Review of Supramolecular Peptide Therapeutic Strategies

Supramolecular peptide therapeutic strategies leverage the predictable, programmable noncovalent interactions between peptide molecules to enable their spontaneous assembly into nanoscale aggregates or materials with specific structures and functions under physiological conditions. This approach represents a cutting-edge field in disease treatment. The core of this strategy lies in transcending the static "lock-and-key" binding model of traditional drugs. Instead, it employs peptides as "intelligent building blocks" that dynamically assemble into higher-order functional structures within the body, enabling more precise spatiotemporal control over the therapeutic process. This approach is delivering innovative solutions to medical challenges such as drug delivery, immune modulation, and tissue regeneration.

I. Core Principles and Design Fundamentals

The therapeutic potential of supramolecular peptides stems from their unique self-assembly principles and customizable biological functions.

1. Driving Forces of Noncovalent Interactions

Peptide assembly is synergistically driven by multiple weak interactions encoded by amino acid sequences, primarily including:

Hydrogen bonds: Dominate the formation of secondary structures like β-sheets or α-helices, serving as the skeletal force for many fibrous assemblies.

Hydrophobic interactions: Drive the aggregation of hydrophobic amino acid residues in water, acting as the core driving force for forming nanostructures such as micelles and vesicles.

Electrostatic interactions: Oppositely charged amino acid residues attract each other, enabling the design of pH-responsive smart systems or the complexation of peptides with therapeutic payloads like nucleic acids or proteins.

π-π stacking: Interactions between aromatic amino acid side chains enhance assembly stability and confer unique optoelectronic properties.

The reversibility and synergistic nature of these forces enable assemblies to respond to external stimuli (e.g., pH, enzymes, temperature) by undergoing assembly, disassembly, or conformational changes.

2. Modular Functional Design

Therapeutic peptide sequences are typically engineered to incorporate two or more functional modules:

Assembly Module: Provides the driving force for self-assembly, often composed of repetitive sequences with distinct assembly propensity.

Therapeutic/Targeting Module: Executes specific biological functions, incorporating sequences such as cell-penetrating peptides, tumor-targeting peptides, antimicrobial peptides, or enzyme substrate peptides.

This “modular” design philosophy allows researchers to flexibly assemble supramolecular systems with diverse therapeutic functions, much like building with blocks.

II. Primary Treatment Strategies and Applications

Based on the aforementioned principles, supramolecular peptide therapeutic strategies have primarily evolved along the following pathways.

1. Targeted Drug Delivery and Controlled Release

This represents the most extensively studied application to date. Supramolecular peptide nanocarriers (e.g., nanofibers, micelles, vesicles) can efficiently encapsulate chemotherapeutic agents, nucleic acids, or proteins.

Passive and Active Targeting: Enhanced permeation and retention effects due to nanoscale dimensions enable passive targeting of pathological tissues such as tumors. Integrating targeting modules onto assembled peptides enables active targeting.

Stimulus-responsive release: Designing peptide sequences sensitive to tumor microenvironment signals (e.g., weak acidity, high concentrations of specific proteases). Drug carriers remain stable in circulation but disassemble or undergo structural changes upon reaching the lesion in

response to local stimuli, enabling precise drug release. This enhances therapeutic efficacy while reducing systemic toxicity.

2. Immunotherapy and Vaccine Design

Supramolecular assembly provides novel tools for regulating the immune system.

Peptide Vaccines: Fusing antigen peptides with assembly modules enables in vivo self-assembly into “nanovaccines.” These nanostructures are more readily taken up and processed by antigen-presenting cells. They can simultaneously carry adjuvant molecules, significantly enhancing immunogenicity and inducing robust humoral and cellular immune responses.

Immune Modulation: Designing immunomodulatory peptides that assemble into specific nanostructures can mimic or disrupt natural immune signaling pathways. For example, Toll-like receptor agonists assembled into fibrillar structures exhibit significantly higher potency and stability than free molecules, enabling more effective activation of innate immunity.

