical research, labeled peptides are instrumental for probing protein–protein interactions, tracking receptor-ligand dynamics, and used in designing vaccine epitopes [13]. The global peptide therapeutics market was valued at approximately $50 billion in 2025 and projected to reach $85 billion by 2035, driven by a combination of aging populations, rising prevalence of chronic diseases, and intensified focus on biologics and targeted therapies [14]. North America currently dominates the market, with significant contributions from both branded and generic peptide formulations [15]. However, this growth is constrained by persistent challenges in peptide synthesis and manufacturing.

Current Methods in Peptide Synthesis

Solid-phase peptide synthesis (SPPS) and, to a lesser extent, liquid-phase peptide synthesis (LPPS) remain the foundational techniques for laboratory- and industrial-scale peptide production due to their modularity, sequence fidelity, and adaptability to automation [16]. For example, Fmoc (9-fluorenylmethoxycarbonyl)/tertiary butyl group solid phase synthesis enables rapid assembly of linear and cyclic peptides with high sequence specificity, while LPPS offers advantages for short sequences or labile residues [17]. Despite their widespread adoption, these methodologies face significant limitations in terms of cost, efficiency, and environmental sustainability.

One of the major constraints is the high consumption and excess use of expensive reagents, particularly activated amino acids and coupling agents, which are often used in large molar excess to drive reactions to completion [18]. The protocols are also time- and labor-intensive, requiring iterative deprotection and coupling cycles, with stringent control over side reactions such as aspartimide formation, racemization, and incomplete coupling [19,20]. Furthermore, both SPPS and LPPS generate substantial volumes of toxic solvent waste, particularly from dimethylformamide (DMF) and dichloromethane (DCM). Both of these solvents have well-documented reproductive toxicity, persistence, and are subject to regulatory scrutiny [21-23].

In addition, the downstream purification of crude peptides typically involves high-performance liquid chromatography with gradient elution, which further amplifies solvent consumption and contributes to high process mass intensity [23]. The yield loss during purification, coupled with the energy and water demands of preparative-scale workflows, significantly elevates the economic and environmental footprint of peptide manufacturing [24]. These limitations highlight an urgent need for greener synthesis alternatives, real-time process analytics, and machine learning–driven process optimization to improve sustainability and cost-efficiency in modern peptide production.

In parallel, the accelerating demand for highly pure, economically viable, and environmentally sustainable peptides across pharmaceutical, cosmetic, and research applications reinforces the imperative for transformative innovations in both synthesis strategies and large-scale manufacturing workflows. The integration of artificial intelligence (AI) and machine learning (ML) into peptide synthesis and manufacturing represents a transformative shift toward data-driven, sustainable bioprocessing. These computational tools facilitate predictive modeling of reaction efficiency, side-product formation, and sequence-dependent synthetic difficulty, allowing for rational design and prioritization of peptide candidates based on manufacturability and stability profiles [25-27]. In parallel, ML algorithms enable real-time optimization of synthesis parameters, including solvent selection, coupling times, and reagent volumes, thereby improving reaction fidelity, yield, and cost-effectiveness [28]. Advanced closed-loop systems, combining automated synthesis platforms with AI-driven feedback controls have further demonstrated the ability to reduce solvent consumption, minimize waste, and enhance scalability. These are critical priorities for both research and commercial-scale peptide production [29,30]. This review will explore the biological significance of peptides, the technological and environmental limitations of current manufacturing approaches, and the emerging AI- and ML-based solutions poised to redefine the landscape of peptide therapeutics in both clinical and industrial contexts.

Peptide Synthesis for Therapeutic Applications

The synthesis of peptides has evolved significantly over the past few decades, with advances in both traditional and automated methods enabling the rapid and efficient production of bioactive sequences for research and therapeutic applications. Three primary approaches dominate the field: LPPS, SPPS, and process optimization strategies that address throughput, environmental concerns, and automation.

1. LPPS involves the sequential coupling of amino acids in solution, typically using carbodiimide-based condensation re-

actions to form peptide bonds. This method provides high-purity intermediates through intermediate purification after each step and has been widely used for the synthesis of short peptides, cyclic peptides, and fragments intended for convergent synthesis of longer chains. LPPS offers advantages in speed and scalability, particularly for sequences requiring only a few residues, and facilitates the incorporation of complex chemical modifications or non-standard residues with minimal steric hindrance[1]. However, the method is labor-intensive for longer peptides due to the increasing complexity of purification after each elongation step and yields often decrease with peptide length.

