

REVIEW ARTICLE

Self-assembled peptide delivery systems: Applications in tumor therapy

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Abstract

Self-assembled peptides are emerging as versatile nanocarriers for cancer therapy, benefiting from programmable sequences, biocompatibility, and dynamic supramolecular assembly. This review summarizes recent advances in the molecular design and assembly mechanisms of peptide-based nanostructures (nanospheres, nanofibers, and nanogels) formed through non-covalent interactions, such as hydrogen bonding, electrostatics, van der Waals forces, and π - π stacking. We discuss how peptide composition, secondary structure, and environmental cues (pH, enzymes, redox state, temperature, and ionic strength) govern assembly, stability, and biological performance, enabling efficient loading and targeted delivery of small-molecule drugs, nucleic acids (DNA/small interfering RNA), and peptide or protein therapeutics. Particular emphasis is placed on stimuli-responsive strategies and *in situ* assembly approaches that enable controlled drug release and, where applicable, provide imaging readouts (fluorescence, photoacoustic, and nuclear imaging) for tumor visualization, image-guided delivery, and treatment-response monitoring. Key translational challenges are also addressed, including serum stability and pharmacokinetics, immunogenicity and off-target effects, endosomal escape and delivery efficiency, scalable manufacturing and cost, controllability of release, and standardized characterization and safety evaluation. Finally, we outline future directions, including multifunctional and smart responsive peptide architectures, hybrid systems combining peptides with liposomes, polymers, or viral vectors, and rational design rules linking assembly state to *in vivo* fate. Collectively, these advances are expected to accelerate the clinical translation of self-assembled peptide delivery systems for precision cancer therapy.

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1. Introduction

Self-assembled peptides are a class of biomaterials with unique structures and functions that have garnered widespread attention in the field of biomedicine, particularly in tumor therapy. Across non-covalent interactions (e.g., hydrogen bonds, van der Waals

forces, and electrostatic interactions), self-assembled peptides can spontaneously form ordered nanostructures, such as nanospheres, nanofibers, and nanogels.¹ These structures can accumulate in tumor tissues through the enhanced permeability and retention effects or active targeting, making them promising carriers for therapeutic applications, with the potential to incorporate imaging modules for tumor visualization and treatment monitoring.²

In the field of drug delivery and tumor theranostics, self-assembled peptides offer several significant advantages. First, their good biocompatibility and biodegradability allow safe drug release within the body, reducing toxicity to normal tissues.³ Moreover, through molecular-level design, these peptides can achieve not only efficient drug loading and targeted delivery to tumor sites but also carry imaging agents for real-time visualization of tumors, thereby improving tumor localization and treatment guidance, and ultimately enhancing therapeutic outcomes.⁴ In addition, the flexible responsiveness of self-assembled peptides enables intelligent drug release in response to changes in the tumor microenvironment, such as pH, temperature, and enzymes, thereby improving therapeutic efficacy while minimizing side effects (Figure 1).⁵

Despite these advantages, challenges remain in the practical application of self-assembled peptides for tumor treatment. For example, the stability and metabolic behavior of peptide assemblies *in vivo* require further optimization to extend their circulation time and enhance tumor-specific accumulation.⁶ Immunogenicity and potential off-target effects also need to be carefully addressed. Therefore, in-depth studies of the structural and functional properties of self-assembled peptides, along with the optimization of their therapeutic performance, are essential to advance their clinical translation in oncology.

To provide a balanced and representative overview of this rapidly evolving field, we conducted a comprehensive literature search and selection process. Specifically, PubMed, Web of Science Core Collection, and Scopus were searched using combinations of keywords related to peptide self-assembly (e.g., “self-assembled peptide,” “peptide self-assembly,” “peptide amphiphile,” and “*in situ* self-assembly”) together with cancer-related terms (e.g., “tumor,” “cancer,” and “neoplasm”) and application-related terms (e.g., “imaging,” “therapy,” “image-guided,” and “treatment monitoring”). Only peer-reviewed articles published in English were considered. We prioritized original research articles describing self-assembled or self-assembling peptide systems for tumor therapy and/or imaging-guided delivery and treatment-response monitoring, including the delivery of small molecules, nucleic acids, and peptides/proteins,

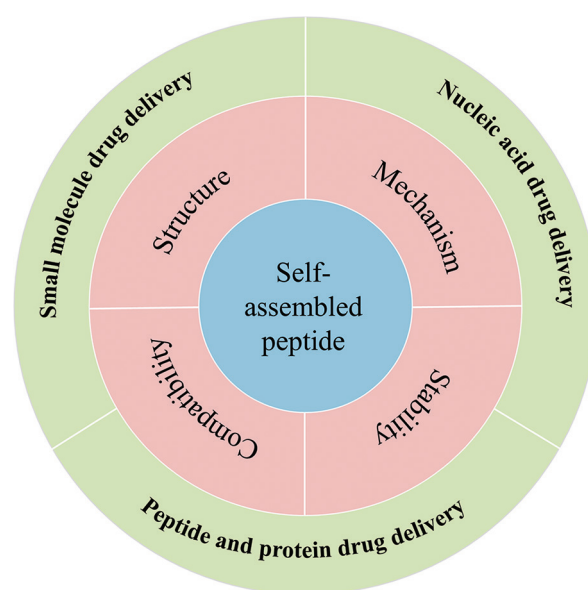


Figure 1. Self-assembled peptides as a versatile delivery system for tumor therapy. Image created by the authors.

with clear mechanistic insights and/or *in vivo* validation. In addition, key studies were identified through manual screening of reference lists from relevant articles and recent reviews. The studies discussed in this review were ultimately selected to represent major design strategies, mechanistic principles, and translational challenges in the field.

