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REVIEW

Peptide-Based Nanocarriers for Targeted Drug Delivery: Recent Advances, Strategies, and Therapeutic Frontiers

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Abstract: The advancement of nanomedicine has significantly reshaped drug delivery strategies by overcoming key limitations of conventional pharmacotherapy, such as off-target toxicity, poor bioavailability, and adverse drug reactions (ADRs). Among emerging delivery platforms, peptide-based nanocarriers offer high biocompatibility, molecular specificity, and structural versatility for precision targeting. This review presents a comprehensive synthesis of current progress in the design, fabrication, and therapeutic application of peptide-functionalized nanocarriers for targeted drug delivery. Literature published between 2016 and 2025 was examined, with particular focus on strategies for peptide incorporation, including physical encapsulation, chemical conjugation, and self-assembly. Diverse nanocarrier platforms are discussed, including liposomes, solid lipid nanoparticles (SLNs), dendrimers, polymeric micelles, mesoporous silica nanoparticles (MSNs), and hybrid systems. Recent innovations in biodegradable polymers, co-delivery platforms, multifunctional assemblies, and stimuli-responsive formulations are highlighted. Advances in peptide design, particularly the use of cyclic and stapled peptides, have improved structural stability, target affinity, and bioavailability. Mechanistic insights into peptide-mediated targeting and physicochemical optimization are reviewed across various therapeutic contexts, including cancer, neurological disorders, infectious diseases, and inflammatory diseases. Their role in gene delivery applications, such as siRNA, mRNA, and CRISPR-Cas9 cargo delivery, is also highlighted, emphasizing the potential of peptide-functionalized systems in enabling safe and targeted nucleic acid therapeutics. Looking ahead, the development of intelligent nanocarriers capable of responding to physiological stimuli, such as pH shifts, enzymatic activity, and redox gradients, will enable spatiotemporal control of drug release. Progress in peptidomimetics and synthetic analogues, including D-amino acids, is expanding the chemical toolkit to overcome limitations of native peptides. In parallel, the integration of artificial intelligence, machine learning, and predictive modeling tools is accelerating the rational design and optimization of peptide sequences and nanocarrier architectures. Nonetheless, clinical translation remains limited by peptide instability, potential immunogenicity, off-target effects, and the complexities of manufacturing and regulatory approval. Together, these advances establish peptide-based nanocarriers as a critical component in the next generation of personalized and precision nanomedicine.

Keywords: peptide-based nanocarriers, targeted drug delivery, peptide-mediated targeting, stimuli-responsive nanomedicine, gene delivery, nucleic acid therapeutics

Introduction

Despite remarkable progress in modern medicine, adverse drug reactions (ADRs) remain a persistent and serious challenge, contributing substantially to patient morbidity, mortality, and global healthcare costs.[1–8] These unintended effects often arise from a combination of patient-specific traits and drug-related factors, including dosage, metabolism,

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and drug–drug interactions.[9,10] Conventional drug delivery systems (DDSs) frequently exacerbate these issues due to poor tissue specificity, uncontrolled release profiles, and their inability to account for interindividual variability, resulting in systemic toxicity and suboptimal therapeutic outcomes.[11–14]

To address these limitations, targeted DDSs have been developed to enable site-specific delivery and controlled drug release, thereby improving efficacy while minimizing off-target effects. Innovative approaches such as nanocarriers, liposomes, microneedles, 3D-printed dosage forms, and smart hydrogels have expanded the possibilities for precise drug transport, enhancing pharmacokinetics, patient compliance, and overall treatment safety.[11,13,15–22] Among these, nanotechnology has emerged as one of the most promising solutions, with nanocarriers offering tunable physicochemical properties that support precise targeting, controlled release, and improved pharmacokinetic behavior. Their small size, modifiable surface chemistry, and ability to encapsulate diverse therapeutic agents enable the selective delivery of therapeutic agents to diseased tissues while minimizing damage to healthy ones. As versatile platforms, nanocarriers are increasingly significant in both research and clinical contexts, enhancing therapeutic efficacy, reducing toxicity, and enabling the delivery of advanced modalities such as RNA therapeutics and gene-editing tools.[23,24]