2. Introduced by Merrifield in 1963 [31], SPPS revolutionized peptide synthesis by anchoring the initial amino acid to an insoluble resin allowing stepwise synthesis of the growing peptide chain by washing away excess reagents y without isolating intermediates [32]. This method is now the standard for synthesizing peptides up to ~50 residues and beyond, particularly in automated platforms. Two primary strategies dominate SPPS: Fmoc and Boc (tert-butyloxycarbonyl) chemistry. Fmoc-SPPS has become the preferred method due to its mild deprotection conditions, which rely on base (typically piperidine) rather than strong acid, as used in Boc-SPPS [33]. Fmoc-SPPS is particularly advantageous for sensitive or hydrophobic sequences and is compatible with automated synthesizers. The high sequence fidelity, owing to on-resin washing and coupling cycles, scalability (with robust automation protocols available for both research and industrial-scale production) and compatibility with diverse modifications, including stapling, lipidation, and cyclization are major strengths of SPSS. Despite these advantages, SPPS is associated with long reaction cycles, extensive solvent consumption, and the use of toxic reagents such as N,N-dimethylformamide (DMF) and dichloromethane (DCM), which pose significant health and environmental concerns [21]. These solvents are globally classified as reproductive toxicants (Category 1B) under the European Union's CLP regulation and are flagged for future regulatory restrictions or bans due to their carcinogenicity, reproductive toxicity, and environmental persistence [18,23]. Additional solvents such as diethyl ether (DEE) and tert-butyl methyl ether (MTBE) pose flammability and volatility risks, further compounding the environmental and occupational hazards of large-scale synthesis [34]. Beyond solvents, the synthesis process itself is characterized by poor atom economy, particularly with the use of fluorenylmethyloxycarbonyl (Fmoc)-protected amino acids, which generate significant protecting group waste18. Common coupling agents (e.g., HBTU, HATU, and DIC/Oxyma) are known to be potentially explosive, allergenic, or sensitizing, raising serious safety concerns during scale-up and manufacturing [35]. Another critical reagent, trifluoroacetic acid (TFA), widely used for resin cleavage and side-chain deprotection, is both highly corrosive and environmentally persistent, necessitating stringent handling protocols and neutralization procedures [36]. Furthermore, incomplete coupling or deprotection reactions can result in deletion sequences, which not only reduce yield but also complicate downstream purification and quality control29. These synthesis inefficiencies require meticulous process monitoring and frequently necessitate resource-intensive purification methods such as preparative HPLC, increasing both economic and ecological burdens [37]. Recent innovations aim to address the limitations of traditional SPPS through improvements in efficiency, environmental sustainability, and cost-effectiveness. Microwave-assisted SPPS accelerates both coupling and deprotection steps by enhancing reaction kinetics through localized heating. This technology has been shown to reduce total synthesis time and improve crude peptide quality, particularly for long or aggregation-prone sequences [35], yet challenges still exist.

3. Multiple process optimization strategies have been developed to address the pressing needs of high-throughput synthesis, environmental sustainability, and automated manufacturing in peptide production. In particular, green chemistry initiatives have gained momentum, focusing on the replacement of toxic solvents (i.e., DMF and DCM), particularly those classified as hazardous by regulatory agencies, with more benign alternatives such as N-butylpyrrolidone (NBP), dimethyl sulfoxide (DMSO), and γ-valerolactone (GVL) [34,38]. These solvents offer reduced toxicity, lower vapor pressure, and improved biodegradability, aligning sustainability goals while maintaining synthetic efficiency. In parallel, engineering efforts revolutionized manufacturing hardware: flow chemistry platforms have emerged as powerful tools for continuous peptide synthesis, enabling precise control over reaction parameters and significantly reducing reagent excess and waste [29]. Unlike traditional batch methods, continuous flow reactors offer enhanced thermal and mass transfer, real-time process scalability, and integration with in-line monitoring technologies such as ultraviolet absorbance, infrared spectroscopy, and mass spectrometry [39]. These capabilities support real-time reaction optimization and feedback-controlled automation, paving the way for deployment in both high-throughput screening and Good Manufacturing Practice (GMP)-compliant commercial production [40]. These innovations not only address long-standing challenges in solvent use, cost, and scalability but also position peptide manufacturing for alignment with regulatory expectations on environmental impact and quality assurance. Together, these trends reflect the field's push toward greener, faster, and more automated peptide synthesis strategies capable of meeting the demands of both academic research and industrial production.

