High-Affinity Peptide Biomaterials

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Abstract: High-affinity binding is a crucial aspect in the design of advanced biomaterials, enabling the creation of materials that can specifically and effectively interact with target objects such as tissues, cells, or biomolecules, mimicking the sophisticated yet well-controlled interactions found in nature. Peptide-based high-affinity biomaterials have emerged as a promising class due to their versatility in chemical design, simplicity in synthesis and formulation, intrinsic ability to mediate biological communication, and key materials features such as tunable biodegradability and modulable biocompatibility. This Opinion article highlights the critical factors to consider in the development of high-affinity peptide materials, including the selection of appropriate peptide ligands, ensuring conformational stability, and optimizing ligand density and conjugation strategies. It also explores how these design considerations have been successfully employed in various applications, including regenerative medicine, drug delivery, and molecular purification.

Keywords: peptides, biomaterials, ligand, high-affinity binding, supramolecular, molecular assembly, nanomaterials

Biological systems rely on specific high-affinity interactions to execute crucial functions. From the Watson-Crick-Franklin pairing of DNA to the lock-and-key mechanism of enzyme-substrate binding, these non-covalent interactions—occurring at intramolecular, intermolecular, or surface levels—drive communication and enable complex biological processes such as gene expression, signal transduction, and mass transport. Harnessing the specificity inherent in biological systems to design synthetic biomaterials has been a central focus of research over the past few decades, with potential applications in regenerative medicine, drug delivery, molecular separation, immunotherapy, and beyond. There are four distinct types of specific interactions commonly used in material design to interface with biological systems. Proteins, due to their conformation-based high specificity and precision, serve as primary mediators of communication within biological systems. They enable a wide range of controlled chemical cascades that drive specific biological functions at the intracellular, cellular and intercellular levels. While specific protein-protein interactions, such as biotin-streptavidin interactions (**Fig. 1a**), have been widely applied [1-3], challenges related to synthesis, purification, structural complexity, environmental instability, and temperature sensitivity have prompted the exploration of alternative approaches that utilize the high-affinity interactions offered by low-molecular-weight ligands [4-6].

Peptides represent a logical choice to emulate the high specificity and accuracy of proteins. Peptides, typically composed of fewer than 50 amino acids, are easier to synthesize, characterize, and analyze. Their sensitivity to the choices of amino acids and peptide sequences allows for detailed studies and rational

design of sequence-specific interactions. *In vitro* and *in vivo* phage display techniques, coupled with computational modeling, have been employed to identify peptide sequences with high-affinity binding properties (**Fig. 1b**) [7-11]. Similarly, aptamers are short single-stranded DNA or RNA molecules that can bind specific biomolecule targets with high affinity and specificity (**Fig. 1c**). Selected from large combinatorial libraries through the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) process and other methodologies, aptamers can bind a wide range of targets, including proteins, small molecules, and cells [12-15]. Aptamers offer advantages such as ease of synthesis, chemical stability, and the ability to be modified with functional groups to enhance their binding properties and biostability. Additionally, small molecule ligands and drugs can be employed to achieve high-affinity interactions, as most therapeutic agents function as agonists or antagonists, relying on highly specific interactions with their molecular receptors. For example, folic acid targets the folate receptor, which is overexpressed in certain cancer cells (**Fig. 1d**). Conjugating folic acid to therapeutic agents or nanoparticles can improve drug delivery specificity, thereby minimizing off-target effects and enhancing therapeutic efficacy [16-18]. Small molecule drugs, including agonists and antagonists, have been harnessed to in modulate biological pathways by binding to specific receptors or enzymes. These interactions can either activate or inhibit the biological activity of the target, allowing for precise control over various physiological processes.