2. Structure and characteristics of self-assembled peptides

2.1. Molecular structure of self-assembled peptides

The molecular structure of self-assembled peptides is the foundation of their self-assembly behavior and functionality. Peptides are composed of amino acids linked by peptide bonds, and the types, sequences, and numbers of amino acids determine their physicochemical properties and biological functions. During the self-assembly process, non-covalent interactions between peptide molecules play a crucial role. These interactions include hydrogen bonds, electrostatic interactions, van der Waals forces, and π - π stacking interactions.⁷ These interactions enable peptide molecules to spontaneously organize into ordered structures, such as nanospheres, nanofibers, and nanogels.

The nanostructures formed by self-assembled peptides possess unique physicochemical properties and biological functions. For example, nanosphere structures have a large specific surface area and excellent drug loading capacity, making them suitable for drug delivery and biosensing applications.⁸ Nanofiber structures, on the other hand, have high mechanical strength and biocompatibility,

making them ideal for tissue engineering and regenerative medicine.⁹ Nanogel structures exhibit excellent water retention and biodegradability, making them useful for controlled drug release and cell culture.¹⁰

2.2. Assembly mechanism of self-assembled peptides

During the self-assembly process, peptide molecules first form nucleation sites through non-covalent interactions. These nuclei then gradually grow into larger nanostructures. This process is influenced by various factors, such as the peptide concentration, temperature, pH, and ionic strength.¹¹ For example, increasing the concentration of peptides can promote the self-assembly process, while lowering the temperature or altering pH may inhibit self-assembly.^{12,13} In addition, certain metal ions or small-molecule compounds can act as catalysts or inhibitors, affecting the self-assembly behavior of peptides.^{14,15}

Because peptide self-assembly is dynamic, it can be controlled by modulating the molecular structure of the peptides or external environmental conditions. For example, by altering the amino acid composition of the peptide sequence, the hydrophilicity or hydrophobicity of the peptide can be tuned, which in turn affects its self-assembly behavior and the nanostructures formed.¹⁶ Moreover, the secondary structure of the peptide, such as α -helix or β -sheet, also plays a crucial role in its self-assembly behavior. Peptides with α -helix structures typically exhibit higher stability and biological activity, while those with β -sheet structures are more likely to form fibrous structures.^{17,18}

In addition to experimental characterization, computational approaches, such as molecular simulations and quantum chemical calculations, can provide atomistic insights into the non-covalent interactions and secondary-structure evolution that drive peptide self-assembly. For example, Ilawe *et al.*¹⁹ combined vibrational spectroscopy with large-scale density functional theory calculations to probe the aggregation of low-molecular-weight peptides and to assess the role of canonical cross- β -sheet structures in fibril/hydrogel formation, offering mechanistic guidance for the rational design of self-assembled peptide nanomaterials.

2.3. Biocompatibility of self-assembled peptides

The biocompatibility of self-assembled peptide nanomaterials is primarily reflected in their low toxicity, low immunogenicity, and good biodegradability in biological systems.²⁰ As peptides are composed of amino acids, they possess natural biocompatibility, which reduces immune responses and inflammation when applied *in vivo*. In terms of toxicity, peptide nanomaterials generally

exhibit low cytotoxicity. For example, self-assembled peptide nanofibers can support normal cell growth and differentiation in cell cultures without causing significant cytotoxic reactions.²¹ Furthermore, surface modifications, such as the incorporation of hydrophilic groups, such as polyethylene glycol (PEG), can further reduce their toxicity, decrease non-specific adsorption and clearance of the nanomaterials in the body, and thereby enhance their biocompatibility.²²

In terms of immunogenicity, peptide-based nanomaterials have low immunogenicity, which is primarily attributed to their structure and composition. Self-assembled peptide nanogels, when injected *in vivo*, do not induce significant inflammation or immune rejection.^{2,23} By designing peptides with specific sequences, such as using naturally occurring amino acid sequences or modified sequences, the recognition and attack by the immune system can be further reduced, lowering immunogenicity.²⁴ Regarding biodegradability, the degradation rate of peptide nanomaterials *in vivo* can be controlled by adjusting their composition and structure. For example, by altering the amino acid composition and sequence of peptides, nanomaterials can be designed to degrade over a specific period, reducing accumulation and potential toxicity in the body.²⁵ Moreover, their degradation products are typically small-molecule amino acids, which can be metabolized by cells, further enhancing biocompatibility.²⁶

2.4. Stability of self-assembled peptides

The stability of self-assembled peptide nanomaterials refers to their ability to maintain structure and function in physiological environments, which is crucial for the effective delivery and therapeutic outcomes of nanomaterials *in vivo*.²⁷ In terms of chemical stability, peptide nanomaterials are generally tolerant to changes in pH, temperature, and ionic strength.²⁸ Studies have shown that self-assembled peptide nanomaterials can maintain stable structure and function at physiological pH (7.4) and body temperature (37°C).^{28,29} Chemical stability can be further enhanced by introducing covalent crosslinks (e.g., disulfide bridges). For example, introducing disulfide bonds between peptide chains can improve the structural stability of nanomaterials and slow their degradation rate *in vivo*.³⁰

In terms of physical stability, peptide nanomaterials are primarily characterized by their dispersion and aggregation behavior *in vivo*.³¹ Studies have shown that self-assembled peptide nanomaterials can maintain excellent dispersion in physiological environments and are less prone to aggregation. By introducing hydrophilic groups (e.g., PEG) onto the surface of peptides, the

aggregation of nanomaterials *in vivo* can be reduced and physical stability improved.^{32,33} In addition, adjusting the molecular weight and chain length of peptides can further optimize their physical stability. Longer peptide chains provide more interaction sites, which enhance the stability of the nanomaterials.^{34,35}

