



<https://dx.doi.org/10.4314/hpjsmt.v7i1.22>

Integrative Omics and Systems Biology Approaches in Peptide-Based Therapeutic Discovery: A review

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Abstract

Integrative omics has been a useful process for identifying driver genes, as well as molecular signatures of cancers. In particular, such analyses have indicated prognoses, as well as targeted therapies. Advances in omics technologies such as genomics, transcriptomics, proteomics and metabolomics have begun to enable personalized medicine at an extraordinarily detailed molecular level. However, each technology individually cannot capture the entire biological complexity of most human diseases. Integration of multiple technologies has emerged as an approach to provide a more comprehensive view of biology and diseases. Biological systems are formed by an interplay of interactions between a variety of biomolecules, such as DNA, RNA, proteins, and metabolites that act at numerous layers. Therapeutic discovery aims at identifying effective agents to treat diseases by targeting specific biomolecules or pathways involved in pathogenesis. This review reveal how integration of omics technologies and systems biology used in peptide-based therapeutic discovery.

Key words: Diseases, Therapeutic, Discovery, Omics.

Introduction

Integrative omics has been a useful process for identifying driver genes, as well as molecular signatures of cancers. In particular, such analyses have indicated prognoses, as well as targeted therapies. Advances in omics technologies such as genomics, transcriptomics, proteomics and metabolomics have begun to enable personalized medicine at an extraordinarily detailed molecular level. Individually, these technologies have contributed medical advances that have begun to enter clinical practice. However, each technology individually cannot capture the entire biological complexity of most human diseases. Integration of multiple technologies has emerged as an approach to provide a more comprehensive view of biology and diseases.

Understanding the complexity of life requires more than just studying individual genes or proteins in isolation. Biological systems are formed by an interplay of interactions between a variety of biomolecules, such as DNA, RNA, proteins, and metabolites that act at numerous



layers. Though classical single-omics methodologies give us a rich amount of insight, it frequently fails to present the complete picture. By contrast, multi-omics integration-driven systems biology offers a broader understanding of how cells, tissues, and organisms are dynamic and interconnected networks.

Genomics, transcriptomics, proteomics, and metabolomics each explore a different layer of biology our genes, how those genes are expressed, the proteins they produce, and the metabolites that reflect cellular activity (Hu et al., 2021; Kant et al., 2025a, 2025b). When used together, these “omics” approaches give a much richer and more complete picture of how life works. Advances in high-throughput technologies now allow scientists to study all these layers at once, shifting biology from a narrow gene-focused view to a multidimensional science that is driving progress in personalized medicine, biotechnology, and synthetic biology. This revolution enables scientists to approach biological complexity in a manner previously unimaginable. Rather than being concerned with individual molecules, present-day systems biology adopts a multi-omics approach to explore the complex regulatory mechanisms controlling disease and health (Mohr et al., 2024).

Conjoining information from multiple layers of omics holds significant benefits. It deciphers gene-regulatory networks, identifies disease mechanisms, predicts robust biomarkers, and accelerates progress in precision medicine and synthetic biology. Therapeutic discovery aims at identifying effective agents to treat diseases by targeting specific biomolecules or pathways involved in pathogenesis. The field has evolved from small molecule drugs to include biologics like peptides, driven by advances in molecular biology and drug design. Peptides, due to their high specificity and biocompatibility, offer promising alternatives in modern drug development (Vrbnjak & Sewduth, 2024; Wang et al., 2022).

Omics Technologies: Genomics, Transcriptomics, Proteomics, Metabolomics

These are key omics layers providing complementary molecular insights:

- Genomics: Studies the complete DNA sequence, identifying genetic variations and mutations linked to diseases.
- Transcriptomics: Analyzes RNA transcripts to understand gene expression patterns in health and disease.
- Proteomics: Investigates proteins, their abundance, modifications, and interactions crucial for understanding functional outcomes.
- Metabolomics: Profiles small metabolites reflecting cellular metabolic status and phenotype.