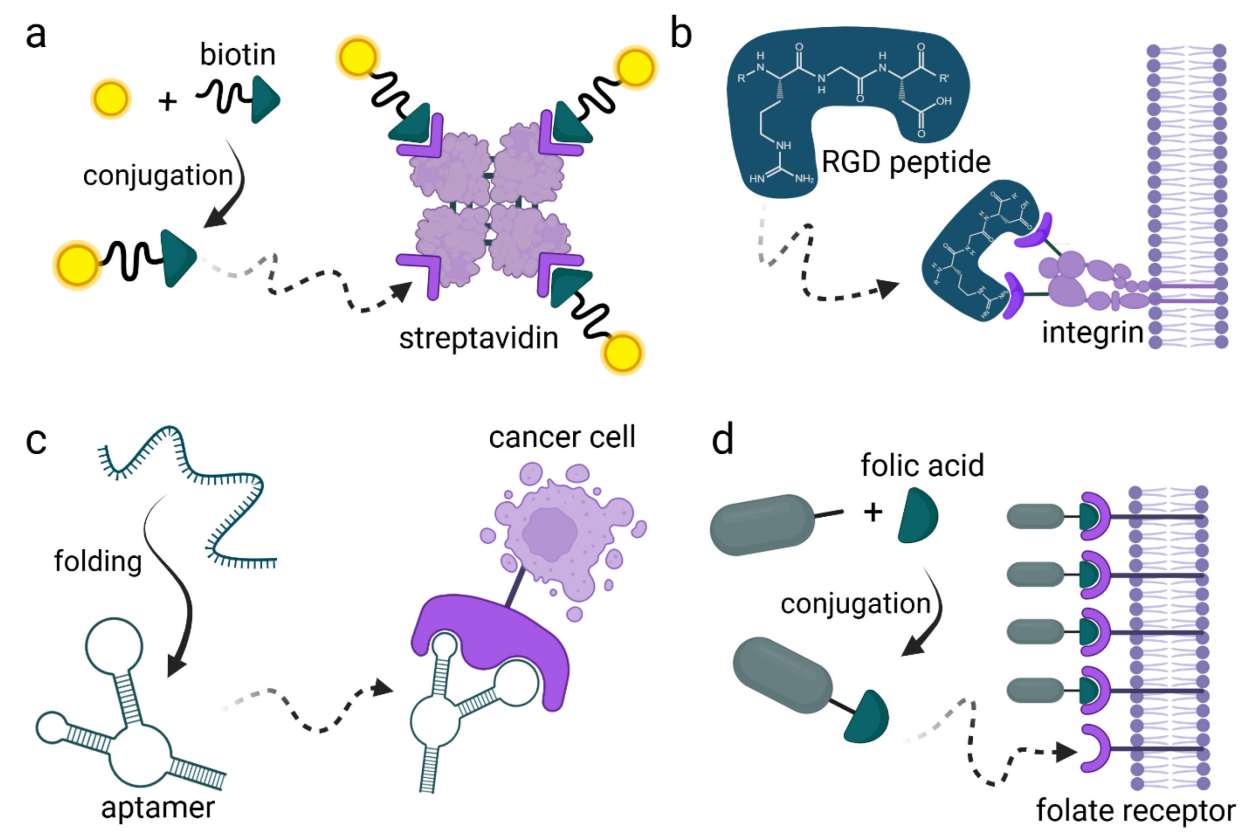

Figure 1. Representative examples of ligand molecules utilized in the development of high-affinity biomaterials. (a) Biotin-conjugated cargos (e.g., imaging agents, therapeutic compounds, or nanoparticles) exhibit high-affinity binding to the tetravalent streptavidin, providing a robust platform for targeted delivery, labelling and detection. (b) The cell adhesion peptide RGD has been extensively explored in regenerative medicine and drug delivery due to its highly specific binding to integrin receptors, facilitating

cell attachment and targeted therapeutic delivery. (c) Aptamers represent an emerging class of high-affinity ligands capable of achieving precise targeting to specific cells of interest, offering great promise for therapeutic and diagnostic applications. (d) Folic acid and other therapeutic compounds can be employed to achieve high-affinity binding through their specific interactions with folate receptors, which are overexpressed on the surface of cancer cells, enabling selective targeting of tumors.

The increasing ease of identifying high-affinity ligand-receptor pairs—largely driven by advances in computational methods—has led to a surge in their use in biomaterials design. By leveraging the specificity and precision of peptides, aptamers, ligand molecules, and small molecule drugs, high-affinity materials can be developed with the goal of improving human health and advancing biomedical technologies. Each type of ligand offers unique advantages depending on the application. However, most small molecule ligands and aptamers require an additional conjugation step to impart high-affinity binding to the materials of interest. In contrast, peptides can serve as both biomaterial building blocks and high-affinity ligands, eliminating the need for complex conjugation steps and enabling a more direct and efficient approach in materials design. In this Opinion article, we will focus our discussion on the development of high-affinity peptide biomaterials.

Peptide as Both Structural Motifs and Functional Units Peptides have emerged as, and evolved into, indispensable molecular building blocks for the design of high-affinity biomaterials due to their inherent and tunable properties, including biodegradability, biocompatibility, and adaptability to biological cues. [19] Their responsiveness to the biological or pathological conditions makes them particularly well-suited for dynamic interactions within living systems. One of the key advantages of peptides is the versatility provided by the 20 naturally occurring amino acids, along with numerous derivatives and D-isomer counterparts. This broad diversity allows for immense flexibility in designing peptide sequences that can dictate hierarchical assembly, fine-tune material properties, and perform specific biological functions. Furthermore, advancements in peptide synthesis techniques enable the creation of precise peptide sequences with exceptional accuracy and yield. Coupled with our growing ability to predict peptide secondary, tertiary, and quaternary structures, these advancements allow for more precise control over their mechanical, chemical, and biological properties.

Identifying ligands with high affinity for the desired receptor is critical. High-affinity ligands are typically defined as having dissociation constants (K_d) in the nanomolar range, ensuring a thermodynamically favorable bound state [20, 21]. While ligand selection has traditionally been performed using *in vitro* or *in vivo* phage display techniques to screen large ligand libraries for the most promising candidates [7-9], recent advances in mass spectrometry techniques and computational modeling have significantly improved this process [22-24]. Even when a single ligand does not achieve the desired affinity, the multivalent presentation of ligands on a material surface can collectively result in high affinity (**Fig. 2a-b**). It has been demonstrated that ligands, which would bind weakly when acting alone (K_d ~1 μM), can collectively achieve significantly higher affinity (K_d ~20 nM) when bound simultaneously to their respective receptors [20]. Along these lines, the Kokkoli Lab demonstrated that nanoparticles functionalized with dual peptide ligands exhibited enhanced delivery into cancer cells compared to those functionalized with a single ligand type. Their research further revealed that for ligands with comparable valencies, a 50:50 ratio of both ligands on the nanoparticle surface resulted in optimal cellular uptake [25]. In another example, Ye and colleagues recently showed that branched forms of the α-Klotho protein-binding ligand Pep-10, showed over 20-fold improvements to their binding affinity [26].

