Review Article

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Advances in the design and manipulation of self-assembling peptide and protein nanostructures for biomedical applications

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Abstract: Self-assembling peptides and proteins offer an unprecedented platform for constructing nanostructures with precise control over architecture and function, leveraging non-covalent interactions to achieve complex formations such as cages, layers, and hierarchical assemblies. Through design strategies like natural oligomerization, rational fusion of protein units, and structural motifs, these biomolecules form versatile nanostructures tailored for biomedical applications, including drug delivery, tissue engineering, biosensing, and catalysis. Advanced techniques, such as atomic force microscopy and epitaxial growth within confined water nanofilms, enable fine control over molecular assembly, paving the way for nanostructures with specific orientations and high spatial resolution. While challenges remain – particularly in achieving physiological stability, minimizing immunogenicity, and ensuring environmental responsiveness – progress in stimuli-responsive and bioadaptive designs holds promise for overcoming these barriers. The rational manipulation of self-assembling peptides and proteins thus stands at the forefront of advancing nanotechnology and synthetic biology, with the potential to develop adaptive, next-generation biomaterials that address critical biomedical challenges.

Keywords: self-assembling peptide, chiral nanostructure, epitaxial growth, synthetic biology, stimuli-responsive system

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1 Introduction

Nanotechnology has revolutionized materials science by enabling atomic- and molecular-level manipulation to engineer structures with unprecedented properties [1,2]. Within this paradigm, the self-assembly of peptides [3–6] and proteins [7,8] has emerged as a transformative strategy, leveraging the innate properties of biomolecules to construct nanostructures with precise control over size, shape, and functionality [9–13]. This biomimetic approach [14,15] mirrors the complexity of natural biological systems, such as cellular vesicles [16–18], extracellular matrix (ECM) [19–21], and viral capsids [22–25], which rely on spontaneous organization through non-covalent interactions – hydrogen bonding, van der Waals forces, electrostatic interactions, hydrophobic effects, and π–π stacking [26–32]. By harnessing these principles, researchers aim to design synthetic nanostructures capable of operating within dynamic biological environments, particularly for biomedical applications [33–36].

Peptides and proteins are uniquely suited for nanostructure design due to their biocompatibility, biodegradability, and the chemical diversity of their amino acid building blocks [37–44]. Their sequences can be tailored

to encode specific assembly behaviors, enabling the creation of multifunctional materials with modular domains for targeting, catalysis, or structural reinforcement [45,46]. Advances in design strategies have shifted from empirical trial-and-error to computational approaches, including molecular dynamics simulations and machine learning (ML)-guided frameworks [47]. Notably, artificial intelligence (AI) tools, such as AlphaFold and Rosetta, have accelerated the prediction of folding patterns and assembly kinetics, unlocking novel protein architectures with atomic-level precision [48,49].

Environmental control further refines self-assembly processes. Techniques like epitaxial growth in confined water nanofilms enable directional alignment of nanostructures [50,51], while stimuli-responsive systems triggered by pH, temperature, or light offer dynamic control over assembly–disassembly transitions [52,53]. Structural characterization relies on advanced tools: AFM and transmission electron microscopy (TEM) resolve nanoscale morphology, while circular dichroism and small-angle X-ray scattering probe secondary structures and solution-phase organization.

In biomedicine, peptide/protein nanostructures show remarkable versatility. Drug delivery systems exploit their cargo encapsulation capacity to enhance therapeutic stability and enable targeted release [46,54–56], while tissue engineering scaffolds mimic ECM architectures to guide cell adhesion and differentiation [57–61]. Their biorecognition capabilities also underpin biosensors for biomarker detection and biocatalysts for industrial applications [62–67]. Despite progress, challenges persist in stability, immunogenicity, and scalability. Proteolytic degradation, immune recognition, and dynamic biological milieus demand innovative solutions, such as non-natural amino acid incorporation [68,69], PEGylation [70–73], or cross-linking strategies [74,75]. AI-driven design and high-throughput screening promise to overcome these barriers by optimizing sequences for robustness and function [76–79].

The field of peptide self-assembly is currently undergoing rapid development; however, there remain many challenges and gaps in the current research. These include an incomplete theoretical framework for molecular design, insufficient precision in the control of dynamic assembly processes, limitations in optimizing biocompatibility, and the immaturity of large-scale fabrication technologies. The existence of these issues not only restricts the application potential of peptide self-assembled materials in biomedical and engineering fields but also hinders the sustainable advancement of related research. This review provides a comprehensive analysis of the design, manipulation, and biomedical applications of self-assembling peptide and protein nanostructures. We explore innovative strategies – from rational fusion of oligomerization domains and structural motifs to AI-driven computational design – that enable precise control over nanoscale architectures such as cages, filaments, and stimuli-responsive systems. Advances in environmental manipulation (such as pH [80,81], temperature [82,83], and organic solvent stimuli [84,85]), epitaxial growth in water nanofilms (directional growth along specific orientations induced by the ordered adsorption and arrangement of polypeptides on crystalline substrates in the presence of nanoscale water films [86]), and AFM-guided assembly (methods that employ atomic force microscope probes to control the initiation and kinetics of polymer crystal growth [87]) are highlighted as critical tools for achieving molecular-level precision. We evaluate breakthroughs in biomedical applications, including targeted drug delivery, gene therapy, virus-mimetic carriers, and light-harvesting hybrids, while addressing persistent challenges in stability, immunogenicity, and scalable fabrication. By synthesizing insights from peptide origami, dynamic supramolecular systems, and nanoparticle–protein interactions, this review underscores the transformative potential of integrating synthetic biology, AI, and nanotechnology to pioneer adaptive biomaterials. Ultimately, we envision peptide–protein self-assembly as a cornerstone of next-generation biomedical innovations, bridging molecular engineering with clinical translation to address unmet needs in diagnostics, therapeutics, and regenerative medicine.

2 Strategies for designing self-assembling peptide and protein nanostructures

2.1 Design of self-assembling peptide and protein nanostructures

The research on the assembly of peptides and proteins includes fundamental regulatory strategies such as the aggregation of hydrogen-bonding networks, the influence of hydrophobic interactions on the shape of assembled structures, and the modulation of electrostatic interactions (Table 1) [88,89]. Studies have shown that the choice and arrangement of repeating unit motifs significantly affect the physicochemical properties and biocompatibility of the resulting nanostructures. The incorporation of amino acids with different charge types can influence the stability and hydrophilicity of the self-assembled system, thereby modulating its behavior in biological environments. The

Table 1: Design of fusion proteins and peptide-based assemblies

	Fusion proteins	Peptide origami	Ref.
Design complexity	Gene fusion technology connects functional peptide segments or protein modules to form a unified multifunctional protein	Amino acid sequences are designed to realize specific secondary structures	[98,99]
Function	Enhances the biological activity of the protein and imparts new functions	By optimizing amino acid sequences, peptides self-assemble into functional nanomaterials	[100,101]
Design factors	Compatibility with protein folding, spatial conformation, and exposure of functional domains	Distribution of hydrophilic and hydrophobic amino acids, electrostatic complementarity, and spatial arrangement	[102,103]
Structural and functional applications	Vaccine development, drug delivery, enzyme encapsulation	Targeted antibacterial effects, antiviral agents	[102,104–107]

hydrophobicity and hydrophilicity of peptide chains can be tuned by adjusting the composition of amino acids, which in turn affects their ability to self-assemble into nanostructures. By introducing specific bioactive sequences into the self-assembling peptide chains, it is possible to achieve recognition and binding to specific biological targets [90–94]. Self-assembling peptides and proteins represent a versatile approach to constructing nanostructures with diverse architectures, leveraging non-covalent interactions to form highly ordered systems. Strategies for designing these self-assembling materials include the use of natural oligomerization domains, rational fusion of protein units, and incorporation of structural motifs, such as coiled-coil segments and α-helical linkers [95]. These methods allow for precise control over the resulting symmetry and geometry of assemblies, leading to various architectures like cages, layers, and filaments [96]. In recent studies, the rational design of fusion proteins has become a popular strategy to create nanostructures by combining natural oligomer-forming proteins, where each domain retains its self-assembling behavior and is strategically fused to achieve desired symmetrical nanostructures [97].