Challenges in Peptide Manufacturing

Despite the significant clinical promise of peptide therapeutics, their large-scale manufacturing presents persistent challenges related to environmental sustainability, economic feasibility, and stringent quality control. As demand grows for complex, modified, and longer peptide sequences, these issues become more pronounced across both research and commercial production

pipelines. One of the foremost environmental concerns in peptide manufacturing is the extensive use of toxic organic solvents, particularly N,N-dimethylformamide (DMF) and dichloromethane (DCM), both of which are widely used in SPPS. These solvents are not only classified as hazardous air pollutants by regulatory agencies such as the EPA and REACH, but they also pose occupational and ecological risks due to volatility, persistence, and challenges in disposal [18,41]. Moreover, SPPS generates large volumes of waste per peptide mole synthesized, including unreacted reagents, cleaved protecting groups, and excess coupling agents. The E-factor (kg of waste per kg of product) for traditional peptide synthesis can exceed 1000, highlighting an urgent need for green chemistry approaches [42]. Strategies such as solvent recycling, use of less hazardous reagents (e.g., ethyl cyano(hydroxyimino)acetate, or Oxyma Pure), and solvent-free or aqueous-phase coupling reactions are actively being explored to address these gaps [19]. Peptide manufacturing is inherently resource intensive. The use of expensive protected amino acid derivatives, stoichiometric coupling agents, and high-purity solvents contribute to elevated raw material costs, particularly for long or modified peptides. Purification steps, often requiring HPLC under preparative conditions, are both costly and time-consuming, especially at commercial scales [43]. These economic burdens disproportionately affect small biotech companies and limit the accessibility of peptide therapies in emerging markets, where cost containment is critical. Although automation has reduced labor input, material costs and yield inefficiencies remain significant barriers to scalability. Process intensification strategies such as flow synthesis and microwave-assisted SPPS are under active development to improve efficiency and cost-effectiveness, but widespread adoption remains limited by capital investment and regulatory inertia [29].

Ensuring high purity and structural integrity is essential for therapeutic peptides, as even trace impurities can alter biological activity, immunogenicity, or stability. Key challenges include incomplete coupling, racemization, truncation, and side reactions (e.g., aspartimide formation or oxidation of methionine/cysteine), which can yield closely related but inactive or harmful byproducts [44]. To ensure compliance with GMP (Good Manufacturing Practice) standards, rigorous quality control using analytical HPLC, MS, and NMR spectroscopy is essential. These tools are used not only for purity assessment, but also for sequence verification, detection of isomeric impurities, and real-time process monitoring [45]. Newer methods such as high-resolution mass spectrometry (HRMS) and multi-attribute methods (MAM) are gaining traction for their ability to detect post-translational modifications and minor impurities with high sensitivity [46]. While these quality control measures are indispensable, they contribute significantly to overall production costs and time, reinforcing the need for integrated analytical solutions and design-for-quality approaches in peptide process development.

Overcoming Challenges in Peptide Manufacturing- AI and ML in Peptide Synthesis

AI and ML are rapidly transforming the landscape of peptide science by accelerating sequence discovery, optimizing synthesis parameters, enhancing automation, and promoting sustainability. These computational tools offer the potential to address longstanding challenges in peptide development, including poor synthesis efficiency, batch-to-batch variability, and environmental burden. AI-based algorithms have shown great promise in de novo peptide design, leveraging generative models (e.g., variational autoencoders, GANs) and large peptide datasets which enable prediction of functional motifs, optimized binding affinity, and enhanced proteolytic stability [47]. Critically, AI tools are now being applied to predict synthetic feasibility, including the likelihood of racemization, aggregation, or difficult coupling steps, thereby minimizing costly side reactions during solid-phase synthesis [48]. Recent work has also demonstrated the use of language models trained on peptide sequences to propose variants with enhanced activity while maintaining synthetic tractability, thus enabling faster lead optimization with fewer experimental iterations [49].

ML models, particularly supervised regression and reinforcement learning algorithms are increasingly being used to optimize real-time synthesis parameters such as coupling duration, temperature profiles, and solvent selection. These models can ingest historical batch data, learning from analysis of variability across production runs to recommend adaptive process adjustments that reduce error and improve overall yield [50]. Integration of spectroscopic feedback (e.g., UV, IR, or MS signals) with ML algorithms allows dynamic modulation of reaction conditions, supporting on-the-fly corrections in temperature or reagent concentration to prevent incomplete couplings or byproduct formation [51]. Modern peptide synthesis is moving toward autonomous, closed-loop systems, where AI interfaces with robotic platforms to carry out iterative synthesis-design cycles with minimal human intervention. Robotic systems equipped with real-time monitoring tools and predictive control algorithms can adjust parameters mid-synthesis based on outcome prediction, reducing error rates and enhancing reproducibility [51].