Transforming Binding Affinity and Accessibility Across Scales. Given that high-affinity binding ligands are often selected and validated in their unassembled monomeric state—where they adopt a specific conformation for binding—their conformation may change after chemical conjugation [27] or assembly into supramolecular nanostructures, potentially altering their binding affinity. Since some of these epitopes must adopt a specific secondary structure—most commonly an α-helical conformation—to effectively interact with their molecular targets, the challenge lies in maintaining their bioactive conformation within their respective supramolecular assemblies. Studies by Tirrell, Fields, and colleagues demonstrated that alkyl tails can stabilize peptide ligands with various secondary structures through hydrophobic interactions, which thermally stabilize the peptides and promote their aggregation into more stable configurations [28-35]. Our lab also reported on alkylation-regulated conformation preservation of α-helical peptides within their filamentous assemblies [36, 37]. Our studies demonstrated that conjugating two short linear hydrocarbons helped maintain the α-helical conformation of protein A-derived peptide sequences while promoting their assembly into filamentous structures. In contrast, a single palmitoyl tail with comparable hydrophobicity led to the formation of β-sheet assemblies. Moreover, we found that the hydrocarbon chain length significantly influences the preservation of the α-helical structure—longer chains favor β-sheet formation, whereas shorter ones stabilize α-helices to a certain degree.

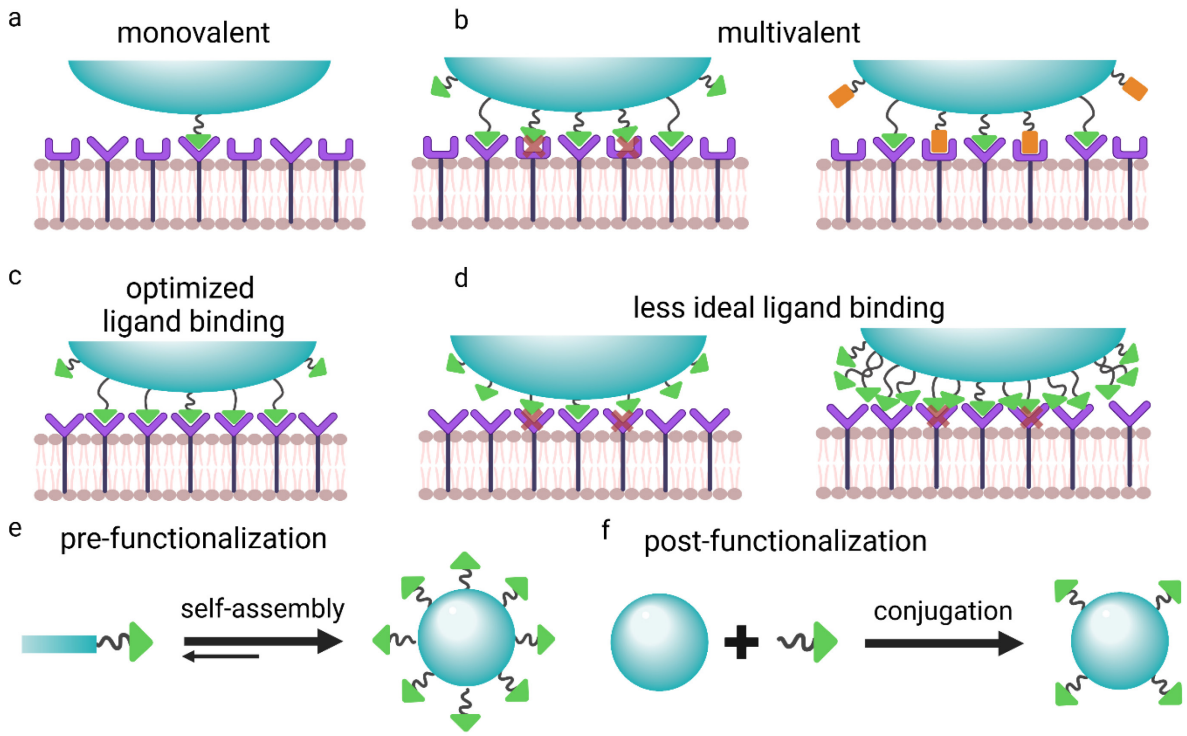

Figure 2. Schematic illustrating key design considerations for incorporating peptide ligands into biomaterials. (a) Monovalent ligand presentation offers only a single chance of high-affinity binding. (b) Multivalent ligands could enhance overall binding affinity, even when individual affinities are low. (c) Optimizing ligand spacing and flexibility can maximize the number of binding events. (d) Improper geometry or steric hindrance can limit ligand-receptor binding accessibility. (e) High-affinity materials generated *via* pre-functionalization methods can achieve high ligand density due to precise control over

ligand incorporation during material synthesis. (f) Materials formed through post-functionalization may face steric hindrance, which can limit the achievable ligand density below a certain threshold.