Fusion proteins designed for self-assembly into nanostructures can be engineered by combining oligomerization domains from different proteins, such as dimeric and trimeric units, to create rigidly linked structures [108,109]. These fusion proteins assemble into distinct nanostructures – including molecular layers and cubic cages – based on the geometry of their symmetry axes and the manner in which the domains are connected. For example, by varying the rigid joining of dimeric and trimeric proteins through α-helical linkers, one can achieve predictable orientations that lead to specific assemblies (Figure 1a) [97]. Another approach involves the creation of a protein nanobuilding block (PN-Block and nanoscale building blocks with specific geometries and interaction capabilities can be created) by fusing a *de novo* dimeric protein (WA20) with a trimeric foldon domain from T4 phage fibritin. This WA20-foldon fusion protein self-assembles into highly symmetric oligomers, forming structures such as 6-mer barrels, 12-mer tetrahedra, 18-mer triangular poles, and 24-mer cubes. The ability of the PN-Block to form various stable and versatile nanostructures illustrates its potential in nanotechnology applications (Figure 1b) [110].

2.2 Challenges and optimization strategies related to stability and immunogenicity

Despite the progress in designing self-assembling peptides and proteins, there are still challenges in constructing functional nanostructures, particularly for *in vivo* applications. Issues such as achieving precise control over the assembly process, ensuring stability under physiological conditions, and overcoming potential immunogenicity hinder the full realization of these materials [111]. Furthermore, the complexity of natural biological environments requires the development of self-assembling systems that can adapt or respond to external stimuli.

To address the stability issues of self-assembling peptides *in vivo*, researchers have proposed various optimization strategies. PEGylation offers advantages in drug delivery by extending circulation half-life, enhancing stability, and reducing immunogenicity; however, it may also lead to accelerated blood clearance and interference with targeting ligand function, necessitating careful optimization based on specific therapeutic requirements [112,113]. Chemical cross-linking strategies, such as disulfide bonds and click chemistry, as well as photo-cross-linking techniques, significantly improve the stability and enzymatic resistance of peptide assemblies; however, they also face challenges related to cytotoxicity and limited tissue penetration, requiring comprehensive evaluation in practical applications [114]. The incorporation of non-natural amino acids, such as D-amino acids and fluorinated

amino acids, has demonstrated remarkable potential in enhancing structural stability, enzymatic resistance, pharmacokinetics, and bioactivity. However, concerns regarding cytotoxicity, metabolic risks, and biosafety must be carefully considered during the design process to ensure a balanced optimization of performance and safety [115].

However, the potential applications of these structures are immense, ranging from drug delivery systems and scaffolds for tissue engineering to biosensors and catalysts. The rational design of self-assembling peptides and proteins continues to be a promising strategy to unlock novel functionalities and applications in nanotechnology and synthetic biology [97,110].

3 Manipulating peptide self-assembly with water nanofilms and AFM

The manipulation of epitaxial growth in peptide self-assembly using water nanofilms and AFM offers precise control over the formation and organization of nanostructures. Water nanofilms confined on solid substrates, such as mica, create a unique environment that significantly influences peptide behavior [51,86,116–118]. In this setting, the thickness and structure of the water nanofilm are dependent on the relative humidity and temperature, which in turn affect the hydrophilicity/hydrophobicity balance of the surface. The nanofilm allows peptides like GAV-9 (sequence: NH2-VGGAVVAGV-CONH2) to diffuse and self-assemble into ordered nanofilaments, with their orientation guided by the lattice structure of the underlying substrate (Figure 2a). The epitaxial growth of these filaments is driven by the peptide's interaction with the water film and the substrate, highlighting the importance of the confined water layer in facilitating such assembly [86].

AFM-based mechanical manipulation further enhances control over peptide self-assembly by enabling real-time adjustments to the growth process. Through AFM, researchers can exert physical stimuli to break and manipulate peptide filaments, creating "active ends" at designated positions on the filaments, which serve as nucleation sites for further growth. This method was successfully demonstrated by Zhang *et al.*, where the AFM tip was used to

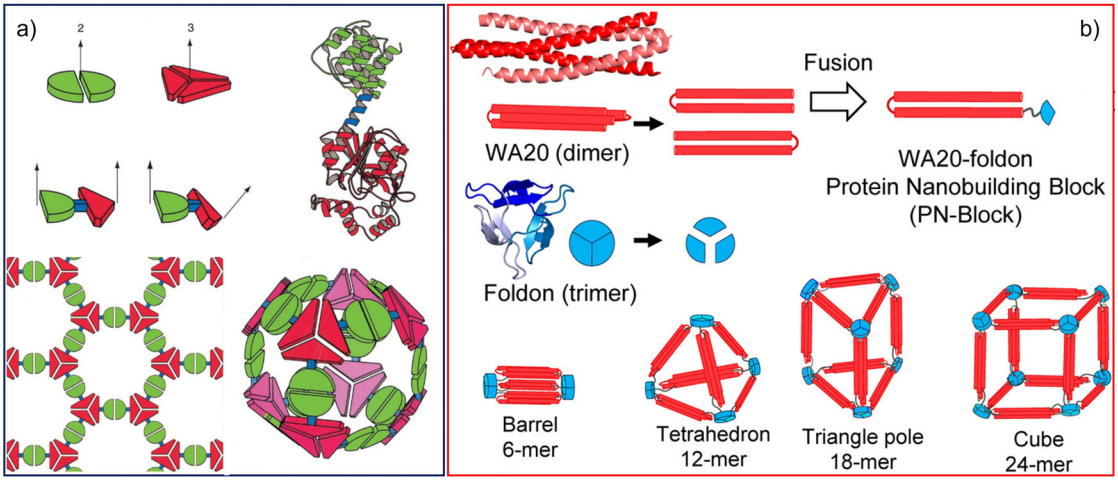

Figure 1: Designing fusion proteins for self-assembling into nanostructures: (a) Strategy for designing fusion proteins to self-assemble into symmetric nanostructures. A natural dimeric protein (green) and a trimeric protein (red) are depicted, with arrows indicating their symmetry axes. These proteins are genetically fused, forming a single protein where each natural oligomer serves as an oligomerization domain. Different geometries are achieved by varying the rigid joining of domains. The ribbon diagram shows the connection of the two domains with an α-helical linker (blue), facilitating a predictable orientation. Depending on the symmetry and arrangement of these domains, the designed fusion proteins can self-assemble into distinct nanostructures, such as molecular layers or cubic cages, depending on the configuration. Reproduced from the study of Padilla *et al.* [97]. Copyright 2001, PNAS. (b) Schematic representation of the construction and assembly of the WA20-foldon fusion protein as a protein nano-building block (PN-Block). The intermolecularly folded WA20 dimer is shown in red, while the trimeric foldon domain from T4 phage fibritin is depicted in blue. The WA20 and foldon domains are fused to create the WA20-foldon PN-Block, designed to form stable and highly symmetric nanoarchitectures through self-assembly. Depending on the arrangement, the PN-Block forms different nanostructures such as a 6-mer barrel, 12-mer tetrahedron, 18-mer triangular pole, and 24-mer cube, resulting from the combination of the WA20 dimer and foldon trimer. Reproduced from the study of Kobayashi *et al.* [110]. Copyright 2015, American Chemical Society.