In terms of biological stability, the stability and bioavailability of self-assembled peptide nanomaterials *in vivo* can be achieved by designing peptides with specific structures and functions. For example, designing peptides with specific secondary structures, such as α -helices or β -sheets, can enhance their stability and bioavailability in the body.³⁶ Furthermore, introducing specific bioactive groups, such as growth factor binding sites, can further improve biological stability. Self-assembled peptide nanofibers, for example, can enhance their stability and bioavailability *in vivo* by binding to growth factors, such as transforming growth factor- β 1 (TGF- β 1).³⁷

3. Applications of self-assembled peptides in tumor therapy

Self-assembled peptides exhibit extensive potential for tumor therapy due to their unique structural and functional characteristics. They can self-assemble into stable nanostructures through non-covalent interactions, enabling efficient drug loading and targeted delivery, thereby improving the bioavailability and therapeutic efficacy of drugs.

3.1. Small-molecule drug delivery

Small-molecule antitumor drugs often suffer from poor solubility, limited targeting ability, and severe off-target effects. Self-assembled peptides can form nanostructures, such as nanoparticles or nanofibers, encapsulating small-molecule drugs in a hydrophobic core, thereby improving their solubility and stability.³⁸ For example, Li *et al.*³⁹ designed nanoparticles co-assembled from glycopeptides, cationic peptides, and doxorubicin. The formulation exhibited good penetration into ocular surface cells and targeted M2 macrophages in the retina, providing an effective strategy for efficient, non-invasive drug delivery to the retina. Chen *et al.*⁴⁰ developed a nanoplatfrom, donor diallyl trisulfide (DATS)@Arg-EA-SA, through the self-assembly of guanidinated dendritic peptides (Arg-EA-SA) to encapsulate the hydrogen sulfide (H_2S) DATS. This platform can release nitric oxide and H_2S in the oral ulcer microenvironment, exhibiting potent antibacterial activity against various bacteria, with bactericidal effects comparable to penicillin, and even better inhibition against resistant strains. Moreover, it also demonstrates synergistic anti-inflammatory and analgesic effects, significantly

promoting the healing of oral ulcers and offering new directions for clinical treatment. Li *et al.*⁴¹ constructed a mixed self-assembled peptide–drug conjugate ^{MA}PDCs, by linking camptothecin or resiquimod with a tandem peptide consisting of matrix metalloproteinase-2 (MMP2)-responsive peptide and angiopep-2 (Ang2), using dithiocarbonate/urethane linkage. This conjugate, through the binding of Ang2 and low-density lipoprotein receptor-related protein 1, facilitates drug transport across the blood–brain barrier and, under the action of MMP2 and glutathione (GSH) in the glioblastoma (GBM) site, releases the drug, significantly inhibiting GBM growth. These results highlight the potential of peptide–drug conjugates as brain drug delivery systems.

In addition, Wen *et al.*⁴² designed a cisplatin prodrug, P-CyPt, that responds to alkaline phosphatase (ALP) and GSH, targeting the non-specific distribution and insufficient tumor accumulation of cisplatin chemotherapy (Figure 2A). This prodrug achieves precise delivery and release of cisplatin in tumor cells through ALP-triggered, tumor-targeted self-assembly and GSH-triggered drug release, thereby improving therapeutic efficacy and reducing side effects. In the tumor microenvironment with ALP overexpression, P-CyPt self-assembles into Pt^{IV}NPs with a size of 160 nm (Figure 2B), activating near-infrared (NIR) fluorescence and photoacoustic imaging signals (Figure 2C). After entering tumor cells, GSH triggers disassembly, releasing cisplatin and consuming GSH to enhance the anticancer effect. *In vitro* experiments showed that the IC₅₀ of P-CyPt for HeLa cells was lower than that of cisplatin and that it could penetrate deeper into tumor tissue.⁴² In HeLa tumor-bearing mice, P-CyPt significantly inhibited tumor growth and reduced nephrotoxicity, demonstrating excellent safety. Moreover, through NIR fluorescence and photoacoustic dual-modal imaging techniques, early detection and therapeutic monitoring of orthotopic liver cancer were achieved (Figure 2D–G). This strategy provides new ideas and methods for the design of stimulus-responsive prodrugs.

3.2. Nucleic acid drug delivery

Nucleic acid drugs, such as DNA and small interfering RNA (siRNA), play a critical role in tumor gene therapy by regulating the expression of cancer-related genes. However, due to their negative charge and susceptibility to nuclease degradation, these drugs face significant challenges in efficient and safe delivery. Self-assembled peptides can form stable complexes with nucleic acids through cationic modifications, protecting them from degradation and enabling efficient intracellular delivery.⁴³ For example, Cen *et al.*⁴⁴ developed a stimulus-responsive cRGD-GR9G-(LLHH)₃-based nanoparticle delivery system for