The Tirrell lab further proposed that the confinement and crowdedness within the micellar corona favors the α-helical conformation, highlighting the significant impact molecular self-assembly can have on peptide chain conformation [31-35]. Indeed, while a peptide's primary sequence largely dictates its potential to assume a specific secondary structure, factors such as aggregation state, microenvironment, and presentation at a solid-liquid interface can all influence its chain conformation and, consequently, its binding affinity. In fact, the strength of many ligand-receptor interactions is dependent upon solution pH and ionic strengths. Shifts in environmental pH, particularly when exceeding or falling below the pKa of charged amino acids, can significantly alter its charge state, impacting peptide chain conformation and, in turn, the overall material properties. This phenomenon has been widely leveraged to create tunable, pH-responsive peptide hydrogels [38-41], but it is equally important to assess how these structural changes may influence the binding affinity of ligands. For example, Lin and Anseth observed that ligands incorporated into more rigid, crosslinked hydrogels exhibited reduced binding affinity [42]. In another example, Heinis and coworkers found that the presence of hydrophilic, polar small molecules at the core of bicyclic peptide ligands formed additional hydrogen bonds, further stabilizing the peptide structure [43].

However, avoiding ligand aggregation that could introduce steric hindrance is also crucial, as it may obstruct accessibility for receptor binding (**Fig. 2c-d**). The Stupp lab and others have explored how steric interactions between ligands or between ligands and the material surface can impair proper ligand exposure and reduce receptor interactions [44-47]. Therefore, to ensure high-affinity binding, it is essential to confirm that the selected peptide ligand retains its desired configuration after integration into the biomaterial.

High-affinity ligands can be incorporated into materials through two main approaches: pre-functionalization and post-functionalization (**Fig. 2e-f**). In pre-functionalization, the ligand is conjugated to the material building block prior to self-assembly. This method is commonly used to achieve a high density of ligand presentation, but it can limit the tunability of material properties since the entire system must be optimized as a whole [28, 29, 46, 47]. In some cases, supramolecular assemblies formed may exhibit an excessively high ligand density, requiring the use of a co-assembly strategy to dilute the ligand concentration. On the other hand, post-functionalization involves assembling the material first and then conjugating the ligand onto its surface. This approach offers greater flexibility, as the material and ligand properties can be tuned independently before conjugation. It also allows for cross-conjugation between peptide and non-peptide materials [17, 48, 49]. However, post-functionalization can make it difficult to achieve high ligand density. In such instances, maximizing the number of ligands conjugated becomes essential, as conjugation efficiency is often low and may be hindered by steric effects.

Optimization of key design characteristics—such as ligand valency, presentation at the interface, and conjugation methods—is critical to the success of engineered high-affinity biomaterials. These design elements are inherently interconnected, meaning that modifying one characteristic often impacts the others. Despite significant progress in the field, tuning these parameters remains largely a case-by-case endeavor, requiring careful tailoring to meet the specific requirements of each system. However, with recent advancements in computational modeling and simulation, there is hope that more generalized design principles can be developed in the future. In the meantime, a systematic and thoughtful

consideration of the principles outlined above can greatly streamline the design process and improve the likelihood of success.

High-Affinity Materials for Regenerative Medicine These design principles have been successfully applied across numerous areas of biomedical research. In the context of regenerative medicine, peptide biomaterials have been extensively explored as extracellular matrix (ECM)-mimicking scaffolds to promote tissue regeneration after trauma, disease, or aging, often conjugated to various cell signaling, cell adhesion, and cell growth-promoting peptide ligand sequences [50-55]. For decades, the Stupp lab has worked to develop and optimize epitope-presenting peptide nanofiber gels as artificial bioactive scaffolds for cell adhesion, with particular focus on factors controlling the presentation of RGD ligands to enhance integrin binding [46, 47, 56]. Studies have consistently demonstrated the importance of spacing ligands both from each other (**Fig. 3a**)—using branched peptides or lower ligand-to-filler peptide amphiphile ratios (ideally 1:9 by weight) [47, 56] —and radially from the fiber surface, through the use of longer linker sequences (**Fig. 3b**) [46]. These findings align with work from the Tirrell lab, which showed that while increasing RGD peptide ligand densities on ECM-mimicking substrates initially improved cell adhesion and proliferation, beyond a certain point, further increases in ligand density offered minimal benefits [57, 58]. Post-functionalization strategies have been employed to stabilize ligand structures and enhance ligand-cell interactions. For example, Hartgerink and coworkers demonstrated that covalently capturing lysine-glutamic acid interactions within collagen-mimicking peptides (CMPs) stabilized their preferred triple helical structure, resulting in improved thermal stability and enhanced integrin binding [48]. Thus, both ligand density control and chemical post-functionalization are powerful tools to ensure peptide ligands are presented in their optimal conformation.