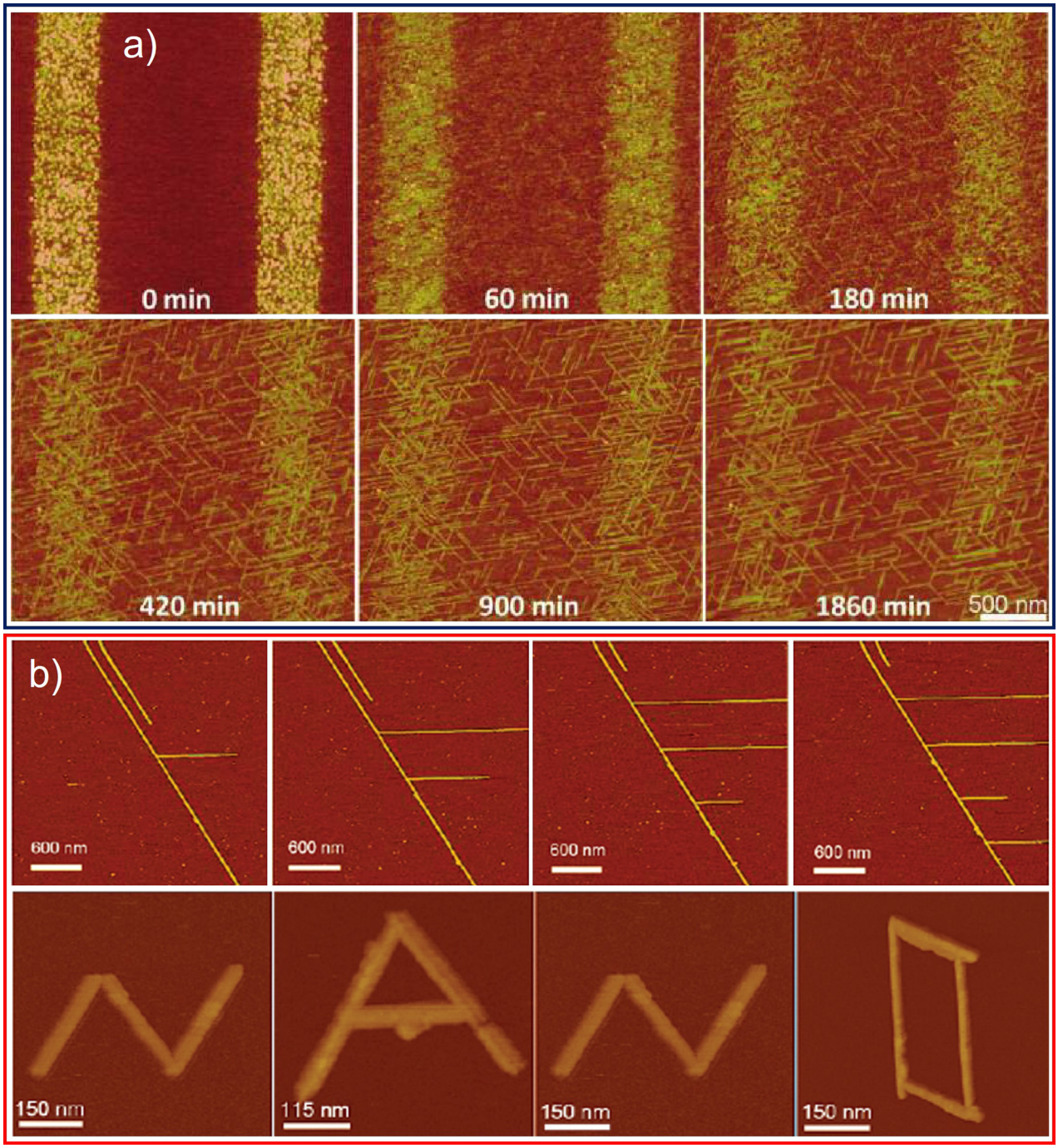

Figure 2: Manipulation of peptide self-assembly. (a) Time-lapse AFM analysis of GAV-9 diffusion and self-assembly in a water nanofilm on mica. GAV-9 micro-contact printing (μCP) strips at the start of incubation; AFM tapping-mode images taken at different time intervals after incubation under 90% relative humidity at 20°C. The images illustrate the gradual self-assembly process of GAV-9, with the same scale bar (500 nm) applicable to all panels. Reproduced from the study of Li *et al.* [86]. Copyright 2009, American Chemical Society. (b) A series of tapping-mode AFM images illustrate the position-guided epitaxial growth of individual GAV-9 nanofilaments. In the first panel, the original GAV-9 nanofilament is manipulated using an AFM tip to reposition it, as indicated by the white arrows. Following AFM manipulation, an active end is generated, leading to the formation of a short new nanofilament next to the original. Additional AFM manipulations performed three times at specific locations along the original filament result in the generation of further active ends, which also extend into longer filaments. The bottom row shows AFM images where individual GAV-9 nanofilaments are positioned to spell out the word "NANO." Reproduced from the study of Zhang *et al.* [119]. Copyright 2010, American Chemical Society.

push and reposition peptide nanofilaments, resulting in guided epitaxial growth along specific orientations that matched the substrate's lattice structure [119]. AFM mechanical manipulation can also repair defects in self-assembled nanofilaments, demonstrating its potential to correct assembly errors *in situ* (Figure 2b). The ability to initiate, guide, and repair peptide growth with AFM offers a powerful tool for precise nanostructure fabrication.

By combining the influence of water nanofilms and the precision of AFM, researchers can achieve unprecedented control over the epitaxial growth of peptides. This dual approach addresses some of the key challenges in self-assembly, particularly the alignment and orientation of nanofilaments, while offering opportunities to design complex nanostructures with high spatial resolution. Such techniques open the door to advanced applications in nanofabrication, where the ability to manipulate growth at the molecular level is critical for developing functional materials, devices, and biomaterials tailored for specific tasks in nanomedicine and biotechnology [86,119].

4 Biomedical applications of peptide self-assembly

The integration of self-assembling peptides, such as the Q11 fibril-forming peptide, into biomedical applications represents a powerful platform for the development of functional biomaterials [120]. By combining epitope-bearing units with well-defined fibrillar structures, these peptides offer a new avenue for stimulating targeted immune responses, creating vaccines, or promoting tissue regeneration (Figure 3a). The flexible modularity of such systems is particularly noteworthy; it allows for the tailoring of properties such as immune presentation, structural integrity,