A landmark example is the automated flow-based peptide synthesizer integrated with AI that selects optimal synthesis routes and coupling agents while monitoring reaction progress in real time [29]. Such platforms drastically reduce turnaround time, improve throughput, and enable parallel synthesis of multiple analogs. AI is also facilitating the transition to greener peptide synthesis by enabling predictive modeling of solvent and reagent impacts on both reaction efficiency and environmental footprint. Optimization algorithms can propose solvent substitutions (e.g., replacing DMF or DCM with NBP, Cyrene, or EtOAc) based on empirical datasets and predictive sustainability scores [18]. Furthermore, life-cycle analysis models informed by AI can simulate the downstream effects of synthesis decisions allowing peptide chemists to design greener pathways from the outset [52]. These developments are crucial for aligning peptide manufacturing with environmental and regulatory expectations in both academic and industrial contexts.

Industrial and Regulatory Landscape

The peptide therapeutics sector is undergoing rapid expansion

fueled by advances in delivery technologies, improved manufacturing capabilities and a growing demand for targeted and biologically compatible drugs. This commercial momentum is being further shaped by strategic decisions in manufacturing, regulatory positioning, and technological integration. The global peptide therapeutics market is estimated to reach approximately $50 billion USD in 2025, with projections indicating growth to over $85 billion USD by 2035; this market growth is driven by increasing approvals and demand for metabolic and oncology peptides along with expanding applications in infectious and rare diseases [53]. The market includes branded peptides (e.g., GLP-1 analogs and somatostatin derivatives) and generic equivalents, with branded products currently accounting for over 70% of revenue share, primarily due to their complexity and regulatory exclusivity [15]. As stated, North America remains the dominant market representing more than 45% of global sales, supported by strong biotech pipelines, favorable reimbursement structures and a robust clinical trial ecosystem, Asia-Pacific is expected to experience the fastest Compound Annual Growth Rate (CAGR) (~9–10%), driven by increased outsourcing, growing domestic research and development (R&D) investments, and biosimilar penetration [54].

Peptide drugs approved in recent years include tirzepatide, setmelanotide, and long-acting vasopressin analogs, illustrating the breadth of indications and the market's willingness to invest in complex formulations [55]. A critical decision for peptide developers is whether to pursue in-house manufacturing or outsource production to contract development and manufacturing organizations (CDMOs). Currently, over 60% of commercial peptide production is outsourced, particularly for GMP-grade and long-sequence peptides [56]. Outsourcing advantages include access to specialized infrastructure, cost savings through economies of scale, and regulatory expertise. This expertise is especially valuable for companies in early-stage development or those lacking large-scale synthesis capabilities. However, in-house manufacturing can offer better control over IP, formulation secrecy, and process optimization [57]. Cost analyses show that peptide synthesis accounts for 30–40% of total production costs, with purification and QA/QC contributing another 20–30%18. Regulatory compliance is a major cost driver; CDMOs that maintain US Food and Drug Administration (FDA), European Medicines Agency (EMA), and US Prescription Drug Marketing Act (PDMA) certifications for peptide APIs are positioned as strategic partners for global commercialization [58].

As the market becomes increasingly competitive, several factors distinguish successful peptide developers. Peptide purity and reproducibility remain essential; therapeutic-grade peptides must meet stringent quality specifications, typically >98% purity with minimal levels of isomeric and truncated impurities. These standards are enforced by International Council of Harmonization (ICH) guidelines and are essential for regulatory approval [59]. Scalability is another determinant of commercial success; the ability to rapidly scale from preclinical to commercial quantities while maintaining consistency and yield can be a barrier for smaller firms but a strategic advantage for CDMOs with integrated platforms. Regulatory navigation is critical, streamlined engagement with authorities like the FDA and EMA experience with 505(b)(2) and biosimilar pathways, along with strong Chemistry, Manufacturing and Control (CMC) documentation are all essential for rapid market entry and lifecycle extension [60]. Finally, strategic integration of AI-based methodologies into discovery, process development, and manufacturing is emerging as a major differentiator. Companies that leverage predictive analytics for yield improvement, machine learning for process control, and automation for closed-loop synthesis are better positioned to reduce costs, improve consistency, and shorten development timelines [29].