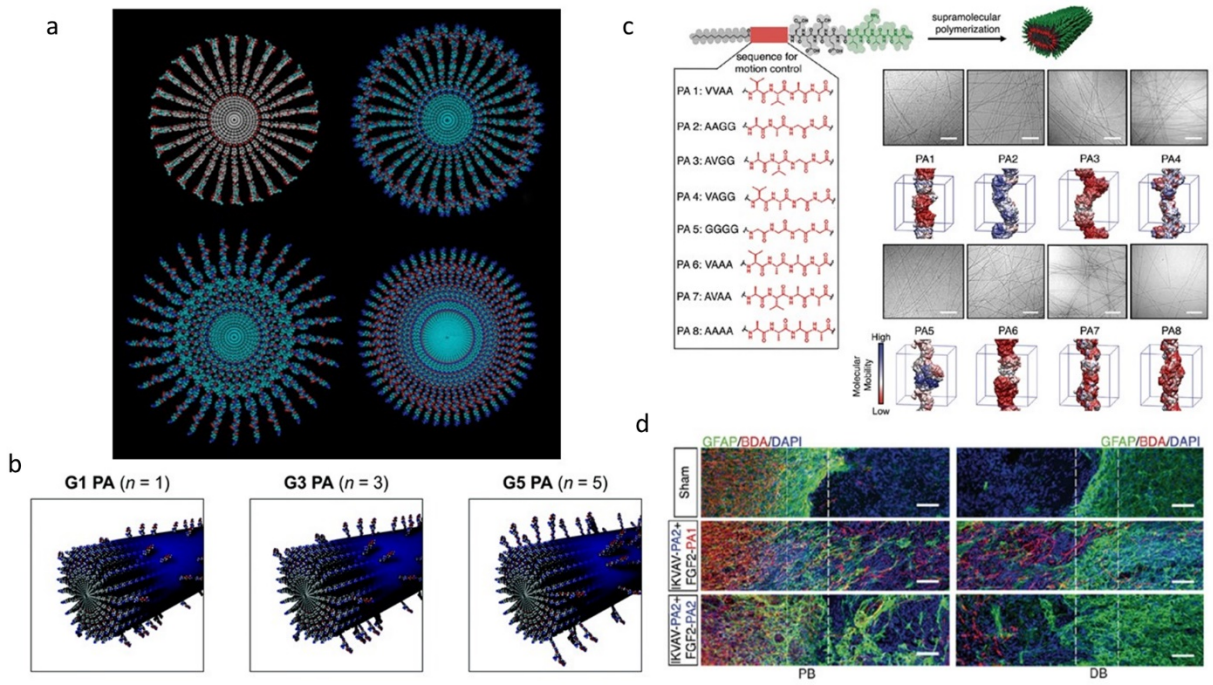

Figure 3. Peptide-based supramolecular nanofibers developed by the Stupp Group for use in regenerative medicine: (a) Cross-sections of nanofibers formed using four different branched and linear peptide

amphiphiles [47]. (b) Molecular graphics representation of RGD ligand display on co-assembled peptide nanofiber surfaces, with linker containing one (G1), three (G3), or 5 (G5) glycine residues [46]. (c) Chemical structures, cryo-TEM micrographs, and color-coded representations of RMSF values of IKVAV-containing peptide amphiphiles (d) Fluorescent micrographs of longitudinal spinal cord sections treated with sham or IKVAV-containing peptide amphiphiles [59].

In their efforts to develop supramolecular peptide nanofiber hydrogels for spinal cord injury, the Stupp Group found that a high density of epitope display is crucial for promoting the rapid differentiation of neural progenitor cells into neurons, while simultaneously discouraging the formation of astrocytes [60]. This selective and accelerated differentiation was attributed to the amplification of bioactive epitope presentation by the IKVAV-bearing nanofibers. To further investigate the role of epitope density in this process, the group conducted experiments using networks with varying ratios of IKVAV-PA and EQS-PA molecules. Immunocytochemistry data from these systems revealed that the epitope density surrounding the cells plays a critical role in promoting neuron differentiation within just one day. The IKVAV nanofibers were shown to amplify the epitope density by approximately a factor of 1000 compared to a laminin monolayer. More recently, the Stupp lab identified another significant factor in enhancing ligand-cell interactions: molecular mobility. Their research demonstrated that alanine-based gels, or co-assemblies of valine and alanine-based molecules, formed more dynamic supramolecular assemblies, likely due to reduced hydrogen bonding interactions (**Fig. 3c**). This increased mobility enhanced the bioactivity of the peptide gels and resulted in higher rates of axon regrowth in murine spinal cord injury models (**Fig. 3d**) [59]. The added molecular movement in these systems may help to alleviate steric hindrance and conformational locking, which can impede cellular interactions. This is further supported by the observation that cells encapsulated in more rigid alanine-based IKVAV gels did not survive. These results suggest that the molecular mobility within ligand-presenting peptide assemblies is an important factor to consider when designing high-affinity biomaterials.

High-Affinity Materials for Drug Delivery High-affinity ligand presentation is crucial in targeted drug delivery, as various ligand molecules, including peptides, small molecules, and antibodies, have been employed to facilitate the preferential accumulation of therapeutic agents at disease sites [61-64] [65] [66]. These ligands enhance the specificity of drug delivery systems by targeting overexpressed receptors on diseased cells, such as those found in cancer or inflamed tissues. By binding to these receptors, drug-laden nanoparticles or delivery vehicles can accumulate in the targeted area, selectively releasing their therapeutic cargo to minimize off-target effects and reduce systemic toxicity. Proper ligand-receptor interactions are essential not only for accumulation in the target tissue but also for influencing key cellular processes such as internalization, signaling, and drug release. For example, triggering receptor-mediated endocytosis can significantly enhance drug uptake, whereas weak or non-specific binding may lead to suboptimal delivery and diminished therapeutic efficacy.