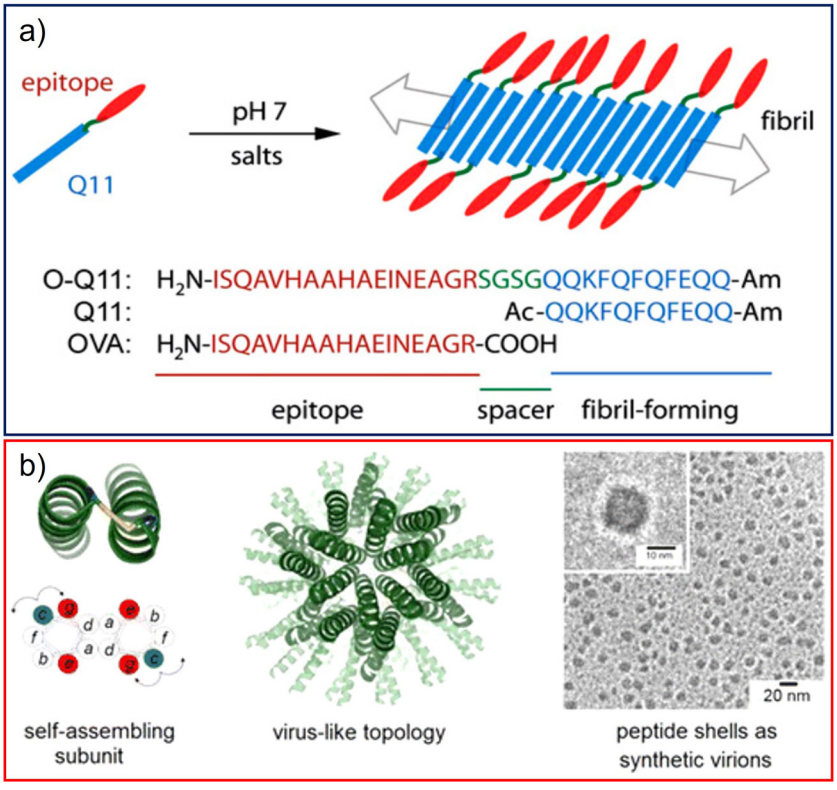

Figure 3: Typical biomedical applications of peptide self-assembling. (a) Illustration and corresponding sequences of peptides incorporating self-assembling epitopes. The Q11 segment (depicted in blue) forms fibrillar structures while presenting the epitope sequence (in red) at one end through a flexible linker (green). Reproduced from the study of Rudra *et al.* [120]. Copyright 2010, PNAS. (b) The illustration depicts the design of a *de novo* virus-like topology. The structure is built from coiled-coil peptide subunits (left) that self-assemble into virus-like architectures (middle). These assemblies form monodisperse, ultrasmall, hollow peptide shells (right) that mimic viral characteristics, capable of encapsulating RNA or DNA for intracellular delivery. The virus-like shells are designed to be compact, structurally adaptable, and biologically functional as synthetic analogs of natural virions. Reproduced from the study of Noble *et al.* [122]. Copyright 2016, American Chemical Society.

and biological interaction by simply modifying spacer regions or epitope sequences. The peptide-based assemblies provide a biodegradable, non-toxic alternative to traditional polymeric or metallic biomaterials, potentially reducing risks related to long-term foreign body responses. Furthermore, their ability to incorporate functional domains (*e.g.*, epitopes or targeting motifs) makes these structures versatile tools for developing biomaterials that adapt to specific therapeutic needs, including cancer immunotherapy, wound healing, and targeted drug delivery. As such, these peptide nanostructures could transform the landscape of material-based therapeutic interventions by providing adaptable, multifunctional materials suitable for a range of biomedical applications.

4.1 Drug/gene delivery

Peptides emulate the structural features of viral capsid proteins to confer analogous capabilities in cargo encapsulation and delivery. This biomimetic strategy not only minimizes the risk of eliciting immune responses but also enhances the targeting specificity and delivery efficiency of therapeutic agents [121]. The development of virus-like peptide nanostructures featuring a *de novo* coiled-coil topology introduces a breakthrough in the engineering of synthetic viruses for genetic delivery [122]. These trifaceted peptide helix assemblies form ultrasmall, monodisperse, anionic shells that mimic the physical and functional attributes of natural viruses (Figure 3b). Notably, the uniform, hollow shells can encapsulate both RNA and DNA and facilitate their delivery into human cells, achieving effective gene silencing and transgene expression. Unlike existing artificial systems, which often face issues of polydispersity and aggregation, these engineered shells possess the same structural uniformity and functional efficiency as native viruses. This precise control over size and assembly yields an adaptable platform for transferring a range of nucleic acids, accommodating both small interfering RNA and larger plasmid DNA. The demonstrated ability to encapsulate and deliver genetic material without aggregation or toxicity opens exciting possibilities for bespoke gene therapies and personalized medicine. Such artificial viruses represent a highly promising solution for controlled, targeted gene delivery, with potential applications in correcting genetic disorders, delivering vaccines, and treating cancers at a genetic level.

The self-assembling peptide-based nanostructures described in these figures highlight significant progress in designing virus-like assemblies that are capable of targeted gene delivery. The coiled-coil helix peptide subunits (Figure 3b) provide a precise way to mimic viral topologies while retaining adaptability to different sizes of genetic cargo [122]. These structures exhibit desirable characteristics such as monodispersity, hollow morphology, and a modular, self-assembling design, making them promising candidates for gene therapy applications.

Compared to traditional delivery systems, commonly used solid lipid nanoparticles offer significant advantages in drug delivery, such as preserving drug activity during storage and transport and reducing the risk of degradation. However, drugs may be prematurely released from the nanoparticles during storage or release, leading to reduced drug loading efficiency, and the high production cost limits their widespread application [123]. In contrast, nanostructured lipid carriers (NLCs), which combine solid and liquid lipids to form an imperfect crystalline structure, demonstrate notable advantages in drug loading and controlled release. Nevertheless, after injection *in vivo* [124], NLCs are prone to being taken up by the reticuloendothelial system, such as the liver and spleen, which reduces drug accumulation at the target site and compromises therapeutic efficacy [125]. Synthetic peptide shells, in comparison, offer lower immunogenicity, ease of production, and customizability. Importantly, the observed pH-responsive behavior allows the shells to effectively disassemble and release their genetic cargo into the cytoplasm, thereby ensuring that the therapeutic material reaches its target without cytotoxic effects. The successful demonstration of siRNA delivery, gene silencing, and transgene expression provides a strong proof-of-concept for these systems as next-generation tools for personalized and precision medicine.

4.2 Tissue engineering

Peptide self-assembly presents a promising strategy for constructing biomimetic scaffolds for tissue engineering applications. Peptide-based materials possess inherent biocompatibility, tunable secondary structures, and the ability to form well-defined nanostructures – such as nanofibers, β-sheet lamellae, and hydrogels – which have been widely explored in biomedical fields [126]. These peptide systems can mimic the microenvironment of the ECM, thereby supporting cell adhesion, migration, and differentiation. Such materials can be assembled from simple molecular building blocks, such as Fmoc-FF (fluorenylmethyloxycarbonyl-diphenylalanine) and Fmoc-RGD (arginine-glycine-aspartic acid), to form nanofibrous networks (Figure 4a). These networks not only closely resemble the complex

three-dimensional architecture of natural ECM but also present bioactive ligands on their surfaces [127]. By leveraging the programmability and antimicrobial properties of peptides, ECM scaffolds modified with antimicrobial peptides can be fabricated through surface functionalization and activation, demonstrating excellent antibacterial performance and enhanced wound-healing capabilities (Figure 4b) [128].

These studies have introduced new perspectives and technological approaches to the field of biomaterials. The former highlights the potential of optimizing material properties through precise molecular composition control, while the latter emphasizes the significance of antimicrobial functionality and its potential in promoting tissue regeneration. However, both approaches face challenges in translating laboratory findings into clinical applications, including – but not limited to – issues related to biocompatibility, stability, and performance in physiological environments.

4.3 Biosensing/catalysis

In the field of biosensors, peptides serve as molecular recognition elements with high affinity toward targets such as proteins, nucleic acids, and small molecules, thereby significantly enhancing detection sensitivity (*e.g.*, as probes for cancer biomarkers). By modifying sensor surfaces, such as electrodes or peptide–nanocomposite interfaces, peptides can also reduce non-specific adsorption and improve stability and response characteristics. This facilitates the development of portable electrochemical or optical sensors for the detection of disease biomarkers