Translating Knowledge to Platform Development

The convergence of AI, automation, and green chemistry has catalyzed a new generation of platforms for peptide discovery, synthesis and drug development. Academic-industry consortia, startups, and established biopharmaceutical companies are forging collaborations to enhance the speed, sustainability, and precision of peptide therapeutic development. Several commercial and translational entities are now leveraging AI-guided peptide synthesis platforms, integrating automated robotics, machine learning algorithms, and real-time process analytics to improve reproducibility, reduce waste, and enable rapid prototyping. Some examples include Cemvita Factory which uses bioinspired models combining generative design tools with automated synthesis modules [61] and ML to design peptide-based therapeutics and enzyme mimetics with improved stability and synthesis feasibility. C4X Discovery integrates AI-based conformational mapping with peptide optimization workflows for target-specific binding and improved pharmacodynamics [62], whereas Evonik Industries has established AI-enhanced manufacturing facilities through its Health Care division, employing continuous flow peptide synthesis and predictive analytics to improve scalability and sustainability for GMP peptide production [63]. The publicly disclosed integration of AI and digital twin algorithms into Novo Nordisk and Amgen's peptide and protein drug manufacturing platforms enable real-time process control, yield forecasting, and adaptive quality assurance [64]. These examples illustrate the diverse and rapidly evolving applications of AI and ML across the peptide development pipeline from sequence design and conformational modeling to automated synthesis and GMP-scale manufacturing. While not exhaustive, they underscore a broader industry shift toward digitally enabled, data-driven biomanufacturing that enhances efficiency, scalability, and sustainability. As the field continues to mature, the integration of AI-driven platforms is expected to become a foundational component of next-generation peptide therapeutics and biologics production.

Leveraging the momentum, collaborative research efforts between academic institutions and industry are now playing a pivotal role in overcoming persistent bottlenecks in scalable, sustainable, and cost-effective peptide synthesis, accelerating innovation across both preclinical and commercial domains. For example, the NIH created a Center for Sustainable Peptide Chemistry, anchored at the University of Pittsburgh and University of Michigan. The collaborative Center is developing green solvents, waste-reducing SPPS protocols, and AI-based life cycle assessment (LCA) tools to im-

prove the environmental footprint of peptide synthesis [65]. Similarly, the Massachusetts Institute of Technology Machine Learning for Molecular Design (MLMD) initiative, in collaboration with biotech startups, is creating open-access ML models for synthetic feasibility scoring, targeting challenging peptide sequences with aggregation-prone or noncanonical residues [66]. Internationally, EU Horizon 2020-funded the CHEM21 project focused on training and deploying green chemistry techniques, including bio-based coupling agents, in peptide synthesis, and laid the foundation for industrial uptake of non-toxic reagents and continuous-flow methods [67].

Furthermore, a surge in venture-backed AI-peptide biotech startups is reshaping how peptide therapeutics are discovered, optimized, and brought to market. Examples and by no means an exhaustive list include: Peptilogics, backed by Peter Thiel and the Novartis Biome, use AI-powered models to design antimicrobial and immunomodulatory peptides via a PEP-GPT platform that integrates sequence design, structure prediction, and manufacturability analysis [68]; Generate:Biomedicines, leverages generative AI to engineer de novo peptide and protein therapeutics using large-scale biological datasets and structure-conditioned design algorithms [69]; Nurix Therapeutics and Insitro have partnered on peptide-based degraders and molecular glues, applying AI/ML to modulate intracellular interactions and streamline synthetic access [70]; DeepCure and Arzeda also employ synthetic biology and deep generative models for custom peptide synthesis and functional screening, in silico before laboratory validation. These initiatives, along with multiple emerging others exemplify a growing interdisciplinary innovation ecosystem, blending computational chemistry, sustainable synthesis, and precision automation to reshape peptide development pipelines.

Future Directions

Peptide therapeutics are poised to play an increasingly prominent role in modern medicine, offering high specificity, tunable pharmacokinetics, and expanding applicability across oncology, metabolic disorders, infectious disease, neurodegeneration, and wound healing. While significant strides have been made in synthesis technologies, delivery platforms, and regulatory acceptance, several strategic frontiers remain that will shape the next decade of innovation and adoption.

Future developments will focus on multi-functional and hybrid peptides, including peptide-drug conjugates, peptide-nanoparticle assemblies, and allosteric modulators targeting traditionally "undruggable" intracellular pathways. Advances in macrocyclic peptides, D-peptides, and stapled peptides will further expand the therapeutic repertoire by improving stability, membrane permeability, and target engagement.