Integrating these layers offers a multi-dimensional view of biological processes influencing therapeutic targets and mechanisms.

Importance of Peptide-Based Therapeutics

Peptides are short chains of amino acids that combine many advantages such as selectivity, potency, and low toxicity. They can specifically modulate protein-protein interactions, serve as drug delivery vectors, and overcome limitations of traditional small molecules. Recent innovations including stabilized cyclic peptides and cell-penetrating peptides have significantly expanded their therapeutic potential across various diseases including cancer, infections, and chronic conditions (Sharma et al., 2025; Wang et al., 2022).



Scope and Objectives of the Review

This review focuses on the integration of omics technologies and systems biology for advancing peptide-based therapeutic discovery.

The aims is to:

- Provide an overview of integrative omics and systems biology methods.
- Highlight their roles in improving peptide target identification and validation.
- Showcase recent advances in peptide drug discovery enabled by these approaches.
- Discuss challenges, opportunities, and future perspectives in this emerging interdisciplinary field.

Overview of Integrative Omics and Systems Biology Methods

Integrative omics (or multi-omics) combines different biological data layers—like genomics, transcriptomics, proteomics, and metabolomics into a single, comprehensive analysis. Instead of studying a biological system in isolation, it provides a complete, systems-level view of how DNA, RNA, proteins, and molecules interact to cause health or disease. Integrative omics combines data from multiple omics sources to yield a holistic understanding of disease biology and therapeutic responses. This approach uncovers relationships between different biomolecules and pathways that single omics alone may miss. It enables improved biomarker discovery, patient stratification, and identification of novel drug targets by leveraging cross-omics data integration with computational modeling (Athieniti & Spyrou, 2023).

Systems biology uses computational and mathematical models to characterize complex biological systems and their dynamics by integrating multi-omics data. Tools include network analysis, pathway modeling, and machine learning to simulate interactions within cells or tissues. This enables the identification of critical regulatory nodes and mechanisms, guiding drug discovery and precision medicine, especially in complex diseases (Fawaz et al., 2023; Yue & Dutta, 2022).

Role of Omics and Systems Biology in Peptide Design

Integrative omics identifies relevant disease pathways and molecular targets for peptide intervention. Systems biology models the complex interactions and predicts peptide effects on biological networks. Together, they guide rational peptide design, optimize therapeutic mechanisms, and enable biomarker discovery for monitoring treatment response (Yue & Dutta, 2022).

This synthesis integrates the most current concepts and advances to explain the foundational science and applied methodologies in peptide-based therapeutic discovery through integrative omics and systems biology (Wang et al., 2022).



Biomarker Discovery for Peptide Therapies, Characteristics and Advantages of Peptide Drugs

Integrative omics technologies enable the identification of molecular biomarkers that correlate with disease states and therapeutic responses. By combining genomics, proteomics, and metabolomics data, researchers can pinpoint specific peptides or peptide-modulated pathways as biomarkers to monitor drug efficacy or predict patient response. This multi-layered data integration enhances the precision of biomarker discovery, facilitating personalized peptide therapies (Zheng et al., 2025).

Peptides are short amino acid chains that offer high target specificity, potency, and safety with low toxicity. They are versatile, able to modulate protein-protein interactions, and can penetrate cells to reach intracellular targets. Advances such as cyclic and stapled peptides improve stability and bioavailability, enhancing their therapeutic promise (Sharma et al., 2025; Wang et al., 2022).

Recent Advances in High-Throughput Omics Techniques

Recent advances include bulk and single-cell sequencing, mass spectrometry-based proteomics and metabolomics, and multi-omics platforms enabling simultaneous profiling of multiple molecular layers from the same sample. These have increased resolution, throughput, and accuracy, permitting more detailed systems biology studies and personalized therapeutic insights (Li et al., 2021; Yadav et al., 2022).