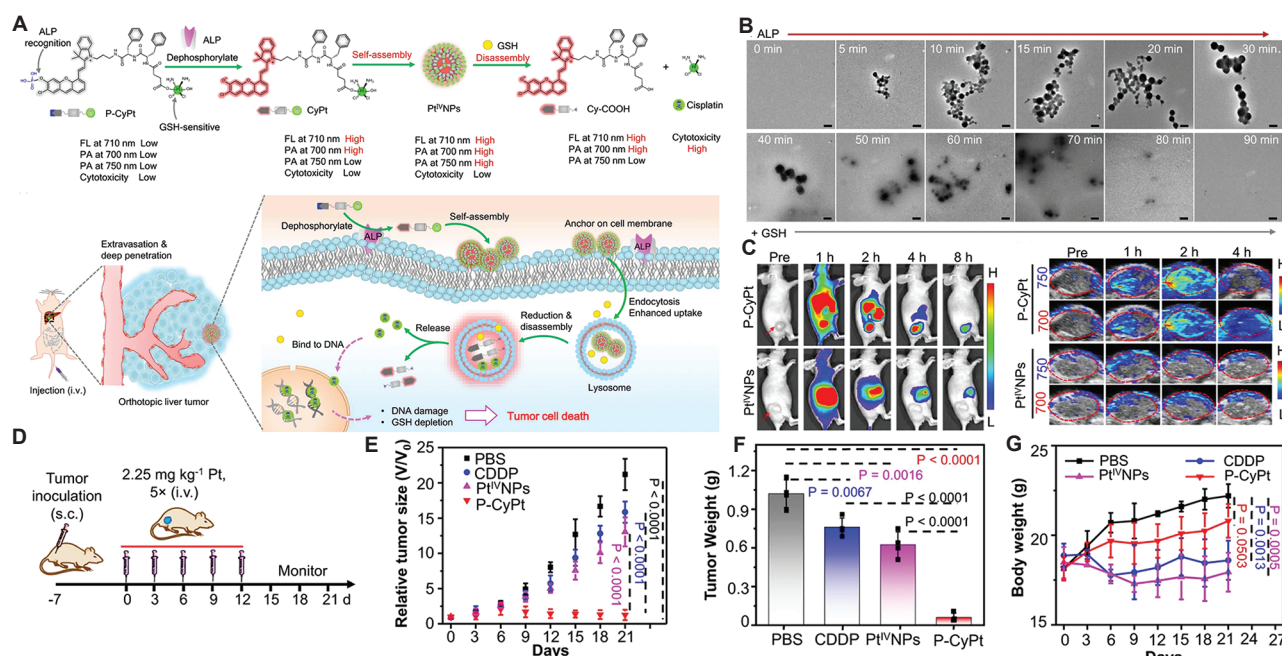


Figure 2. Stimuli-responsive cisplatin prodrug P-CyPt for alkaline phosphatase (ALP)-triggered *in situ* self-assembly and GSH-driven disassembly, enabling dual-modal (near-infrared fluorescence/photoacoustic) imaging-guided chemotherapy and treatment monitoring. (A) Schematic diagram of the design and mechanism of P-CyPt for imaging-guided tumor therapy and treatment monitoring. (B) Transmission electron microscopy analysis of ALP-triggered self-assembly and GSH-driven disassembly of P-CyPt. (C) Longitudinal fluorescence and photoacoustic imaging images of subcutaneous HeLa tumors in living mice mediated by P-CyPt. (D) Schematic diagram of the chemotherapy experimental process for subcutaneous HeLa tumors in living mice. (E) Changes in tumor volume (V/V_0) of mice treated with phosphate-buffered saline, cisplatin, Pt^{IV}NPs, or P-CyPt. (F) Comparison of average tumor weight at the end of treatment (21 days) among different groups. (G) Trends in average body weight changes of mice in different treatment groups. Images reprinted from Wen *et al.*⁴²

siRNA targeting *EGFR* and *RELA/P65* genes, aiming to inhibit the expression of these two genes associated with radioresistance in GBM. These nanoparticles can self-assemble into stable structures under physiological conditions. After cellular uptake, the (LLHH)₃ peptide responds to the acidic environment *in vivo*, disrupting the cell membrane and releasing siRNA into the tumor cell cytoplasm. *In vivo* experiments showed that this system effectively inhibited tumor growth, prolonged the survival of mice, and exhibited low toxicity, highlighting its significant potential for GBM treatment. Cao *et al.*⁴⁵ designed a multifunctional peptide that self-assembles into stable nanoparticles and co-assembles with DNA to form artificial viruses. These artificial viruses mimic the structure and function of natural viruses, enabling efficient gene transfection, especially in cancer cells, and providing a promising gene delivery vehicle for cancer therapy. Yang *et al.*⁴⁶ developed a synthetic extracellular matrix (ECM)-anchored DNA/peptide hybrid nanoagonist EaCpG. This nanoagonist targets the tumor ECM and retains long-term CpG drug activity while reducing its immunotoxicity. EaCpG not only enhances local immune stimulation in tumors but also improves the efficacy of various standard treatments. When combined with photodynamic therapy,

it can induce an immunogenic tumor phenotype and enhance antitumor immune responses, providing new ideas and strategies for combination cancer immunotherapy.

In addition, Wang *et al.*⁴⁷ designed peptide self-assembly-based virus-like nanovesicles (pVLNs) that integrate targeting sequences and enzyme-responsive sites to achieve efficient siRNA delivery and synergistic anticancer effects (Figure 3A). The pVLNs are composed of a peptide bilayer membrane encapsulating siRNA, with RGD sequences on its surface that can specifically target cancer cells (Figure 3B). The MMP-7-responsive sites trigger partial hydrolysis of the pVLNs in the tumor microenvironment, forming a membrane structure (Figure 3C and D) that promotes the escape of siRNA from lysosomes and its release (Figure 3E). Experimental results showed that the siRNA silencing efficiency of pVLNs in HeLa cells reached 92%. Across the synergistic action of peptide self-assembly and siRNA, the cancer cell death rate reached 96%, demonstrating significant anticancer activity (Figure 3F). Moreover, pVLNs exhibited low toxicity to normal cells; showing good biocompatibility and targeting ability (Figure 3G). This strategy provides a new research direction and approach for anticancer therapy.