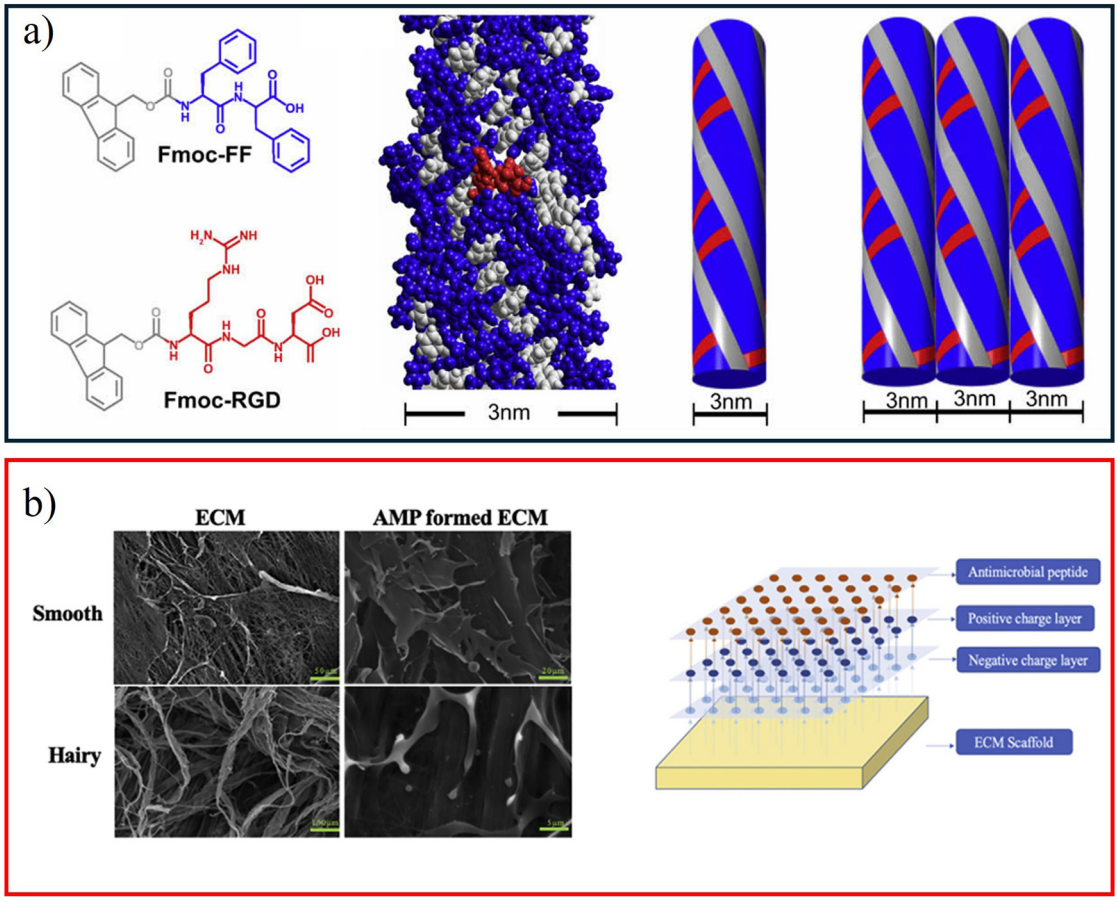

Figure 4: Peptide-based applications in tissue engineering. (a) Chemical structures of hydrogel building blocks: Fmoc-FF and Fmoc-RGD. The blue supramolecular model illustrates the formation of 3 nm protofibrils and their subsequent lateral assembly into larger ribbon-like structures. The red molecular model represents the RGD sequence displayed on the fiber surface, enhancing fiber accessibility and bioavailability. Reproduced from the study of Zhou *et al.* [127]. Copyright 2009, Biomaterials. (b) Scanning electron microscopy images of ECM and AMP-modified ECM scaffolds. The right panel shows the surface potential distribution of the AMP-modified ECM scaffold. Bar: 100 μm. Reproduced from the study of Liang *et al.* [128]. Copyright 2021, Biochem Biophys Res Commun.

(*e.g.*, inflammation-related molecules), enabling high-precision monitoring in complex environments [129–131]. Recent studies have further demonstrated notable progress in peptide-based electrochemical biosensors for infectious disease detection. These sensors exhibit excellent sensitivity and specificity, while also enabling portable formats and rapid detection, meeting the growing demand for fast diagnostic tools during pandemics [132].

In catalysis, peptides can mimic the active sites of natural enzymes (*e.g.*, hydrolases or oxidoreductases), such as by coordinating metal ions through histidine-rich sequences [133], thereby exhibiting efficient catalytic performance, for example, in organophosphate degradation or pharmaceutical synthesis [134]. However, their catalytic activity and stability are generally lower than those of natural enzymes. To address this, structural modifications (*e.g.*, incorporation of non-natural amino acids) and self-assembly strategies have been employed to enhance catalytic efficiency, promoting innovative applications in environmental remediation and biocatalysis.

4.4 From targeted therapy to vaccine development

In cancer therapy, pH-responsive self-assembling peptides have demonstrated remarkable potential as targeted drug delivery systems. These peptides can undergo conformational changes under the acidic conditions of the tumor microenvironment, thereby enabling site-specific drug release. For instance, pH-induced self-assembly strategies allow polymer–peptide conjugate-based nanocarriers to effectively penetrate cancer cells and release therapeutic agents [135]. Such systems not only enhance drug accumulation at the tumor site but also significantly reduce toxic side effects on normal tissues. Moreover, self-assembling systems modified with integrin-targeting RGD peptides have shown unique advantages in tumor vascular targeting. The RGD peptide facilitates precise localization and cellular uptake of the self-assembled carriers by binding to tumor-associated integrins, thereby enhancing the antitumor efficacy of the delivered drugs [136]. Additionally, peptide-based nanostructures formed through self-assembly can improve tumor cell penetration, leading to increased cell death [137]. The aromatic nature of tryptophan and tyrosine enables these amino acids to play a crucial role in light absorption and energy transfer processes, effectively capturing ultraviolet light and converting it into visible light, an attribute particularly important in photosynthesis [138]. Through specific self-assembly processes, peptides can bind to gold nanoparticles (AuNPs) to form stable hybrid materials, which exhibit excellent performance in photocatalysis and photothermal therapy, enabling precise treatment of cancer cells [139,140].

Self-assembling peptide nanoparticles also present unique advantages as antigen carriers in vaccine development. Their design principles primarily rely on the peptides' self-assembly capability and biocompatibility. Typically, self-assembling peptides are composed of two segments: a self-assembling domain and an antigenic epitope. Through rational design, these peptides can spontaneously assemble into nanoparticles under physiological conditions, providing an ideal platform for antigen delivery. Studies have shown that these nanoparticles not only protect antigens from degradation *in vivo* but also enhance immune responses by promoting cellular adhesion and antigen presentation [141,142]. Furthermore, the shape and size of these nanoparticles can be optimized by adjusting peptide sequences and concentrations, thereby improving the efficiency of antigen delivery.

In neurodegenerative diseases, the self-assembly processes of β-amyloid (Aβ) and α-synuclein (α-syn) have become a focal point of research, as their pathological aggregation is a hallmark of Alzheimer's and Parkinson's diseases. β-Amyloid, for example, can form aggregates and fibrils *via* non-covalent interactions – a process influenced by temperature, pH, and other environmental factors. In the context of self-assembling peptides, researchers have developed multiple models to mimic the aggregation behaviors of pathological proteins such as tau. These self-assembling peptides not only replicate the morphological features of pathogenic aggregates but also enable systematic investigation of aggregation conditions, such as pH and ionic strength, providing valuable tools for exploring the underlying mechanisms [143]. Furthermore, studies have revealed that different self-assembly conditions significantly impact the stability and structural characteristics of aggregates, thereby laying a foundation for designing targeted therapeutic strategies [144].

5 Development of stimuli-responsive supramolecular nanostructures

The hierarchical self-assembly of chiral nanostructures can be achieved using a ferrocene-modified dipeptide (Fc-FF), where the incorporation of counterions during self-assembly transforms flat β-sheets into helical and

twisted β-sheets [145]. This transformation generates chiral architectures with precise control over pitch, diameter, and handedness. Control over structural elements such as temperature, solvent, and counterion type is crucial for achieving these diverse and stable chiral morphologies. The resulting nanostructures offer promising applications in fields requiring chirality, such as chiroptics, chiral sensing, and separation technologies (Figure 5a).