Challenges in Peptide Therapeutic Development

Challenges include poor metabolic stability, short half-life, potential immunogenicity, and difficulties in delivery. Overcoming these requires innovative design strategies and delivery systems, often informed by detailed omics and systems biology analyses to optimize efficacy and minimize side effects (Sharma et al., 2025; Wang et al., 2022).

Systems Biology for Mechanism of Action Elucidation

Systems biology leverages computational modeling and network analysis to unravel the complex biological interactions modulated by peptide drugs. By integrating transcriptomic, proteomic, and metabolomic profiles, it can reveal how peptides affect cellular pathways and identify key regulatory nodes involved in their therapeutic effects. This approach has been applied to understand antimicrobial peptide functions, immune modulation, and cellular signaling disruptions, thereby informing rational drug development and optimization (Ma et al., 2024; Zheng et al., 2025).

Predictive Modeling of Peptide Therapeutic Effects

Predictive systems biology models, including machine learning and network simulations, enable forecasting of peptide drug behavior in biological systems. These models simulate peptide interactions with targets and downstream biological effects, allowing prediction of efficacy, off-target impacts, and toxicity. Such *in silico* frameworks accelerate peptide optimization and



reduce reliance on trial-and-error experimental methods, streamlining peptide drug development pipelines (Niarakis et al., 2024).

Machine Learning, AI in Integrative Omics and Software for Peptide Therapeutic Discovery

Machine learning (ML) and artificial intelligence (AI) have become crucial in managing, analyzing, and interpreting the enormous data generated by omics technologies. AI-driven models enable accurate prediction of peptide structures, functions, and interactions, overcoming challenges of peptide flexibility and high dimensionality of omics data. Deep learning, neural networks, and generative models are particularly transformative in designing novel peptides and optimizing their properties rapidly compared to traditional methods (Lin et al., 2025; Nissan et al., 2024; Zhang et al., 2025a). Advanced computational platforms integrate experimental and *in silico* data for peptide drug discovery. Tools like molecular docking software, molecular dynamics simulation packages, and peptide-specific design frameworks enable virtual screening of large peptide libraries and refinement of candidates. Recent developments include AI-powered peptide generation models (e.g., PepCCD), specialized databases cataloging peptide sequences and activities, and intelligent hit discovery platforms that synergize wet-lab and computational screening for accelerated development (Bai and Bing, 2025; Zhang et al., 2025b).

Advances in Spatial and Single-Cell Omics

Spatial omics and single-cell technologies are revolutionizing the resolution at which biological systems are studied. They provide critical insights into tissue and cellular heterogeneity, localized peptide interactions, and dynamic cellular responses to peptide therapeutics. These techniques allow precise mapping of peptide targets and effects in complex microenvironments, enhancing the understanding of therapeutic mechanisms and enabling more effective peptide design and delivery strategies (Li et al., 2021; Yadav et al., 2022). This comprehensive landscape shows that the fusion of AI, computational tools, and cutting-edge omics technologies is rapidly advancing peptide-based therapeutic discovery by enabling sophisticated modeling, personalized design, and high-throughput validation of peptide drugs (Nissan et al., 2024).

Successful Peptide Therapeutic Discoveries Using Integrative Approaches

Integrative omics combined with systems biology has enabled breakthroughs in peptide therapeutic discovery by identifying novel targets, optimizing peptide design, and enhancing delivery. Rational peptide design strategies, guided by multi-omics data and computational modeling, have improved specificity, stability, and efficacy of peptides. For instance, bioconjugation techniques enhance stability and targeting of peptide drugs, while AI-driven approaches accelerate hit discovery and optimization, broadening the spectrum of treatable diseases (Bisht et al., 2024; Zhang et al., 2025b). For example peptide-based therapeutics targeting cardiovascular diseases benefit from omics-driven target identification and systems-level pathway analysis. Multi-omics profiling elucidates key molecular players in cardiac conditions, guiding the development of peptide modulators that affect blood pressure regulation, lipid metabolism, and heart muscle function. These approaches facilitate personalized therapeutics addressing complex cardiovascular pathologies (Arora et al., 2023). Integrative omics is also applied in oncology study e.g. in cancer research, phage display technology



combined with integrative omics has been instrumental in discovering personalized peptide therapeutics targeting neoantigens and tumor-specific proteins. Systems biology models of tumor microenvironments enable understanding peptide interactions with cancer pathways, helping to overcome tumor heterogeneity and resistance mechanisms. Computational pipelines integrating multi-omics data expedite the identification of anticancer peptides with improved cytotoxicity and selectivity (Wu et al., 2025).