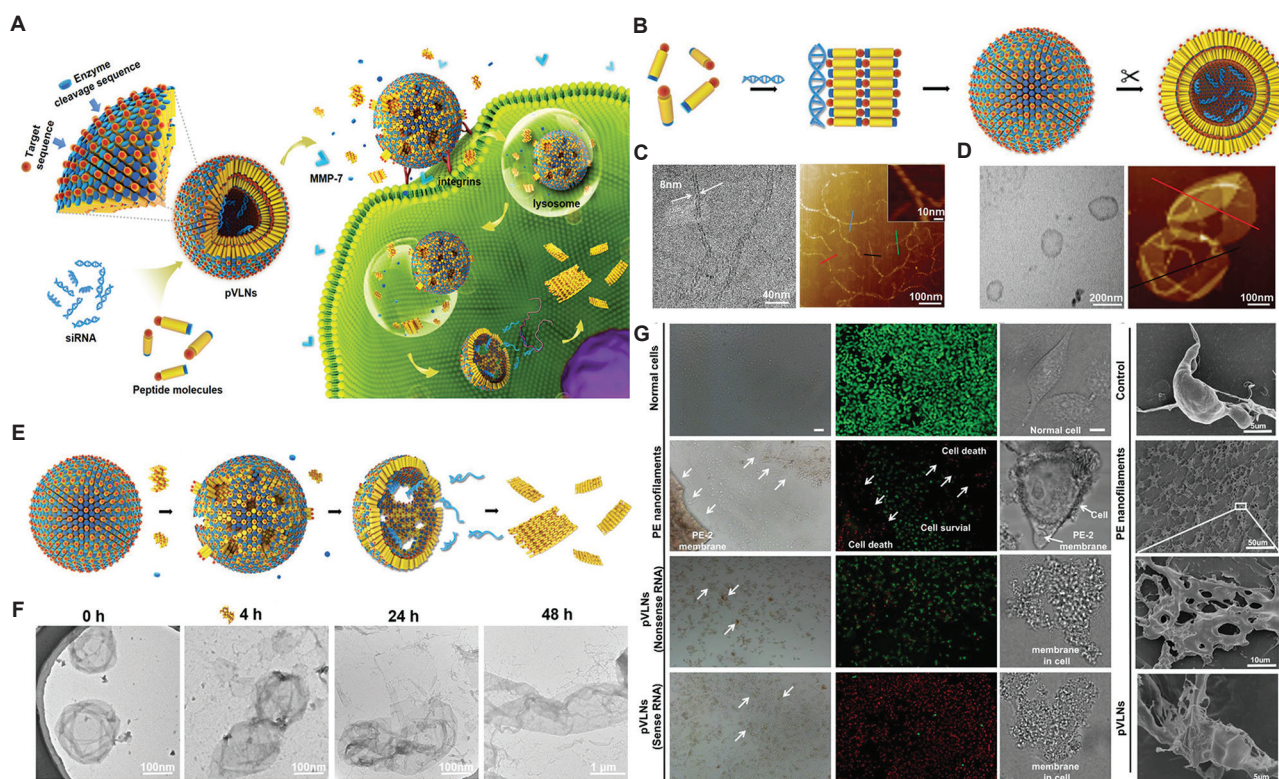


Figure 3. Matrix metalloproteinase (MMP)-7-responsive, targeted peptidyl virus-like nanovesicles (pVLNs) formed by peptide/intracellular small interfering RNA (siRNA) co-assembly to enhance siRNA delivery and synergistic anticancer efficacy. (A) Schematic diagram of the co-assembly system of pVLNs and their antitumor mechanism. (B) Schematic diagram of the co-assembly process of the enzyme-responsive peptide, PE, and siRNA to form pVLNs. (C) Cryo-transmission electron microscopy (TEM) and atomic force microscopy (AFM) images of PE nanofibers. (D) Cryo-TEM and AFM images of pVLNs. (E) Schematic diagram of the degradation process of pVLNs catalyzed by MMP-7. (F) TEM images showing the transformation of large membrane structures of pVLNs after catalysis by MMP-7 for 0, 4, 24, and 48 h. (G) Live/dead staining analysis of HeLa cells co-incubated with medium control, PE nanofibers, and pVLNs for 48 h. Images reprinted with permission from Wang *et al.*⁴⁷

3.3. Peptide and protein drug delivery

Peptide- and protein-based drugs have immense potential for the treatment of various diseases. However, their clinical application is limited by their susceptibility to enzymatic degradation and their short half-life *in vivo*.⁴⁸ Self-assembled peptides can form stable nanostructures that prolong the circulation time and stability of these drugs in the body. For example, Cai *et al.*⁴⁹ engineered a peptide, glucagon-like peptide-1-phenylalanine-phenylalanine-glycine (GLP-1-FFG), by attaching the self-assembled FFG tripeptide to the C-terminus of natural GLP-1, and co-assembled it with SupraGel to form a hydrogel. This hydrogel could promote islet function and maintain islet survival *in vitro*, inhibit the expression of hypoxia-related genes, and activate the protein kinase B (AKT) signaling pathway. In a mouse islet transplantation model, local application of this hydrogel significantly improved the transplant outcome, enhanced blood glucose control, increased the diabetes reversal rate, improved glucose tolerance, and boosted islet graft survival. It provides a