The density, orientation, and spatial arrangement of ligands on the surface of the delivery vehicle are critical factors influencing binding affinity and cellular uptake (**Fig. 4a-c**). High ligand density can increase receptor engagement, but excessive clustering or improper orientation can result in steric hindrance, reducing binding efficiency. Therefore, precise control over ligand presentation is necessary to optimize interactions between the drug delivery vehicle and target cells, ultimately improving treatment outcomes. For instance, the Collier lab found that ligand valency and density were key factors in generating broad antibody responses in mouse models using peptide nanofibers for vaccines (**Fig. 4b**). Mice immunized with fibers containing multiple ligands produced higher antibody levels than those

immunized with a single ligand type [67]. In developing anti-HIV vaccines, the Collier group also discovered that high crosslinking and low ligand loading concentrations reduced ligand presentation on the fiber surface, leading to lower antibody titers (**Fig. 4a**). This reduction was partially linked to fewer T and B cells in murine lymph nodes, though additional factors beyond antigen spacing, such as complementary binding, were also suggested [68].

Ligand spacing remains a critical factor in drug delivery vehicle efficacy. Anderson et al. demonstrated that unassembled DX600 peptide ligands were more effective at binding and immobilizing ACE2 enzymes than when presented on supramolecular peptide filaments (**Fig. 4c**). The high local concentration of ligands on the filament surface caused steric hindrance, limiting enzyme diffusion and binding. Increasing the filler-to-ligand ratio alleviated these effects, improving enzymatic inhibition [69]. Ligand distribution on drug carrier surfaces also plays a crucial role in effective docking with target cells, as the method of ligand conjugation can significantly impact uniformity. Chemical branching has been utilized to control the placement and density of folate ligands on peptide-polymer dendrimer surfaces. Moderate clustering of ligands facilitated multiple ligand-receptor interactions, but excessive clustering led to steric hindrance and reduced binding efficiency [17, 70]. However, controlling ligand presentation, particularly for pre-functionalized carriers, can be challenging. Jackson et al. observed that the self-assembled outer layer of ligands around metallic particle cores formed distinct bands, compromising uniformity [71].

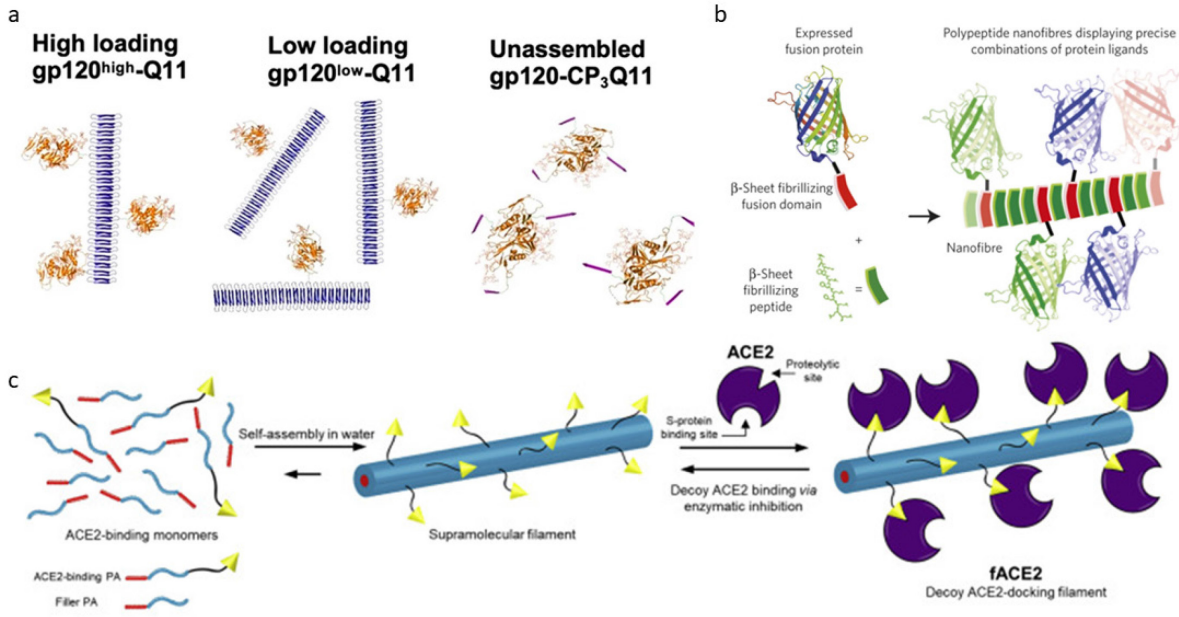

Figure 4. High-affinity peptide materials developed for use in drug delivery. (a) Schematic of antigens displayed on peptide nanofibers at varying loading concentrations, compared to unassembled antigens modified with non-assembling antigens [68]. (b) Schematic representation of fusion proteins engineered with a fibrillizing domain to integrate into peptide nanofibers [67]. (c) Co-assembly of ACE2-binding and filler peptide amphiphiles to form supramolecular filaments capable of binding to the proteolytic site of ACE2 [69].