In parallel, peptide-based DDSs have gained attention as complementary approaches to targeted therapy. Peptides, composed of 2–50 amino acids, offer high biological specificity, efficient cellular penetration, and controllable pharmacokinetics.[25] They can mimic endogenous molecules such as hormones, ligands, and growth factors, enabling precise interaction with cellular receptors. Their biocompatibility, ease of synthesis, chemical versatility, and stability further support their pharmaceutical potential. While peptide-drug conjugates (PDCs) exemplify how peptides enhance targeting and reduce off-target toxicity, these small covalent constructs typically lack nanoscale carrier components and are therefore distinct from nanocarrier-based systems.[26–30]

The term peptide-mediated drug delivery is often used broadly to encompass PDCs, self-assembling peptide carriers, and peptide-functionalized nanocarriers. However, these strategies differ in design and mechanism. Peptide-based nanocarriers refer specifically to nanoscale delivery platforms, such as liposomes, polymeric nanoparticles, micelles, dendrimers, or self-assembled peptide nanostructures that incorporate peptides as targeting ligands, structural elements, or stimuli-responsive components. This review focuses on this category, emphasizing how peptides can be strategically integrated into nanocarrier architectures to enhance delivery specificity, tissue penetration, and therapeutic efficacy.[26–30] A conceptual overview of how peptide-based nanocarriers overcome the limitations of conventional DDSs, as well as their distinct roles within the broader landscape of peptide-mediated therapeutics, is illustrated in Figure 1.

Incorporating peptides into nanocarriers significantly improves targeting precision and biological interactions. Peptides can be grafted onto carrier surfaces to mediate receptor-specific binding, embedded within carrier matrices to tune release kinetics, or used as stimuli-responsive motifs for triggered release. These strategies offer important therapeutic benefits, including enhanced efficacy, reduced systemic toxicity, and improved outcomes in disease-specific applications.[28] Consequently, peptide-based nanocarriers represent a powerful and versatile platform for next-generation therapeutics, particularly in oncology, inflammation, and nucleic acid delivery.[31–37]

Notably, a small number of nanocarrier systems incorporating peptide components have achieved clinical translation. The peptide-containing liposomal formulation mifamurtide (Mepact®) has been approved in Europe for osteosarcoma, representing a clinically validated peptide-based nanocarrier.[38,39] In addition, glutathione-decorated PEGylated liposomal doxorubicin (2B3-101), which uses the tripeptide glutathione as a targeting ligand to enhance blood–brain barrier delivery, has been evaluated in early-phase clinical trials for brain tumors, demonstrating safety and preliminary central nervous system (CNS) delivery.[40,41] Although these examples highlight the feasibility of peptide-functionalized nanocarriers in humans, the overall clinical translation remains limited, with most systems still in preclinical development.

Key challenges include optimizing carrier design, achieving stable and efficient peptide incorporation, understanding complex biological interactions, and ensuring safety and reproducibility.[42] Addressing these challenges is crucial for realizing their full therapeutic potential. While several reviews have focused on self-assembled carriers or surface-functionalized systems, relatively few have examined peptide incorporation strategies across diverse nanocarriers, particularly for stimuli-responsive and gene delivery platforms. This review addresses this gap by linking peptide design, carrier engineering, and translational considerations. It surveys major nanocarrier classes and incorporation strategies, examines targeting mechanisms, highlights recent design advances, evaluates therapeutic applications, and focuses on