Emerging classes such as self-assembling peptides, cell-penetrating peptides (CPPs), and immune-modulatory peptides are already being explored in clinical contexts, particularly in vaccines, checkpoint modulation, and regenerative medicine. The integration of AI-guided design and autonomous synthesis platforms is transforming peptide discovery and manufacturing into a data-driven, iterative process. Future systems will likely incorporate self-optimizing closed-loop platforms, capable of real-time adjustments in sequence design, synthesis conditions, and purification workflows. This paradigm shift could drastically reduce the cost, waste, and development timelines traditionally associated with peptide therapeutics, making them more accessible and commercially viable.

As environmental concerns mount, future peptide production will need to be sustainably engineered, with emphasis on green solvents, minimal E-factors, and renewable feedstocks. AI-based modeling of PMI and life cycle assessments will support the design of low-impact manufacturing pipelines. Parallel efforts to harmonize regulatory pathways across agencies like the FDA, EMA, PMDA, and WHO Prequalification Programme will be critical to accelerating global access to peptide-based medicines, especially in low- and middle-income countries.

Peptide therapeutics represents a dynamic and rapidly expanding domain at the intersection of biology, chemistry, engineering, and data science. From fundamental sequence design to sustainable, scalable production, this nascent field is experiencing a convergence of technological breakthroughs and clinical demand. Ongoing investment in AI-driven discovery, automation coupled with environmental responsibility will be essential to unlock the full translational potential of peptides. As academic, industrial, and regulatory ecosystems align, peptide drugs are poised to become central pillars of precision medicine in the 21st century.

References

1. Zaky AA, Simal Gandara J, Eun JB, Shim JH and Abd El Aty AM (2021) Bioactivities, Applications, Safety, and Health Benefits of Bioactive Peptides From Food and By-Products: A Review. Front Nutr 8: 815640.
2. Gregnani MF, Hungaro TG, Martins-Silva L, Bader M and Araujo RC (2020) Bradykinin B2 Receptor Signaling Increases Glucose Uptake and Oxidation: Evidence and Open Questions. Front Pharmacol 11: 1162.
3. Rubinić I, Kurtov M and Likić R (2024) Novel Pharmaceuticals in Appetite Regulation: Exploring emerging gut peptides and their pharmacological prospects. Pharmacol Res Perspect 12(4): e1243.
4. Fosgerau K and Hoffmann T (2015) Peptide therapeutics: current status and future directions. Drug Discov Today 20(1): 122-128.
5. Lau JL and Dunn MK (2018) Therapeutic peptides: Historical perspectives, current development trends, and future directions. Bioorg Med Chem 26(10): 2700-2707.
6. Otvos L (2008) Peptide-based drug design: here and now. Methods Mol Biol Clifton NJ 494: 1-8.
7. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, et al (2021) A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med 384(12): 1113-1124.
8. Oliveira de Souza C, Sun X and Oh D (2021) Metabolic Functions of G Protein-Coupled Receptors and β-Arrestin-Mediated Signaling Pathways in the Pathophysiology of Type 2 Diabetes and Obesity. Front Endocrinol 12: 715877.
9. Nauck MA, Quast DR, Wefers J and Meier JJ (2021) GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab 46: 101102.
10. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, et al (2021)

Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 384(11): 989-1002.