Another key consideration in targeted delivery is the potential for ligands to become embedded within the PEG corona. PEGylation of nanoparticle surfaces is commonly used to impart stealth characteristics and extend circulation time in the bloodstream, but dense PEG coronas can mask high-affinity ligands, limiting

accessibility to cell receptors. The Tirrell lab demonstrated that adjusting the relative lengths of PEG chains and peptide ligands can control ligand accessibility and human melanoma cell adhesion to membrane surfaces [72]. Membranes with shorter PEG chains compared to peptide ligands exhibited high cell adhesion, while those with longer PEG chains showed minimal adhesion. Even when PEG and ligand lengths were comparable, cells adhered but did not spread, likely due to PEG masking the cell receptors required for spreading. These findings highlight the importance of carefully considering drug delivery vehicle synthesis and conjugation density when designing high-affinity carriers.

High-affinity interactions have been effectively utilized in the design of peptide-based hydrogels for controlled drug release applications.[19] Many existing systems predominantly rely on electrostatic complexation, where therapeutic cargoes carrying opposite charges (e.g., RNA, DNA, STING agonists, antibodies, and proteins) form stable complexes with peptide assemblies, enabling efficient drug encapsulation and prolonged release. [73-79] By leveraging the responsive nature of peptides and their assemblies, these affinity-controlled systems can be further engineered to respond to environmental triggers—such as changes in pH or enzymatic activity—allowing for sustained or stimuli-responsive drug release. [80-83] Incorporating ligand-receptor systems into peptide-based hydrogels presents additional opportunities for achieving high specificity and precisely tunable release profiles. [84-86] However, this strategy requires careful optimization to preserve both the binding affinity and ligand accessibility within the hydrogel matrix, ensuring that drug loading capacity and release kinetics meet therapeutic objectives. While still in its early stages, the versatility of high-affinity peptide hydrogels positions them as a promising platform for delivering therapeutic molecules.

High-Affinity Materials for Molecular Purification The specificity and high-binding efficiency of peptides can be leveraged to enhance the purification of biomolecules or ions of interest. Peptide-based materials have become indispensable across various fields, including biotechnology, biopharmaceuticals, and environmental science, due to their ability to target and bind with precision. In the biopharmaceutical industry, the growing and widespread use of monoclonal antibodies (mAbs) in therapeutic applications—such as cancer treatments, autoimmune disorders, and immunotherapies—has created an urgent need for more efficient and cost-effective purification methods [87]. Traditional techniques, such as chromatography, are often time-consuming, expensive, and labor-intensive, creating bottlenecks in the production process. High-affinity peptide biomaterials offer an innovative alternative. The Cui Lab, for example, has utilized high-affinity peptide biomaterials to optimize the purification of mAbs through affinity precipitation [37, 88]. By employing peptide ligands like Z33, which exhibit strong binding affinity to the Fc region of mAbs, they were able to significantly improve both the yield and purity of mAbs from complex cell culture mixtures. This method provides a more streamlined and efficient alternative to traditional chromatographic techniques, illustrating how peptide biomaterials can be customized for specific targets, thus enhancing overall purification processes. Peptide-based materials have also been developed for environmental applications. For instance, Tirrell and coworkers applied peptide ligands for phosphate extraction from wastewater, addressing both pollution control and resource recovery [89]. By selecting a phosphate-binding hexapeptide sequence, the team was able to efficiently capture and recycle phosphate ions, which can then be repurposed for agricultural or industrial use. This approach not only addresses environmental concerns related to wastewater management but also offers a sustainable method for reclaiming valuable resources.

A key consideration in both applications is the presentation and density of peptide ligands on the material surface. The Cui Lab found that fibers composed solely of high-affinity ligand molecules were ineffective

at purifying mAbs, despite their strong affinity in the monomeric, unassembled state. The introduction of filler molecules to space out the ligands along the fiber surface reduced steric hindrance and allowed for proper mAb-fiber binding (**Fig. 5a-c**). This adjustment led to a significant increase in the yield of pure mAbs from cell culture effluent [88]. In developing high-affinity elastin-like polypeptides (ELPs) for mAb purification, the Chen Lab discovered that a ligand-to-mAb ratio higher than the theoretically sufficient 2:1 ratio is often required to successfully precipitate more than 95% of the mAbs in solution (**Fig. 5d-e**) [90]. By contrast, He et al has recently shown that their supramolecular system, which involves the formation of self-assembled fibers presenting the WPRWLEN binding epitope, had 38-fold higher binding affinity to their target mAb than monomeric ligand alone, a fact the authors attributed to their fiber's polyvalent ability to bind to multiple sites on a single mAb. Nevertheless, purely maximizing ligand density did not lead to the highest mAb recovery [91]. In the phosphate separation work by the Tirrell Lab, pH control was critical to the success of their phosphate-binding system. While free hexapeptide ligands showed optimal binding at high pH levels (10-11), their assembled hexapeptide micelles exhibited peak binding at pH 6. Simulation studies revealed that at higher pH, the neutralization of lysine charges in the phosphate-binding region caused the peptide amphiphile headgroup to collapse, restricting access to the binding sites [89]. This highlights the importance of carefully tuning environmental conditions, such as pH, to maintain ligand conformation and optimize binding efficiency.