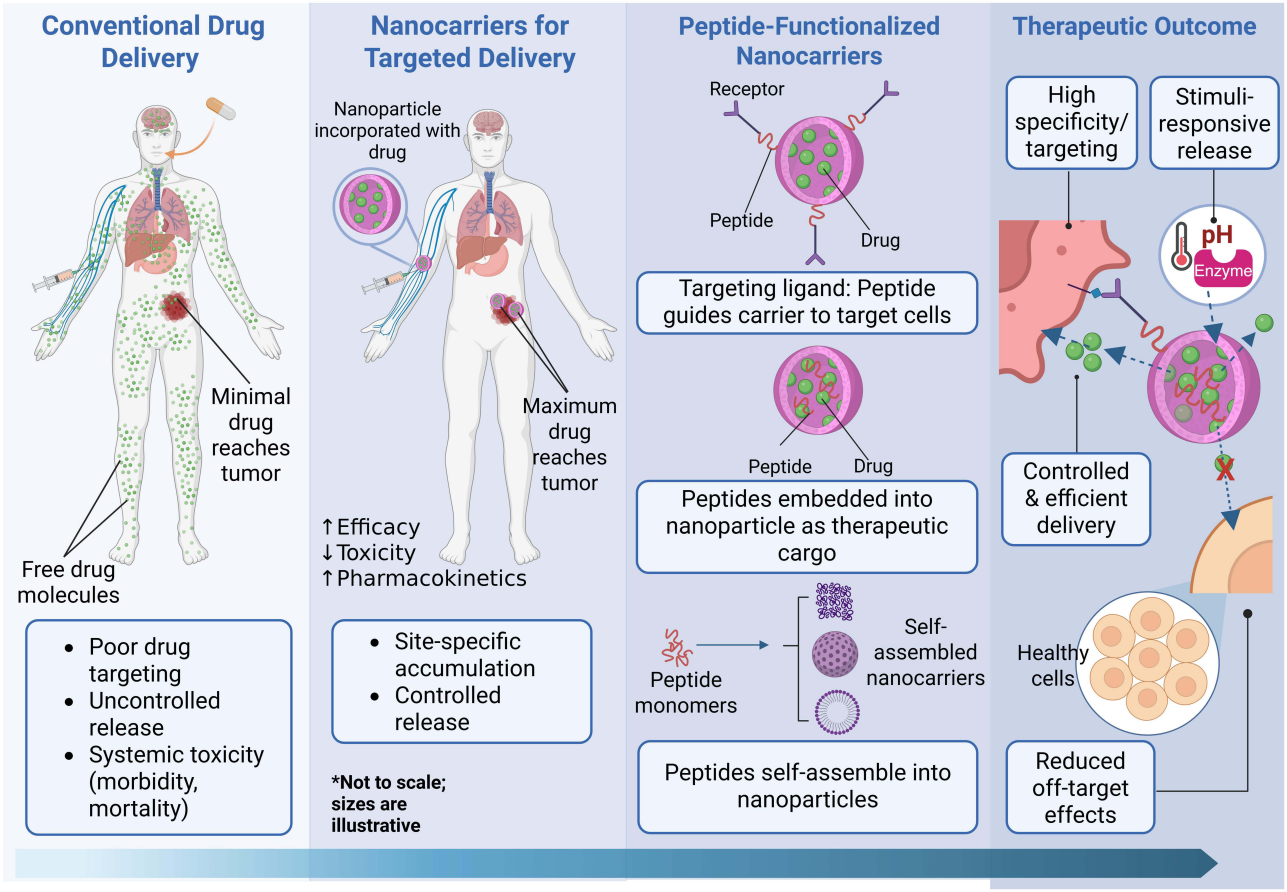

Figure 1 Conceptual Overview of Peptide-Based Nanocarriers for Targeted Drug Delivery. Conventional drug delivery systems are often limited by poor specificity, uncontrolled release, and systemic toxicity. Nanocarriers offer enhanced targeting, controlled release, and improved pharmacokinetics. Peptides, with their high specificity and biological activity, can be integrated into nanocarriers as targeting ligands, structural components, or stimuli-responsive motifs, thereby enhancing the precision of delivery and therapeutic efficacy. Peptide-based nanocarriers encompass a diverse range of platforms, including self-assembled peptide nanostructures and peptide-functionalized nanoparticles, and hold significant promise in applications such as oncology, inflammation, and nucleic acid therapeutics. Upward arrows (↑) indicate an increase, downward arrows (↓) indicate a decrease; dashed blue arrows represent active targeting or functional interactions with diseased cells, while the red cross denotes the absence of interaction with healthy cells.

studies from 2016 to 2025, reflecting the shift toward rational peptide engineering and translationally oriented nanomedicine.

Data Extraction Management

A literature search was conducted for studies published between 2016 and 2025 using PubMed, Web of Science (WoS), Scopus, and Google Scholar, reflecting a period of rapid advancement in peptide-based nanocarrier design and application. The search strategy employed the following keywords: “peptide-based nanocarriers”, “targeted drug delivery”, “peptide-mediated targeting”, “stimuli-responsive nanomedicine”, “gene delivery”, “nucleic acid therapeutics”.