3. In Situ Barrier Formation and Tissue Regeneration

Leveraging the rapid hydrogel formation of peptide solutions upon injection at target sites creates temporary three-dimensional microenvironments.

Hemostasis and Physical Barrier: Injection of peptide solutions at surgical wounds or tissue injury sites rapidly forms nanofibrous gel

networks that seal wounds, absorb blood, and concentrate coagulation factors for rapid hemostasis. Simultaneously, it serves as a physical barrier to prevent tissue adhesion.

Tissue Engineering Scaffolds: Functionalized peptide hydrogels highly mimic the physical and biochemical characteristics of natural extracellular matrices, supporting cell adhesion, proliferation, and differentiation. By integrating specific bioactive sequences, they can guide directed differentiation of stem cells, promoting the repair and regeneration of diverse tissues including nerves, cartilage, and blood vessels.

4. Directly Killing Pathogens and Abnormal Cells

Certain peptides with inherent therapeutic activity can significantly enhance their efficacy through supramolecular assembly.

Antimicrobial Therapy: Aggregation on membrane surfaces is a critical step for many antimicrobial peptides to kill bacteria. Peptides engineered for self-assembly can form more ordered, stable channels or coatings on bacterial membranes, substantially improving bactericidal efficiency while reducing toxicity to host cells. This offers novel approaches to addressing antibiotic resistance.

Antitumor Therapy: Certain peptides that specifically target and disrupt tumor cell membranes can enhance their retention at tumor sites and membrane-disrupting capabilities by assembling into larger aggregates.

III. Challenges and Future Outlook

Despite promising prospects, the clinical translation of supramolecular peptide therapeutic strategies faces a series of challenges:

1. Precise prediction and control of in vivo behavior: Transitioning from controlled in vitro environments to complex in vivo settings, the assembly process is influenced by numerous physiological factors, making its kinetics, final morphology, and stability difficult to fully predict and control.

2. Long-term biosafety: Systematic evaluation is needed for the final metabolic pathways, long-term retention effects, and potential immunogenicity of these dynamically assembled nanomaterials within the body.

3. Quality control in large-scale production: Ensuring high batch-to-batch consistency for peptide APIs and formulations exhibiting complex self-assembly behavior remains a technical bottleneck in industrial manufacturing.

4. Regulatory science pathway: As novel therapeutic products exhibiting characteristics of both “drugs” and “medical devices,” their evaluation criteria and regulatory frameworks remain under exploration.

Future development will trend toward intelligent, systematic, and personalized approaches:

Computational rational design: Combining artificial intelligence and

molecular dynamics simulations to predict and optimize peptides with ideal assembly behavior and therapeutic functions from vast sequence libraries.

Multi-level, logic-responsive systems: Develop cascading supramolecular systems capable of sequentially responding to multiple biological signals, executing “detection-diagnosis-therapy” logic steps.

Dynamic and adaptive therapy: Design adaptive materials that dynamically adjust their assembly states and functions in real-time based on therapeutic progress (e.g., tumor shrinkage, inflammation resolution).

Combination therapy platforms: Construct integrated supramolecular platforms capable of simultaneously delivering multiple therapeutic modalities (e.g., chemotherapy, immunotherapy, gene therapy).

IV.Conclusion

Supramolecular peptide therapeutic strategies represent a paradigm shift from static molecular drugs to dynamic “smart” therapeutic systems. They ingeniously leverage peptides' inherent biocompatibility and programmability by encoding noncovalent interaction “programs” within their sequences, guiding the precise in vivo assembly and functional execution of therapeutic nanostructures. From precision drug delivery to revolutionary vaccine design and complex tissue regeneration, this strategy demonstrates disruptive potential across multiple therapeutic domains. With deepening insights into the “sequence-assembly-function”

relationship and ongoing convergence of interdisciplinary technologies, supramolecular peptides are poised to catalyze a new generation of smarter, safer, and more efficient disease therapies, propelling biomedical treatment into a new era driven by molecular self-assembly.