A different mechanism of supramolecular assembly is demonstrated through the photoreconfigurable behavior of a chaperonin-derived bionanotube [146]. In this system, Mg^{2+}-induced supramolecular polymerization of a GroEL mutant bearing spiropyran (SP) units at the apical domains is used to generate nanotubes that can be manipulated by UV and visible light. Under UV light, the SP units are converted into their ionic form, merocyanine (MC), facilitating

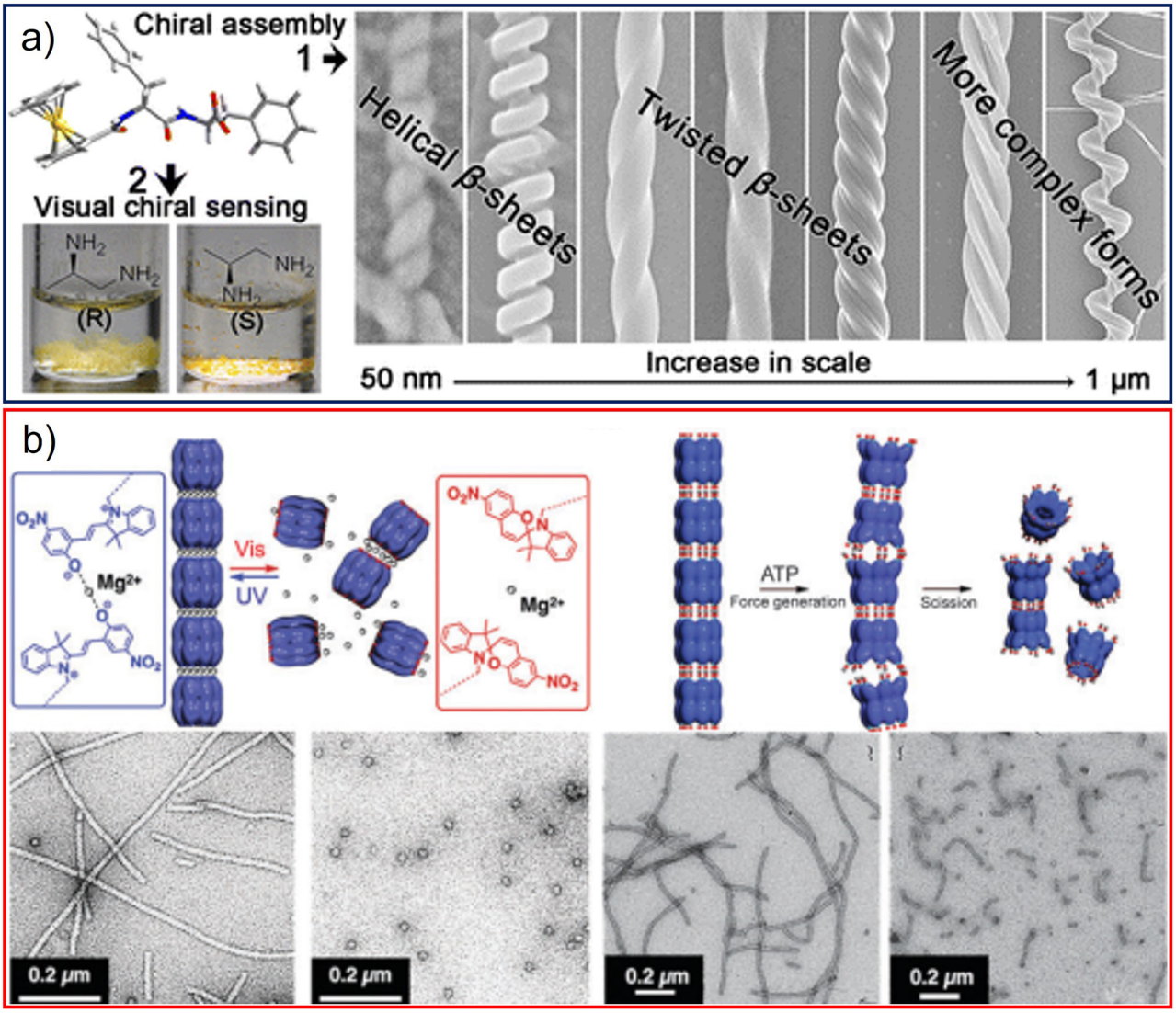

Figure 5: The development and manipulation of chiral and photoreconfigurable supramolecular nanostructures: (a) Hierarchical chiral nanostructures formed by the self-assembly of a ferrocene-modified dipeptide (Fc-FF). The incorporation of counterions induces a transition from flat to twisted β-sheets, resulting in the formation of helical chiral structures. Fine control of counterions, temperature, and solvent allows precise modulation of pitch, diameter, and handedness, enabling the creation of diverse chiral architectures [145]. Reproduced from the study of Wang *et al.* [145]. Copyright 2015, American Chemical Society. (b) Photoreconfigurable nanotubes formed *via* Mg^{2+}-induced supramolecular polymerization of GroELSP, a mutant chaperonin with photochromic SP units. UV irradiation induces isomerization from SP to ionic MC, facilitating polymerization into stable nanotubes. These nanotubes can be dissociated into shorter oligomers, including GroEL monomers, through visible light exposure, and subsequently reconfigured under UV light. TEM images illustrate the reversible changes in nanotube morphology during this light-mediated process, highlighting the dynamic nature of the system for potential use in controlled guest delivery applications [146]. Reproduced from the study of Sendai *et al.* [146]. Copyright 2013, American Chemical Society.

polymerization into long nanotubes. Conversely, exposure to visible light induces a transformation back to SP, leading to depolymerization and scission of the nanotubes into smaller oligomers and monomeric units. This reversible photoreconfiguration demonstrates the dynamic responsiveness of the nanotubes and is particularly relevant for non-invasive applications such as targeted drug delivery, where stimulus-triggered assembly and disassembly can be employed for controlled release (Figure 5b).

Together, these studies represent advancements in the development of highly controllable supramolecular systems that exhibit responsiveness to external stimuli [145,146]. While the Fc-FF assemblies provide insights into creating stable chiral nanostructures through hierarchical control mechanisms, the GroEL-derived nanotubes introduce an unprecedented level of configurability through light-responsive polymerization and depolymerization. Both systems demonstrate significant potential for applications that demand precision at the nanoscale, such as drug delivery, chiral sensing, and separation technologies. The development of such supramolecular systems opens pathways for engineering materials with intricate functions, allowing control over both structure and dynamic behavior in a non-invasive manner. Future research could focus on integrating these stimuli-responsive nanostructures with biological systems, expanding their applicability in medicine, diagnostics, and environmentally responsive materials.

6 Nanoparticle–protein conjugation and assembly

The exploration of nanoparticle–protein conjugation has focused on the robust interactions between proteins and polymer-coated AuNPs [147–151]. For instance, the formation of SP1 protein nanorings combined with cadmium telluride (CdTe) quantum dots (QDs) yields highly ordered nanostructures capable of efficient light harvesting [152]. Förster resonance energy transfer (FRET) between the QDs and SP1 nanorings is facilitated by the proximity of the nanocrystals, leading to effective energy transfer depicted through varying photoluminescence (PL) intensities across different ratios of nanoring to QD (Figure 6a). This demonstrates how spatial arrangement and molecular proximity in nanoparticle assemblies can significantly enhance light-harvesting efficiencies, suggesting promising applications in optoelectronic devices and bioimaging.

Highlighting the role of hydrophobic interactions in nanoparticle–protein conjugation, the interaction between bovine serum albumin (BSA) and amphiphilic polymer-coated AuNPs showcases the gradual formation of nanoparticle–protein complexes as the concentration of BSA increases [153,154]. The electrophoretic gel image highlights the ability of the amphiphilic polymer coating on AuNPs to facilitate robust physical adsorption of BSA molecules, overcoming the repulsive electrostatic interactions that typically occur between similarly charged species (Figure 6b). Schematics of AuNP–BSA interactions further illustrate the amphiphilic properties of both components that contribute to the stable formation of these conjugates. These findings indicate that hydrophobic interactions between the exposed regions of the polymer-coated AuNPs and BSA enables the formation of stable nanoparticle–protein conjugates, which can be further manipulated for various biomedical applications.