Nanocarrier Platforms for Peptide Encapsulation

Therapeutic agents can be encapsulated inside, entrapped within, chemically linked to, or adsorbed onto the surface of nanoparticles, enabling delivery of a wide range of payloads, including both hydrophilic and hydrophobic compounds of varying molecular sizes.[43] Nanomedicine supports advancements in treatment, prevention, and diagnosis across numerous diseases. Nanocarriers are typically below 500 nm in size, with a high surface area-to-volume ratio that enhances drug solubility, stability, and preservation of bioactivity. These features also support controlled and targeted delivery, reducing systemic toxicity and off-target effects. Moreover, nanocarriers help circumvent biological barriers, including

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the blood-brain barrier, and facilitate the delivery of novel therapeutics such as RNA-based drugs and gene-editing technologies. Collectively, these advantages underscore the pivotal role of nanocarriers in overcoming limitations of conventional pharmacotherapy and improving the efficacy and safety of both current and next-generation therapeutics.[24]

To address the specific challenges associated with peptide delivery, a diverse range of nanocarrier platforms has been developed. These can be broadly classified according to their composition, structure, and functional attributes. Lipid-based nanocarriers, such as liposomes and solid lipid nanoparticles, are extensively studied due to their high biocompatibility, structural versatility, and capacity to protect peptides while enabling controlled and targeted delivery. Polymeric nanocarriers, including dendrimers and polymeric micelles, offer precise control over size, architecture, and surface functionality, facilitating efficient peptide encapsulation or conjugation, enhanced cellular uptake, and tunable release profiles. Inorganic nanocarriers, exemplified by mesoporous silica nanoparticles, provide high loading capacity, exceptional structural stability, and stimuli-responsive release capabilities, making them attractive for delivering sensitive peptide cargos. To overcome the limitations of single-material systems, hybrid nanocarriers integrate organic and inorganic components, combining biocompatibility with mechanical robustness and improved release control. In parallel, stimuli-responsive nanocarriers represent an advanced class of delivery systems capable of releasing peptides in response to specific physiological or external triggers, thereby enhancing site-specific delivery and minimizing off-target effects.[24,40,41] These major classes of nanoparticles are illustrated in Figure 2, and their key structural features, advantages, representative applications, and clinical status in peptide delivery are summarized in Table 1.

Lipid-Based Nanoparticles

Liposomes

Liposomes remain one of the most clinically successful nanocarriers for peptide delivery, with multiple approved formulations and several liposome-based vaccines already on the market, although most approved products are not