11. Jones B (2022) The therapeutic potential of GLP-1 receptor biased agonism. Br J Pharmacol 179(4): 492-510.
12. Badilli U and Inal O (2025) Current Approaches in Cosmeceuticals: Peptides, Biotics and Marine Biopolymers. Polymers 17(6): 798.
13. Agoni C, Fernández-Díaz R, Timmons PB, Adelfio A, Gómez H, et al (2025) Molecular Modelling in Bioactive Peptide Discovery and Characterisation. Biomolecules 15(4): 524.
14. Fabbri E, Zoli M, Gonzalez-Freire M, Salive ME, Studenski SA, et al (2015) Aging and Multimorbidity: New Tasks, Priorities, and Frontiers for Integrated Gerontological and Clinical Research. J Am Med Dir Assoc 16(8): 640-647.
15. Grand View Research. Peptide Therapeutics Market Size, Share & Trends Analysis Report By Application, By Type (Innovative, Generic), By Type of Manufacturer (Inhouse, Outsourced), By Route Of Administration, By Synthesis Technology, By Region, And Segment Forecasts.
16. Behrendt R, White P and Offer J (2016) Advances in Fmoc solid-phase peptide synthesis. J Pept Sci Off Publ Eur Pept Soc 22(1): 4-27.
17. Mijalis AJ, Thomas DA, Simon MD, Adamo A, Beaumont R, et al (2017) A fully automated flow-based approach for accelerated peptide synthesis. Nat Chem Biol 13(5): 464-466.
18. Isidro-Llobet A, Kenworthy MN, Mukherjee S, Kopach ME, Wegner K, et al (2019) Sustainability Challenges in Peptide Synthesis and Purification: From R&D to Production. J Org Chem 84(8): 4615-4628.
19. El-Faham A and Albericio F (2011) Peptide coupling reagents, more than a letter soup. Chem Rev 111(11): 6557-6602.
20. Hussein MA, Al-Ameed K, Almansori AK and Owaid NJ (2024) Efficient amide bond formation via tropylium ion organocatalysis. RSC Adv 14(46): 34428-34434.
21. Kekessie I, Wegner K, Martinez I, Kopach ME, White TD, et al (2024) Process Mass Intensity (PMI): A Holistic Analysis of Current Peptide Manufacturing Processes Informs Sustainability in Peptide Synthesis. J Org Chem 89(7): 4261-4282.
22. Chetty LC, Kruger HG, Arvidsson PI, Naicker T and Govender T (2024) Investigating the efficacy of green solvents and solvent-free conditions in hydrogen-bonding mediated organocatalyzed model reactions. RSC Adv 14(12): 7992-7998.
23. European Chemicals Agency (ECHA). DMF and DCM Classification and Restrictions. Published online 2025.
24. Tobiszewski M, Marć M, Gałuszka A and Namieśnik J (2015) Green Chemistry Metrics with Special Reference to Green Analytical Chemistry. Mol Basel Switz 20(6): 10928-10946.
25. Merk D, Friedrich L, Grisoni F and Schneider G (2018) De Novo Design of Bioactive Small Molecules by Artificial Intelligence. Mol Inform 37(1-2): 1700153.
26. Nielsen DS, Shepherd NE, Xu W, Lucke AJ, Stoermer MJ, et al (2017) Orally Absorbed Cyclic Peptides. Chem Rev 117(12): 8094-8128.
27. Mohapatra S, Hartrampf N, Poskus M, Loas A, Gómez-Bombarelli R, et al (2020) Deep Learning for Prediction and Optimization of Fast-Flow Peptide Synthesis. ACS Cent Sci 6(12): 2277-2286.
28. Mohapatra S, Hartrampf N, Poskus M, Loas A, Gómez-Bombarelli R, et al (2020) Deep Learning for Prediction and Optimization of Fast-Flow Peptide Synthesis. ACS Cent Sci 6(12): 2277-2286.
29. Hartrampf N, Saebi A, Poskus M, Gates ZP, Callahan AJ, et al (2020) Synthesis of proteins by automated flow chemistry. Science 368(6494): 980-987.
30. Hein JE (2021) Machine learning made easy for optimizing chemical reactions. Nature 590(7844): 40-41.
31. Merrifield RB (1969) Solid-phase peptide synthesis. Adv Enzymol Relat Areas Mol Biol 32: 221-296.
32. Fields GB and Fields GB (2002) Introduction to peptide synthesis. Curr Protoc Protein Sci Chapter 18 (18): 1-18.
33. Góngora-Benítez M, Tulla-Puche J and Albericio F (2014) Multifaceted roles of disulfide bonds. Peptides as therapeutics. Chem Rev 114(2): 901-926.
34. Varnava KG and Sarojini V (2019) Making Solid-Phase Peptide Synthesis Greener: A Review of the Literature. Chem Asian J 14(8): 1088-1097.
35. Collins JM, Porter KA, Singh SK and Vanier GS (2014) High-efficiency solid phase peptide synthesis (HE-SPPS). Org Lett 16(3): 940-943.
36. Subirós-Funosas R, Prohens R, Barbas R, El-Faham A and Albericio F (2009) Oxyma: an efficient additive for peptide synthesis to replace the benzotriazole-based HOBt and HOAt with a lower risk of explosion. Chem Weinh Bergstr Ger 15(37): 9394-9403.
37. Rossino G, Marchese E, Galli G, Verde F, Finizio M, et al (2023) Peptides as Therapeutic Agents: Challenges and Opportunities in the Green Transition Era. Mol Basel Switz 28(20): 7165.
38. Wang P, Zhang Y, Hu J and Tan BK (2024) Bioactive Peptides from Marine Organisms. Protein Pept Lett 31(8): 569-585.
39. Trojanowicz M (2020) Flow Chemistry in Contemporary Chemical Sciences: A Real Variety of Its Applications. Mol Basel Switz 25(6): 1434.
40. Jaradat DMM (2018) Thirteen decades of peptide synthesis: key developments in solid phase peptide synthesis and amide bond formation utilized in peptide ligation. Amino Acids 50(1): 39-68.
41. (2021) US Environmental Protection Agency. Technical Fact Sheet—N,N-Dimethylformamide (DMF).
42. Kent SBH (2025) Fundamental Aspects of SPPS and Green Chemical Peptide Synthesis. J Pept Sci Off Publ Eur Pept Soc 31(5): e70013.
43. Loffet A (2002) Peptides as drugs: is there a market? J Pept Sci Off Publ Eur Pept Soc 8(1): 1-7.
44. Behrendt R, White P and Offer J (2016) Advances in Fmoc solid-phase peptide synthesis. J Pept Sci Off Publ Eur Pept Soc 22(1): 4-27.
45. Lam AK, Zhang J, Frabutt D, Mulcrone PL, Li L, et al (2022) Fast and high-throughput LC-MS characterization, and peptide mapping of engineered AAV capsids using LC-MS/MS. Mol Ther Methods Clin Dev 27: 185-194.
46. Yang F, Zhang J, Buettner A, Vosika E, Sadek M, et al (2023) Mass spectrometry-based multi-attribute method in protein therapeutics product quality monitoring and quality control. mAbs 15(1): 2197668.
47. Greener JG, Kandathil SM, Moffat L and Jones DT (2022) A guide to machine learning for biologists. Nat Rev Mol Cell Biol 23(1): 40-55.
48. Schneider P, Walters WP, Plowright AT, Sieroka N, Listgarten J, et al (2020) Rethinking drug design in the artificial intelligence era. Nat Rev Drug Discov 19(5): 353-364.
49. Ferruz N, Schmidt S and Höcker B (2022) ProtGPT2 is a deep unsupervised language model for protein design. Nat Commun 13(1): 4348.
50. Mohapatra S, Hartrampf N, Poskus M, Loas A, Gómez-Bombarelli R, et al (2020) Deep Learning for Prediction and Optimization of Fast-Flow Peptide Synthesis. ACS Cent Sci 6(12): 2277-2286.
51. Coley CW, Eyke NS and Jensen KF (2020) Autonomous Discovery in the Chemical Sciences Part I: Progress. Angew Chem Int Ed Engl 59(51): 22858-22893.
52. Veeramanoharan A and Kim SC (2024) A comprehensive review on sustainable surfactants from CNSL: chemistry, key applications and