Taken together, these studies illustrate significant advances in designing nanoparticle-based systems with controllable interactions for functional applications [155–159]. The protein–QD assemblies for efficient light harvesting offer a viable strategy for enhancing the efficiency of optoelectronic devices (Figure 6a). Meanwhile, insights into the mechanisms of nanoparticle–protein interaction through amphiphilic coatings could be leveraged for applications ranging from targeted drug delivery to biosensing (Figure 6b). Both approaches underscore the importance of engineering the nanoparticle surface, whether for facilitating energy transfer or achieving robust protein binding, to achieve functional outcomes that bridge the gap between nanomaterial synthesis and biological systems. Future work may focus on integrating such controlled nanoparticle assemblies into biological environments to study their behavior, efficacy, and potential impact on medical treatments and diagnostics [153,154].

7 Peptide origami: A versatile approach to nanostructure construction

In recent years, the field of nanotechnology has witnessed significant advancements in the design and assembly of nanoscale structures using biological molecules. DNA origami, in particular, has emerged as a powerful technique for constructing precise nanostructures due to the predictable base-pairing interactions of DNA strands [160,161]. However, researchers are increasingly exploring the use of peptides as alternative building blocks to overcome some limitations inherent in DNA-based assemblies. A

comparison of DNA and peptide origami approaches for constructing nanostructures highlights the versatility and complexity of using peptides as building blocks (Figure 7). On the left side of the figure, DNA origami begins with simple nucleotide sequences (A, T, G, and C), which pair according to Watson–Crick base pairing, ultimately leading to the design of linear nanostructures such as nanowires or nanorings. However, due to the limited variety of building blocks, only four nucleotide bases, the structural and functional versatility of DNA-based nanostructures remains constrained, restricting the complexity of the generated architectures [162].

In contrast, peptide origami utilizes the greater diversity of amino acids as building blocks, allowing the design of more complex and multifunctional structures [163]. Complementary pairing among peptide sequences, analogous to nucleotide base pairing, enables the formation of diverse peptide nanostructures such as nanorings, branched nanostructures, and monolayers. Peptides can be organized into specific sequences that complement each other, yielding a variety of configurations (Figure 7). The right side of the figure depicts different nanostructures achieved through protein assembly, including protein nanocages, nanorings, and nanotubes, which can be built using either biological or chemical strategies. The combination of interfacial protein design and the diversity of amino acid sequences enhances the structural and functional potential of peptide-based origami, providing more versatile platforms for diverse applications [162].

The development of peptide origami, with the ability to design protein assemblies based on more than just the primary sequence, is a promising advancement in synthetic biology and nanotechnology [165–167]. Compared to DNA origami, peptide-based assembly benefits from the vast number of potential building blocks and the ability to harness protein–protein interactions to form elaborate, functional nanostructures. This diversity makes peptide origami suitable for a wide range of applications, including drug delivery, biosensing, and materials science. The increased complexity, functionality, and scalability of peptide nanostructures highlight

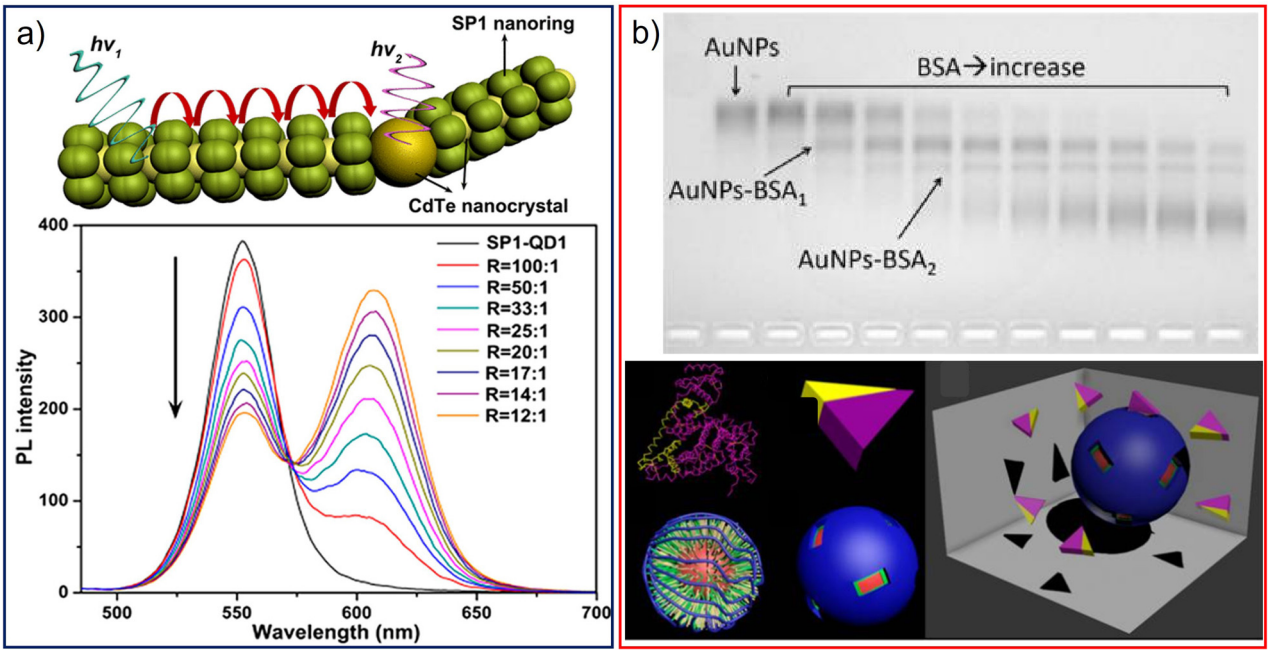

Figure 6: Co-assembly of nanoparticles with proteins: (a) Electrostatic self-assembly of SP1 protein nanorings and CdTe QDs into highly ordered nanostructures for efficient light harvesting. The illustration shows FRET within SP1 nanowires mediated by CdTe QDs, with excitation light of two different wavelengths ($h\nu_1$ and $h\nu_2$). The PL spectra below illustrate changes in PL intensity based on different molar ratios (R) of QD1 to SP1, demonstrating efficient energy transfer with varied assembly ratios. The ordered nanowire structure provides an ideal scaffold for light-harvesting applications by optimizing energy transfer efficiency through controlled spatial arrangement of the QDs [152]. Reproduced from the study of Miao *et al.* [152]. Copyright 2014, American Chemical Society. (b) Interaction between AuNPs and BSA. Gel electrophoresis demonstrates the gradual formation of AuNP–BSA complexes as BSA concentration increases. The AuNPs bind to BSA *via* hydrophobic interactions, forming discrete complexes denoted as AuNPs–BSA_1 and AuNPs–BSA_2. The lower panels depict schematic representations of AuNPs and their interaction with BSA, highlighting the amphiphilic properties and the resulting structural conformations. This interaction demonstrates the robust affinity of amphiphilic AuNPs for BSA, offering insights into nanoparticle–protein conjugation for biomedical applications [153,154]. Reproduced from previous studies [153,154]. Copyright 2014 and 2016, American Chemical Society.

the advantage of moving beyond DNA origami toward protein and peptide engineering for developing next-generation biomaterials and devices.

8 Industrial translation of peptide self-assembly for large-scale production

Peptide self-assembly technology has garnered increasing attention due to its wide-ranging applications in drug delivery, biomaterials, and nanotechnology. However, its transition to industrial-scale production faces several significant obstacles, including high production costs, insufficient reproducibility, technical bottlenecks in scale-up processes, and stringent quality control requirements. These challenges not only impact the economic feasibility of peptide self-assembly technologies but also hinder their widespread adoption in practical applications.