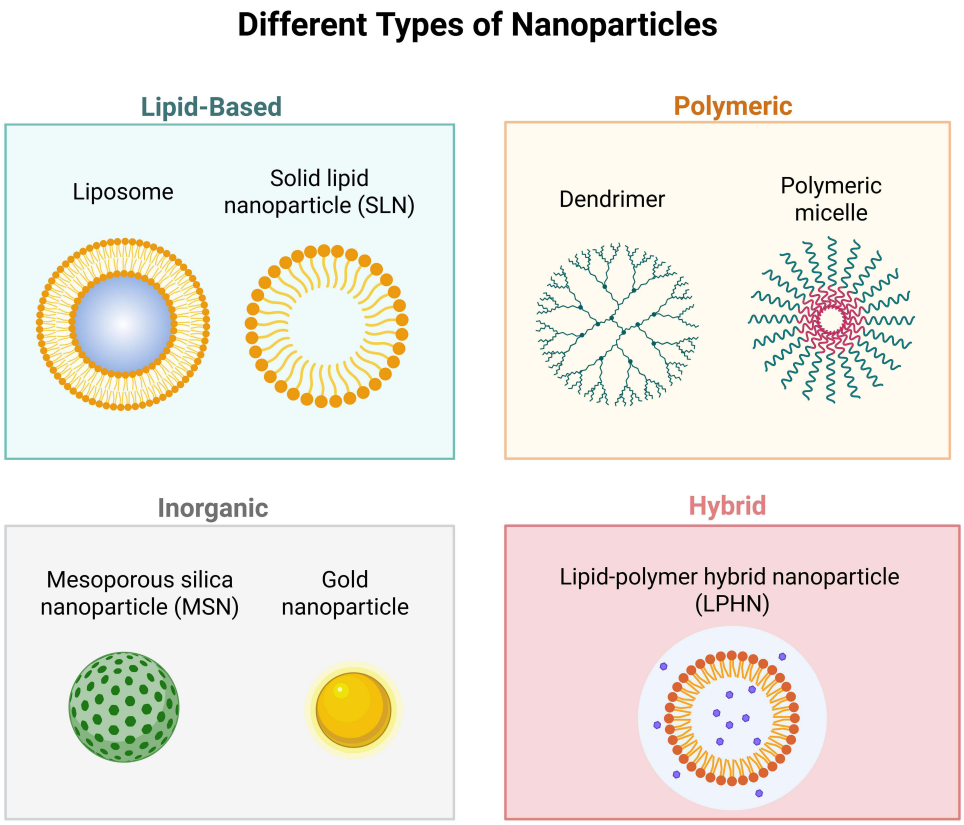

Figure 2 Overview of nanoparticles as drug delivery systems. Four major types of nanoparticles are shown: 1) lipid-based, including liposomes and solid lipid nanoparticles (SLN); 2) polymeric, including dendrimers and polymeric micelles; 3) inorganic, including mesoporous silica nanoparticles (MSN) and gold nanoparticles; and 4) hybrid systems such as lipid–polymer hybrid nanoparticles (LPHN).

Table 1 Summary of Major Nanocarrier Types for Peptide Delivery, Including Structural Characteristics, Key Advantages, Representative Applications, and Clinical Status or Limitations

Nanocarrier Type	Structure & Size	Key Advantages of Peptide Delivery	Applications/ Examples	Clinical Status/ Limitations	Refs.
Liposomes (lipid-based)	Spherical lipid vesicles with one or more bilayers surrounding an aqueous core; typically ~50–500 nm	High biocompatibility and low immunogenicity; encapsulate hydrophilic peptides (aqueous core) and hydrophobic/ amphiphilic peptides (bilayer); protect peptides from enzymatic degradation; prolonged circulation (PEGylation); surface functionalization for targeting; controlled/ sustained release	Cancer therapy (anticancer peptides via EPR or active targeting); vaccine delivery (peptide antigens); metabolic and cardiovascular diseases; examples include uterine-targeted leuprolide acetate liposomes and angiogenic peptide-loaded PEGylated liposomes	Several FDA/EMA-approved products (eg., Doxil®, Mepact®); strong clinical translation record; challenges include stability, leakage, and scale-up for complex functionalized systems	[39, 44–53]
Solid lipid nanoparticles (SLNs; lipid-based)	Solid lipid core stabilized by surfactants; ~50–1000 nm; lipids remain solid at room and body temperature	Improved physical stability vs liposomes; protection from enzymatic degradation; controlled and sustained release; enhanced bioavailability; suitable for oral, parenteral, and topical delivery; low toxicity and scalable production	Cancer therapy; hormone replacement (eg., insulin, leuprolide); vaccines; neurodegenerative diseases; topical antifungal SLN gels (oxiconazole, miconazole)	Mostly preclinical; very limited clinical translation (one Phase I SLN trial); need more robust clinical data despite a favorable safety profile	[54–61]
Dendrimers (polymer-based)	Highly branched, monodisperse polymers with core–shell architecture and multivalent surface groups; size depends on generation (typically <10–20 nm)	Precise size and surface control; multivalency enables high peptide loading and targeting; peptides can be encapsulated or conjugated; improved stability, bioavailability, and cellular uptake; potential self-adjuvanting effects	Vaccine delivery (peptide antigens); immunotherapy; peptide stabilization and targeted delivery; poly(amidoamine) (PAMAM) dendrimers commonly used	Very limited clinical success; only one approved product (VivaGel®); peptide-loaded dendrimers largely remain preclinical; concerns include cytotoxicity, long-term safety, and large-scale synthesis	[62–67]
Polymeric micelles (polymer-based)	Self-assembled amphiphilic block copolymers with hydrophobic core and hydrophilic shell (often PEG); ~10–100 nm	Excellent solubility and stability in circulation; suitable for hydrophobic or amphiphilic peptides; long circulation and EPR-based tumor accumulation; surface functionalization and stimuli responsiveness enable controlled release	Anticancer, antidiabetic (insulin, insulin glargine), and antimicrobial peptides; Genexol® PM (paclitaxel micelle) as a clinical example	Some formulations approved or in trials (mainly for small molecules); limitations include low drug-loading capacity and potential instability upon dilution	[68–74]

(*Continued*)

Table 1 (Continued).