promising strategy for islet transplantation therapy for diabetes and offers direction for further optimization of therapeutic effects and expansion of clinical applications. Chen *et al.*⁵⁰ synthesized peptide amphiphile (PA)-GLP1 by linking GLP-1 receptor agonists with peptide amphiphiles and mixed it with a diluent PA (dPA), which then self-assembled into a nanofiber reservoir. This reservoir allowed for sustained drug release *in vitro*, maintaining stable blood drug concentrations that effectively reduced blood glucose levels in diabetic rats and slowed their weight gain. This modular approach can be applied to other peptide-based therapeutics, providing promising new options for the treatment of diabetes, obesity, and metabolic disorders. Yang *et al.*⁵¹ innovatively combined vancomycin, aggregate-induced emission luminogens with both luminescent and therapeutic functions, and self-assembled peptides to successfully develop a highly sensitive *in situ* assembly probe, E-probe, for detecting Gram-positive bacterial infections. This probe exhibited high sensitivity for detecting Gram-positive bacteria *in vitro*, efficiently generated reactive oxygen species to

inhibit bacterial growth, and showed greater antibacterial activity against *Escherichia coli* than vancomycin under the tested conditions. *In vivo* experiments demonstrated that the E-probe had targeted properties, enabling effective imaging and infection inhibition, and displayed good biocompatibility, providing a new and effective strategy for the treatment of Gram-positive bacterial infections.

In addition, Zhang *et al.*⁵² developed a novel peptide-antibody combination supramolecular *in situ* assembled dual-target inhibitor (PAC-SABIs), aimed at blocking the cluster of differentiation 47 (CD47) and CD24 signaling pathways to enhance macrophage-mediated phagocytosis and antitumor immune responses (Figure 4A and B). PAC-SABIs undergo biomimetic surface propagation on the cancer cell membrane through ligand-receptor binding and enzyme-triggered reactions, simultaneously inhibiting CD47 and CD24 signaling (Figure 4C and D). This significantly enhanced the phagocytic capacity of macrophages both *in vitro* and *in vivo* and demonstrated remarkable antitumor effects in breast cancer and

pancreatic cancer mouse models (Figure 4E and F). Moreover, the macrophage repolarization and CD8⁺ T cell tumor infiltration induced by PAC-SABIs laid the foundation for subsequent anti-programmed cell death protein 1 treatment, further inhibiting the progression of 4T1 tumors and prolonging survival (Figure 4G and H). This study provides an efficient nanostructured platform for maximizing therapeutic efficacy through the synergistic action of innate and adaptive immunity.

4. Challenges of self-assembled peptides in tumor therapy

As an emerging drug delivery system, self-assembled peptides demonstrate significant potential for tumor therapy. However, they face several distinct challenges in practical biomedical applications. Challenges include molecular stability and immunogenicity, manufacturing scalability and cost, limited delivery efficiency and bioavailability, and difficulties in achieving robust targeting, controlled drug release, and integration with