As peptide self-assembled materials move toward industrialization, economic and technical challenges become particularly prominent. First, the high cost of synthesis remains a critical issue. Traditional solid-phase peptide synthesis involves expensive protecting groups, resins, and large volumes of organic solvents, along with labor-intensive steps and relatively low efficiency. Although liquid-phase peptide synthesis offers certain cost advantages in large-scale production, it still faces issues such as a high yield of by-products and difficulties in achieving high purity when synthesizing long peptide chains. Moreover, the purification process relies on multiple steps, including high-performance liquid chromatography and lyophilization, which further increase production costs [168].

From a technical standpoint, the design and structural prediction of self-assembling peptides still largely depend on empirical rules and experimental validation. This leads to long development cycles and high trial-and-error costs, severely limiting the efficiency of new material development. In particular, the prediction of complex peptide conformations and control over self-assembly behavior remain constrained by the lack of stable and high-throughput modeling tools. Additionally, batch-to-batch variability and low stability of assembled products present significant challenges for scale-up production and quality control [168].

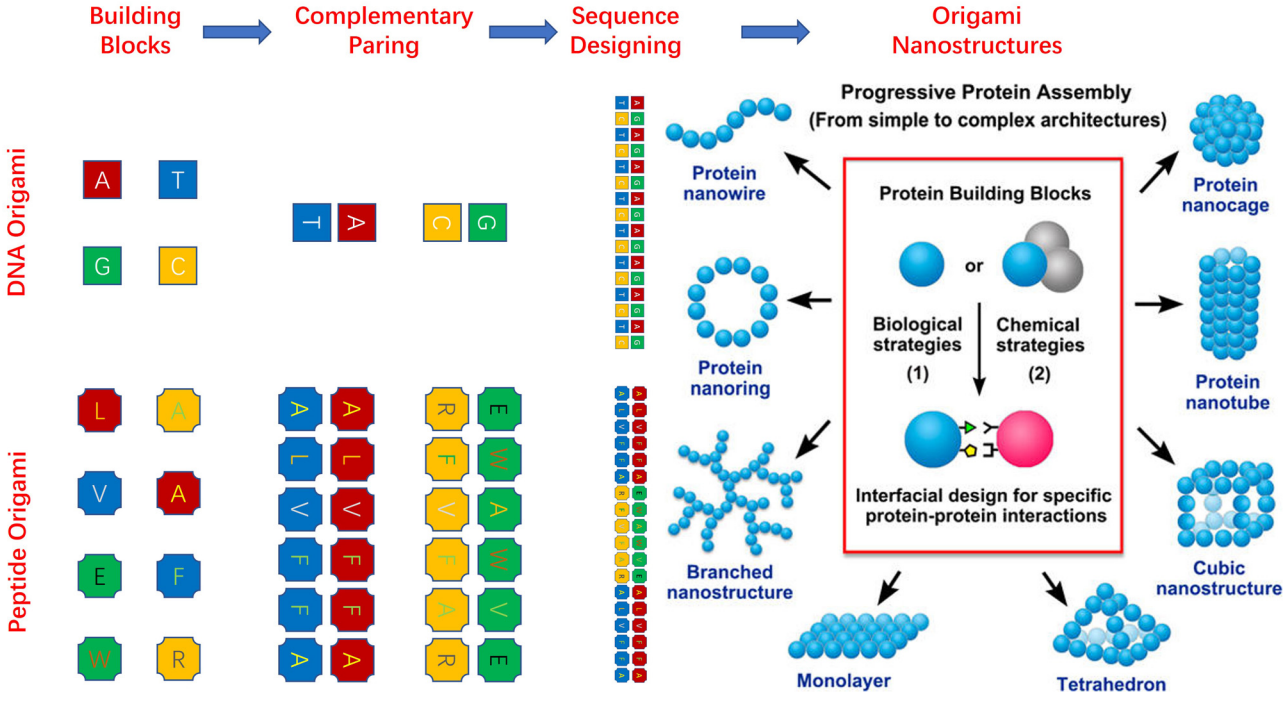

Figure 7: The versatile applicability of peptide origami. DNA origami utilizes nucleotide sequences (A, T, G, C) that pair through complementary interactions to form linear nanostructures such as nanowires and nanorings. Peptide origami, utilizing diverse amino acid sequences, allows for more complex pairing and assembly, resulting in various nanostructures like nanorings, branched structures, and monolayers. The figure highlights the formation of protein nanostructures through progressive protein assembly, employing biological or chemical strategies, to create advanced architectures such as protein nanocages, nanotubes, and tetrahedral assemblies. Reproduced from the study of Ma *et al.* [162]. Copyright 2022, Royal Society of Chemistry. Reproduced from the study of Luo *et al.* [164]. Copyright 2016, American Chemical Society.

To address these issues, researchers are increasingly incorporating advanced computational methods, such as ML, to assist in the functional prediction and structural optimization of self-assembling peptide sequences. By training models on large-scale datasets, AI tools can significantly improve the screening efficiency of candidate peptides in the early stages, reduce experimental workload, and enhance R&D efficiency. Furthermore, modular synthesis strategies, the integration of green chemistry approaches, and the development of continuous purification systems provide potential solutions for future large-scale production [169].

In summary, although self-assembling peptides exhibit great potential in the field of biomaterials, they still face numerous obstacles during industrial production. To overcome these challenges, future research should focus on optimizing peptide synthesis and self-assembly processes to enhance their feasibility and economic viability in practical applications. This will provide critical support for advancing the commercialization of peptide self-assembly technologies.

9 Conclusion and outlook

The field of self-assembling peptides and proteins represents a transformative platform for the construction of nanostructures with unprecedented precision in architecture and functional adaptability. By harnessing advanced design principles – such as natural oligomerization domains, the rational fusion of protein modules, and integration of structural motifs like coiled-coil segments – scientists have crafted an array of nanostructures, including cages, layers, filaments, and hierarchical assemblies. The development of high-resolution techniques, such as AFM and epitaxial growth in confined water nanofilms, enables precise molecular control over self-assembly, unlocking new avenues in drug delivery, tissue engineering, biosensing, and catalysis.

However, there are still obstacles and challenges in translating these nanostructures into practical biomedical tools, concentrated in areas such as stability control, biocompatibility optimization, scalable production, and regulatory approval. Stability in physiological environments (issues of enzyme degradation, temperature sensitivity, and pH sensitivity), immunogenicity minimization (immune recognition and clearance), and adaptive responsiveness to biological conditions (evaluation of cytotoxicity and blood compatibility) are essential for effective *in vivo* applications [170–173]. Addressing these issues will require multi-faceted approaches that incorporate stimuli-responsive elements, bioinspired assembly processes, and dynamic architectures capable of interacting seamlessly with complex biological systems.

AI technologies such as deep learning and transfer learning have significantly advanced peptide drug design by improving prediction accuracy and screening efficiency. The combination of peptides with inorganic materials and polymers further enhances their potential in targeted delivery and controlled release. Despite these advances, peptide drugs face major regulatory challenges due to inconsistent standards and varied approval pathways, highlighting the urgent need for unified frameworks to facilitate clinical translation. Meanwhile, rapid developments in synthetic biology and personalized medicine raise safety and ethical concerns, such as gene transfer risks and unequal access to treatment, that require attention. Moreover, limited public awareness and policy gaps hinder societal acceptance, emphasizing the need for effective communication and strong regulatory measures to ensure the safe and broad adoption of these technologies.

Looking forward, advancing the rational design and molecular manipulation of self-assembling peptides and proteins holds significant promise for developing the next generation of adaptive biomaterials. Future research should prioritize engineering modular, multifunctional nanostructures with tunable responses to biochemical stimuli, aiming for enhanced therapeutic and diagnostic performance in clinical settings. By converging expertise across molecular engineering, synthetic biology, and biophysics, the field is well-positioned to produce innovative biomaterials that bridge the gap between fundamental science and applied biomedicine, ultimately driving forward the capabilities of nanotechnology in addressing critical challenges in medicine and beyond.

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