Nanocarrier Type	Structure & Size	Key Advantages of Peptide Delivery	Applications/ Examples	Clinical Status/ Limitations	Refs.
Mesoporous silica nanoparticles (MSNs; Inorganic-Based Nanoparticles)	Rigid silica framework with ordered mesopores (2–50 nm); particle size ~50–200 nm	High surface area and peptide loading; protection from enzymatic degradation; chemical and thermal stability; tunable pores; stimuli-responsive gatekeepers; easy surface functionalization	Anticancer peptides; antimicrobial peptides (eg., LL-37); peptide-based vaccines; theranostic platforms	Mainly preclinical; concerns over long-term accumulation and biodegradability; biodegradable MSNs under development	[75–83]
Hybrid nanocarriers (eg., lipid–polymer hybrids)	Composite of organic + inorganic materials (polymeric core + lipid shell); ~50–200 nm	Combines lipid biocompatibility with polymer/inorganic stability; high peptide encapsulation; controlled release; versatile functionalization	Cancer therapy, metabolic disorders, immunomodulation, lipid–polymer hybrid nanoparticles (LPHNs) are widely studied	Mostly preclinical to early clinical; formulation complexity and scale-up challenges	[84–86]
Enzyme-responsive systems	Nanocarriers with enzyme-cleavable elements (protease/ phospholipase-sensitive motifs)	Enzyme-triggered, site-specific peptide release; mild reaction conditions; self-regulated, on-demand delivery	Targeted peptide delivery in enzyme-rich pathological microenvironments (eg., tumors, gastrointestinal tract); collagenase-responsive PEG hydrogel enabling on-demand antimicrobial peptide release to prevent MRSA-induced osteomyelitis in SD rats	Preclinical; strong translational potential; clinical applicability limited by scalability, safety, regulatory validation	[37, 87, 88]
Thermo-responsive nanocarriers	Nanocarriers incorporating temperature-responsive elements that undergo reversible phase transitions at mildly elevated temperatures (~40–42 °C)	Temperature-triggered, site-specific peptide release; sustained/tunable release; preserves peptide stability	PNIPAM–I3K peptide hydrogel that undergoes sol–gel conversion above 33 °C for antibacterial peptide $G(IIKK)_3I\text{-}NH_2$ delivery	Preclinical; proof-of-concept studies; clinical validation pending	[37, 88]

peptide-functionalized systems.[44] As summarized in Table 1, their bilayered structure enables versatile peptide loading, allowing hydrophilic peptides to be encapsulated within the aqueous core while amphiphilic or hydrophobic peptides are incorporated into the lipid bilayer. This structural flexibility, combined with high biocompatibility and low immunogenicity, makes liposomes particularly effective at protecting peptides from enzymatic degradation and improving systemic stability.[45–47,53]

Beyond passive encapsulation, liposomal performance is strongly influenced by rational design parameters, including particle size, surface chemistry, and functionalization. For example, PEGylation (ie., coating with polyethylene glycol) is widely employed to prolong circulation time by reducing opsonization and reticuloendothelial clearance, while ligand- or peptide-functionalized surfaces enable enhanced tissue specificity through active targeting mechanisms.[48,49] Preclinical

studies have demonstrated that such design features can markedly affect biodistribution and therapeutic outcomes, as illustrated by uterus-targeted leuprolide acetate liposomes and angiogenic peptide-loaded PEGylated liposomes optimized for myocardial uptake.[50–52]

Clinically, the success of formulations such as Doxil®, a PEGylated liposomal doxorubicin that improves pharmacokinetics and reduces cardiotoxicity, and Mepact® (mifamurtide), a liposomal delivery system for the peptide-based immunomodulator muramyl tripeptide phosphatidyl-ethanolamine (MTP-PE), underscores the translational viability of liposomes as peptide carriers.[39] However, despite their maturity, challenges remain, particularly in maintaining formulation stability, minimizing peptide leakage, and achieving scalable manufacturing for increasingly complex, multifunctional systems. Ongoing clinical trials evaluating peptide-functionalized liposomes highlight continued efforts to address these limitations and further enhance specificity and therapeutic efficacy.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) represent a distinct class of lipid-based nanocarriers in which the lipid matrix remains solid at physiological temperatures, conferring enhanced physical stability and sustained drug release compared with vesicular systems such as liposomes (Table 1). This solid-core architecture is particularly advantageous for peptide delivery, as it improves protection against enzymatic degradation and enables prolonged maintenance of therapeutic concentrations.[54,55]