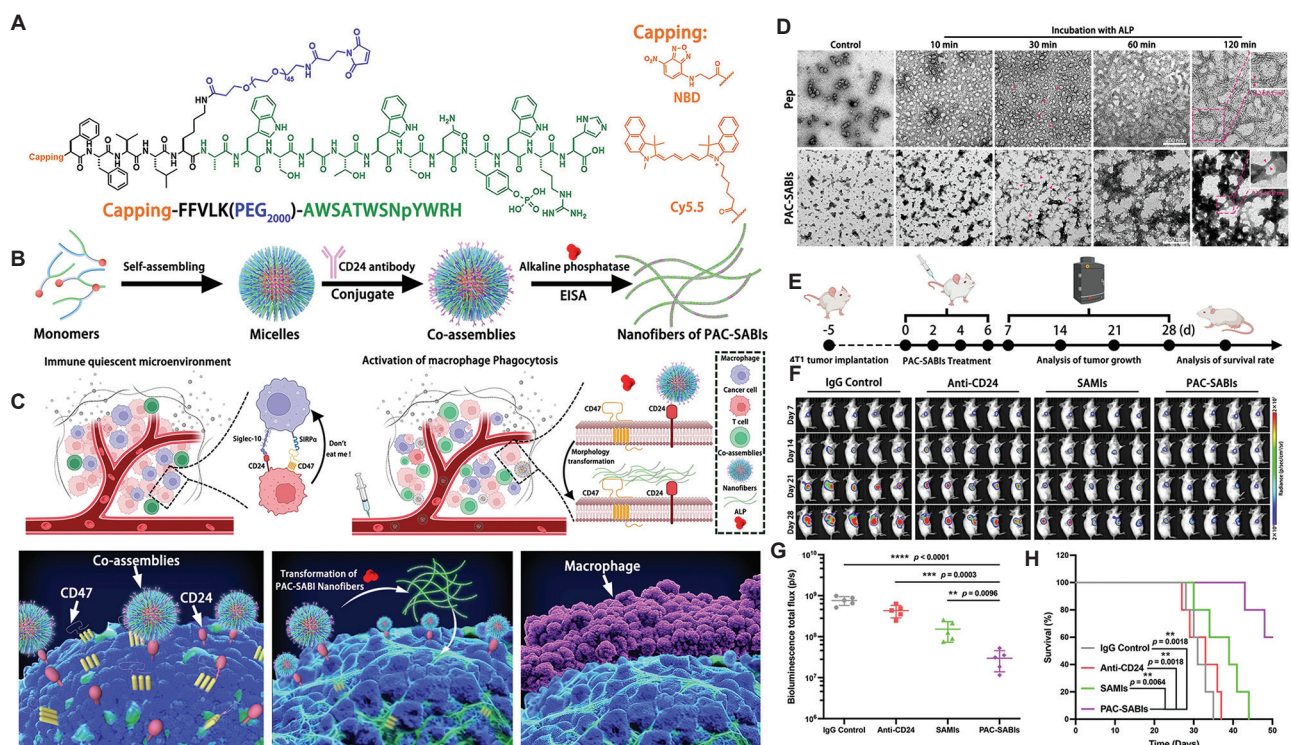


Figure 4. Alkaline phosphatase (ALP)-catalyzed peptide-antibody combination supramolecular *in situ* assembled dual-target inhibitors (PAC-SABIs) for dual blockade of cluster of differentiation 47 (CD47)/CD24 signaling to potentiate macrophage-mediated phagocytosis and antitumor immune responses *in vivo*. (A) Peptide molecular structure design of peptide (Pep)-polyethylene glycol. (B) Schematic diagram of PAC-SABIs formation process, including peptide self-assembling, antibody modification, and ALP catalysis. (C) Schematic diagram of the immune quiescent microenvironment and *in vivo* construction process of PAC-SABIs. (D) Time-dependent transmission electron microscopy images of Pep and PAC-SABIs. (E) Schematic diagram of the experimental design for treating 4T1 orthotopic tumors with PAC-SABIs. (F) Bioluminescence imaging results of 4T1 tumor-bearing mice on days 7, 14, 21, and 28. (G) Quantitative analysis of bioluminescence signals of 4T1 tumors across different treatment groups. (H) Kaplan-Meier survival curves of 4T1 tumor-bearing mice. Images reprinted from Zhang *et al.*⁵²

multimodal imaging technologies in precision medicine. These interrelated issues limit the further development and widespread application of self-assembled peptides in tumor theranostics.

4.1. Stability and immunogenicity

First, the stability of self-assembled peptides is significantly influenced by their molecular structure and the external environment. In the complex *in vivo* environment, self-assembled peptides are prone to disassembly or degradation, leading to pre-mature drug release or loss of efficacy. For example, some peptides have a short circulation time in the bloodstream and require surface modifications, such as PEGylation, to extend circulation time.⁵³ In the tumor microenvironment, factors, such as pH and enzyme activity can also affect their self-assembly state, thereby impacting drug delivery efficiency.^{54,55} Second, the risk of immunogenicity cannot be overlooked. Although self-assembled peptides generally exhibit good biocompatibility, longer peptide sequences or specific amino acid combinations may trigger immune responses. Peptides with more than nine amino acids carry a potential immunogenic risk, which could lead to the body rejecting the drug delivery system, thereby reducing therapeutic efficacy and even causing adverse reactions.^{56,57}

4.2. Cost control in large-scale production, delivery efficiency, and bioavailability

In terms of production, although solid-phase synthesis is the preferred method for peptide synthesis, it has limitations in large-scale production and cost control. Large-scale production of self-assembled peptides is expensive and technologically demanding, thereby restricting their clinical application.⁵⁸ The synthesis process is complex, involving multiple reaction and purification steps, which increases both the production cost and difficulty.⁵⁹ Furthermore, the delivery efficiency and bioavailability of self-assembled peptides *in vivo* still require improvement. After some peptides enter cells, the drug release rate and efficiency are suboptimal, resulting in insufficient drug concentration at the target site.⁵⁹ The distribution and metabolic processes of self-assembled peptides in the body also affect bioavailability. For example, certain peptides may be metabolized in organs, such as the liver, preventing them from reaching the target site and thereby reducing therapeutic efficacy.

4.3. Targeting, drug release, and integration with multimodal imaging

The targeting ability and specificity of self-assembled peptides need further improvement. While targeted delivery can be achieved by introducing targeting ligands

or receptor-binding sites, non-target tissue accumulation remains a challenge in practical applications, reducing therapeutic efficacy and increasing side effects.⁶⁰ The controllability of drug release is also a critical issue. At present, some peptides release the drug too quickly or too slowly *in vivo*, failing to meet therapeutic needs.² Moreover, with the development of multimodal imaging technologies, integrating self-assembled peptides with these technologies for real-time monitoring of drug delivery is an important direction. However, challenges remain in integrating multimodal imaging with therapeutic delivery, such as designing self-assembled peptides with multiple imaging capabilities and synchronizing imaging signals with drug delivery outcomes.⁶¹⁻⁶³

In addition to improving targeting and release, standardized characterization and reporting are essential for comparing systems across studies and for eventual regulatory evaluation. Key parameters include peptide purity and sequence fidelity, critical aggregation concentration, secondary-structure signatures, morphology distribution, drug-loading content, and release profiles in physiologically relevant media (e.g., serum, albumin, and enzyme-rich environments).⁶⁴ Because supramolecular assemblies can exchange monomers and remodel *in vivo*, stability should be assessed dynamically rather than only at equilibrium, and imaging probes should be validated for signal fidelity after assembly and disassembly. Quantitative pharmacokinetics and biodistribution (e.g., blood half-life, organ accumulation, and tumor-to-background ratios) are needed to link the assembly state with therapeutic outcomes.⁶⁵ Such datasets help identify failure modes (e.g., pre-mature disassembly, protein-corona masking of ligands, or rapid mononuclear phagocyte system clearance) and guide rational optimization.

5. Research outlook on self-assembled peptides in tumor therapy

Self-assembled peptides are experiencing a new wave of development in tumor therapy. Future research will focus on the design and synthesis of novel peptides, as well as their combined application with other delivery systems. On one hand, strategies, such as multifunctional design, the synthesis of novel structures, hybridization with other materials, and high-throughput screening and optimization will be utilized to expand the performance and application scope of self-assembled peptides. On the other hand, combining peptides with liposomes, polymer nanoparticles, viral vectors, cell-penetrating peptides, and other systems will leverage their respective advantages, complement each other's shortcomings, and work synergistically to enhance the efficiency and targeting

of drug delivery. This integrated approach is expected to accelerate the clinical translation of self-assembled peptide systems and play an increasingly important role in precision cancer medicine.