research perspectives. RSC Adv 14(35): 25429-25471.

53. (2025) Markets and Markets. Peptide Therapeutics Market by Type, Route of Administration, Synthesis Technology, Application - Global Forecast to 2035.
54. (2025) Mordor Intelligence. Asia-Pacific Peptide Therapeutics Market – Growth, Trends, COVID-19 Impact, and Forecasts (2023–2028).
55. (2025) FDA. Approved Drug Products: Tirzepatide, Setmelanotide, and others.
56. Singh S and Patel S (2023) Outsourcing trends in peptide manufacturing. BioProcess Int 21(7): 44-51.
57. Almeida JR (2024) The Century-Long Journey of Peptide-Based Drugs. Antibiot Basel Switz 13(3): 196.
58. (2016) EMA. Guideline on the quality of synthetic peptide APIs.
59. (2012) ICH. Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities).
60. (2022) FDA. CDER 505(b)(2) Application Guidance for Industry.
61. Company Pipeline and AI Platform Overview. Cemvita Factory.
62. Proprietary technologies. C4X Discovery.
63. Evonik Industries. Peptide CDMO Capabilities. Evonik Health Care.
64. Digital transformation and manufacturing. Novo Nordisk Annual Report.
65. Center for Sustainable Peptide Chemistry. NIH Chemical Methodologies and Library Development Center. 2025.
66. MIT MLMD Program. Machine Learning for Molecular Design.
67. CHEM21 Consortium. Green Chemistry Manufacturing Technologies.
68. Peptilogics. The PEP-GPT Platform. Company whitepaper.
69. Generate:Biomedicines. AI-Driven Therapeutic Design. Published online 2025.
70. Nurix Therapeutics and Insitro Collaboration Announcement.