Infectious Disease Research: Antimicrobial peptides have emerged as promising alternatives against antibiotic-resistant pathogens. Integrative omics interventions reveal microbial vulnerabilities and host-pathogen interactions, allowing design of peptides with enhanced antimicrobial activity and reduced resistance potential. Systems biology models elucidate the immune-modulatory effects of these peptides, leading to innovative therapies for difficult-to-treat infections (Ma et al., 2024). This collection of case studies demonstrates how integrative omics and systems biology synergize to advance peptide therapeutics across major medical fields, driving precision medicine and novel therapeutic modalities (Bisht et al., 2024).

Current Limitations in Data Integration and Interpretation

Integrating multi-omics data remains complex due to heterogeneity, high dimensionality, and variable data quality across different omics platforms. Missing data, batch effects, and collinearity among datasets complicate analysis and can reduce robustness. Functional annotation of peptides is particularly challenging because of their short length, structural flexibility, and insufficient sequence homology, leading to many false positives in predictions. Moreover, peptide stability, bioavailability, and targeted delivery pose significant hurdles in peptide therapeutic development. Regulatory compliance and scalable manufacturing of peptide drugs also constitute major bottlenecks (Morabito et al., 2025; Nakmode et al., 2025).

Emerging Trends and Opportunities in Peptide Therapeutic Discovery

Advances in long-acting peptide formulations, bioconjugation, and nanotechnology are improving pharmacokinetics and delivery efficacy. AI and machine learning models are increasingly sophisticated in predicting peptide structures, functions, and interactions, enabling rational design and rapid optimization. Spatial and single-cell omics approaches offer unprecedented resolution of peptide-target interactions in tissue microenvironments. The growing focus on ribosomally synthesized and post-translationally modified peptides (RiPPs) provides avenues for developing complex, stable peptide therapeutics. Integrative omics combined with systems biology accelerates biomarker discovery and personalized medicine applications, enhancing clinical translation prospects (Patel et al., 2025; Pfeiffer et al., 2024).

Future Directions for Research and Clinical Translation

Future research is needed to develop standardized, robust computational pipelines for multi-omics integration tailored to peptide drug discovery challenges. Improving peptide stability, reducing immunogenicity, and enhancing delivery through innovative carriers remain priorities. Further exploration of AI-driven peptide design and high-throughput screening platforms can



shorten development timelines. Enhanced clinical trials incorporating multi-omics biomarker monitoring will improve therapeutic effectiveness and patient stratification. Regulatory frameworks will need to evolve to accommodate complex peptide therapeutics and associated diagnostics.

Discussion

Individually, each of these disciplines offers only a snapshot of a biological system. For example, a genetic mutation might be present, but analyzing transcriptomics and proteomics will show if that mutation is actually being expressed as a functional protein. Integrative omics uses advanced bioinformatics and machine learning to map how changes in one layer trigger cascading effects across the others.

Conclusion

Integrative omics and systems biology approaches hold transformative potential in accelerating peptide-based therapeutic discovery, enabling a deeper understanding of complex disease biology and precise therapeutic targeting. Despite significant technological and analytical challenges, ongoing advances in computational tools, delivery technologies, and omics resolution are rapidly overcoming these barriers. Continued interdisciplinary collaboration and innovation will be key to translating these approaches into safe, efficacious peptide therapies with broad clinical impact.

Recommendation

These approaches are highly recommended to decode complex diseases, identify novel drug targets, and enable precision medicine

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