From a translational perspective, peptide-based theranostic carriers must be designed with manufacturability and robustness in mind. Solid-phase peptide synthesis enables precise sequences but can become costly for long or highly modified peptides; therefore, shortening sequences, adopting modular building blocks, and simplifying purification are practical strategies. Formulation issues, including scalable self-assembly processes, sterility and filtration compatibility, lyophilization, and long-term storage stability, should be considered early. For eventual good manufacturing practice production, defining critical quality attributes (e.g., peptide identity and purity, size and morphology distributions, surface charge, drug-loading content, and residual solvents) together with in-process controls is essential to ensure batch-to-batch consistency. In parallel, safety evaluation should move beyond acute cytotoxicity to include complement activation, immunogenicity, and the long-term fate of both the peptide scaffold and any imaging labels. Finally, given the heterogeneity of tumor microenvironments, patient-stratification markers (e.g., enzyme levels, pH, and redox status) and adaptive designs may be required to achieve predictable activation of stimulus-responsive assemblies.

5.1. Design and synthesis of novel self-assembled peptides

One important direction for future research is the design of multifunctional peptides. By cleverly introducing specific functional groups or targeting ligands into peptide sequences, self-assembled peptides with multiple functionalities can be created. For example, by combining targeting ligands and cell-penetrating peptides, efficient targeted delivery to specific cell types can be achieved.⁶⁶ At the same time, the development of smart, responsive peptides is also a hot topic. Self-assembled peptides that respond to multiple physiological signals (such as pH, temperature, enzymes, and redox conditions) will enable precise drug release and regulation. For example, peptides designed to respond to both low pH and high levels of reactive oxygen species in the tumor microenvironment can significantly enhance drug targeting and effectiveness.^{67,68}

In addition, future research will explore the synthesis of more novel self-assembled peptide structures. Beyond traditional nanospheres, nanofibers, and nanogels, new structures, such as nanocages and multilevel architectures will be investigated. These novel structures possess unique

physicochemical properties, offering more options for drug delivery. Nanocages can be used to encapsulate and deliver large-molecule drugs, such as proteins and nucleic acids, while multilevel structures enable the multi-step release of drugs, improving delivery efficiency.⁶⁹ These innovations will not only enhance drug stability and bioavailability but also increase the accumulation of drugs in target tissues, thereby improving therapeutic outcomes.

5.2. Combined application of peptides with other delivery systems

Peptides can be combined with other delivery systems, such as liposomes, polymer nanoparticles, viral vectors, and cell-penetrating peptides, to leverage synergistic advantages. Liposomes are known for their high biocompatibility and low toxicity. However, they suffer from poor stability and susceptibility to enzymatic degradation. When peptides are used to modify the surface of liposomes, they can not only significantly extend the circulation time of liposomes *in vivo* but also enhance their targeting to tumor cells. Peptides can serve as targeting ligands, improving the accumulation of drugs in tumor tissues, thereby enhancing therapeutic efficacy.^{70,71} Polymer nanoparticles are characterized by good stability and controllable drug-release profiles, but their biocompatibility is relatively poor. After combining with peptides, the biocompatibility, stability, and circulation time of polymer nanoparticles can be significantly improved. The targeting effect of peptides further increases drug accumulation at the targeted site.^{72,73}

Viral vectors are highly regarded for their strong transfection ability and favorable targeting properties. However, their high immunogenicity is a major drawback. By modifying viral vectors with peptides, their immunogenicity can be significantly reduced, enhancing drug accumulation at targeted sites. In addition, peptides can act as responsive elements, facilitating precise drug release.^{74,75} Cell-penetrating peptides have excellent cell penetration ability and low toxicity, but their stability and targeting need improvement. When combined with other peptides, the stability and targeting of cell-penetrating peptides can be enhanced, increasing drug accumulation within target cells. This, in turn, enables precise drug release and broadens the application range of cell-penetrating peptides in tumor theranostics.⁷⁶

6. Conclusion

This review summarizes the research progress of self-assembled peptides in the context of tumor therapy, exploring in depth their structure and properties, mechanisms of action across different types of drug delivery systems, and the advantages and challenges they present, and provides an outlook on future research directions. Self-assembled

peptides, with their unique self-assembly behavior, can form ordered nanostructures, such as nanospheres and nanofibers. They exhibit excellent biocompatibility, biodegradability, and efficient drug encapsulation and targeted delivery capabilities. They show tremendous potential to deliver small-molecule, nucleic acid, peptide, and protein drugs, significantly improving drug bioavailability and therapeutic efficacy. However, several challenges still exist in practical applications, such as their stability being highly affected by molecular structure and external environments, leading to disassembly or degradation *in vivo*. Immunogenicity risks cannot be ignored, and issues related to large-scale production cost control, delivery efficiency, bioavailability, targeting, controlled drug release, and integration with multimodal imaging technologies need to be addressed.

Future research will focus on the design and synthesis of novel peptides, expanding their performance and application range through multifunctional design, the development of smart responsive peptides, and the exploration of new structural synthesis. At the same time, combining peptides with other delivery systems, such as liposomes, polymer nanoparticles, viral vectors, and cell-penetrating peptides, will leverage synergistic advantages, jointly enhancing the efficiency and targeting of drug delivery. This approach is expected to drive the widespread application of self-assembled peptides in integrated tumor therapy (with imaging-guided monitoring where applicable). In conclusion, research on the application of self-assembled peptides in tumor theranostics has significant scientific and clinical value. With deeper understanding and continuous optimization of their structure and function, self-assembled peptides are expected to play an even more prominent role in biomedical fields, bringing breakthroughs and hope for more effective and safer tumor therapy.

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Conflict of interest

The authors declare no conflicts of interest.

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