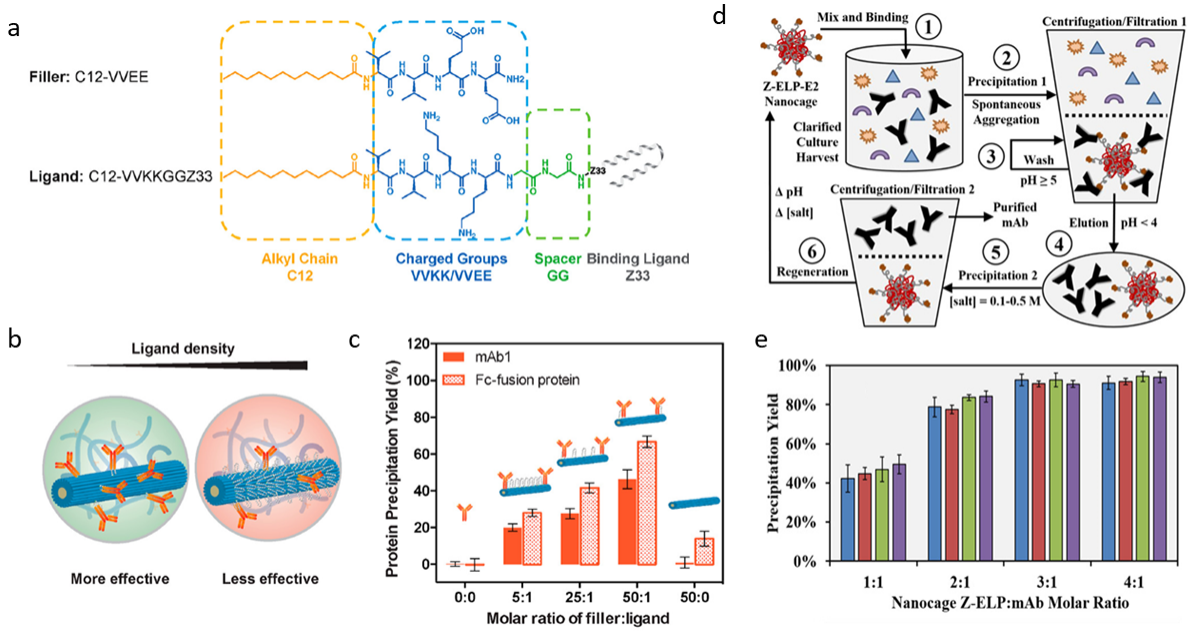

Figure 5. High-affinity peptide biomaterials developed for purification of monoclonal antibodies (mAbs). (a) Chemical structures of co-assembling ligand and filler peptide amphiphiles. (b) Schematic representation of the effect of ligand density on peptide nanofibers and their binding to mAbs. (c) Macroscopic phase separation yield of mAbs and Fc proteins at varying ligand densities, illustrated by different filler-to-ligand ratios [88]. (d) Schematic of the Z-ELP-E2 nanocage process for mAb purification. (e) Phase separation yield of mAbs at different nanocage-to-mAb ratios [90].

These examples illustrate that simply conjugating a high-affinity ligand to a material does not guarantee success. Careful consideration of material design principles—including ligand presentation, density, and

environmental factors such as pH—is essential to ensure the effectiveness of the technology. The balance between ligand accessibility, steric hindrance, and environmental responsiveness is key to achieving high-performance purification systems for both biopharmaceutical and environmental applications.

Conclusion The simplicity of synthesis, versatility in sequence design, potential for self-assembly, and inherent ability to interface with biological systems make peptides highly attractive for a wide range of applications.[92] However, despite these advantages, designing high-affinity peptide biomaterials demands meticulous attention. Beyond selecting an appropriate ligand—ideally multivalent ligands to enhance interactions—factors such as conformational stability, ligand density, accessibility, and the method of conjugation to the underlying material must be carefully optimized to achieve optimal binding and desired functionality. Each of these parameters must be balanced to ensure that the material performs effectively for its intended application. In this Opinion, we have highlighted how thoughtful design and engineering have enabled high-affinity peptide materials to succeed in fields such as regenerative medicine, drug delivery, and molecular purification. These successes underscore the importance of a systematic and integrated design strategy to fully exploit the unique properties of peptides. Nevertheless, the complexity of peptide-based systems, including the diversity of ligand-receptor interactions, the complexity of biological environment, and the dynamic and sometimes kinetically trapped nature of self-assembly, often presents significant challenges to achieving precise material performance.

Looking ahead, continued research and the integration of advances in computational modeling will further unlock the potential of these technologies. Computational tools such as molecular dynamics simulations, docking algorithms, and machine learning offer new ways to predict, analyze, and optimize peptide-receptor interactions with greater accuracy and efficiency. Molecular simulations can reveal critical insights into the structural and energetic landscapes of multivalent ligand-receptor complexes, enabling researchers to fine-tune binding affinity, stability, and accessibility. Machine learning approaches, on the other hand, are rapidly emerging as powerful tools for processing large datasets to identify patterns, predict outcomes, and accelerate the discovery of novel peptide sequences optimized for specific targets or functions. [93] The integration of these computational frameworks into the design process will allow researchers to rapidly explore vast design spaces that would be infeasible using experimental methods alone. This synergy between experimental and computational approaches will not only drive innovation but also help overcome current challenges in achieving high-affinity interactions, optimizing self-assembly, and engineering multifunctional materials.

Acknowledgements

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