From a design perspective, the key differentiating feature of SLNs lies in their solid lipid matrix, which favors controlled release and formulation robustness, albeit with less flexibility for loading highly hydrophilic peptides compared with liposomes.[56] Consequently, SLNs have been most extensively explored in applications where stability, scalability, and low toxicity are prioritized, including cancer therapy, hormone replacement, vaccine delivery, and topical administration.[54,55,57,58]

Despite a substantial volume of preclinical research demonstrating favorable pharmacokinetics and safety profiles, clinical translation of classical SLNs remains limited. Analysis of registered clinical studies reveals that, although nanoparticle-based lipid systems have expanded considerably in recent years, only one conventional SLN formulation has progressed to a Phase I clinical trial (NCT03823040). In this study, oxiconazole-loaded SLNs incorporated into a carbopol gel showed improved patient satisfaction and reduced side effects compared with a marketed topical formulation, likely due to enhanced skin deposition and sustained drug release.[54,59] These findings are consistent with earlier reports demonstrating improved transdermal permeation and prolonged skin localization using miconazole-loaded SLNs.[60]

Collectively, these results highlight the promise of SLNs as safe and scalable peptide delivery platforms, particularly for topical and sustained-release applications. However, the limited number of clinical studies underscores the need for further translational research, standardized manufacturing strategies, and sustained investment to bridge the gap between preclinical success and clinical adoption.

Polymer-Based Nanoparticles

Dendrimers

Dendrimers are highly branched, monodisperse polymeric nanocarriers characterized by precise control over size, surface functionality, and architecture (Table 1). Their defining feature for peptide delivery is multivalency, which enables the simultaneous attachment or encapsulation of multiple peptide molecules, targeting ligands, or stabilizing moieties within a single nanostructure. This architectural precision allows dendrimers to address key challenges associated with peptide therapeutics, including poor stability, limited bioavailability, and inefficient cellular uptake.[62,63]

Among polymer-based nanocarriers, dendrimers are particularly attractive for vaccine delivery and immunotherapy, where the spatial presentation of peptide antigens plays a critical role in immune activation.[62] Preclinical studies, especially those involving poly(amidoamine) (PAMAM) dendrimers, have demonstrated enhanced peptide stability, improved immunogenicity,[64] and, in some cases, self-adjuvanting effects that eliminate the need for conventional adjuvants.[65] These features highlight the potential of dendrimers as modular platforms for peptide antigen delivery and immune modulation.

Despite these promising attributes, clinical translation of peptide-loaded dendrimers remains highly limited. To date, only a small number of dendrimer-based systems have entered clinical evaluation, largely focusing on safety and pharmacokinetics rather than peptide therapeutics.[66] Currently, VivaGel® (SPL7013) remains the sole approved dendrimer-based product, underscoring the significant translational gap between preclinical success and regulatory approval.[67] This gap is primarily attributed to persistent concerns regarding cytotoxicity, long-term biocompatibility, and the complexity of large-scale, reproducible synthesis.[63]

Ongoing advances in dendrimer engineering, including surface modification, PEGylation, and generation optimization, aim to mitigate these limitations and improve clinical feasibility.[63] Nevertheless, further systematic studies and translational investment are required before dendrimers can be widely adopted as clinically viable platforms for peptide delivery.

Polymeric Micelle

Polymeric micelles are self-assembled nanocarriers formed from amphiphilic block copolymers, featuring a hydrophobic core and a hydrophilic shell (Table 1). This core–shell architecture makes them particularly well-suited for the delivery of hydrophobic or amphiphilic peptides, while the hydrophilic corona, commonly composed of PEG, enhances colloidal stability, circulation time, and biocompatibility.[68]

A major advantage of polymeric micelles lies in their structural tunability, which enables surface functionalization with targeting ligands and the incorporation of stimuli-responsive polymers for controlled, site-specific peptide release. This design flexibility has been widely implemented in oncology and metabolic disease models, where micelles can capitalize on the enhanced permeability and retention (EPR) effect while minimizing premature peptide degradation or clearance.[69]

Preclinical studies have demonstrated improved pharmacokinetics and cellular uptake for peptide therapeutics, including anticancer, antidiabetic, and antimicrobial peptides.[70–72] Despite these promising attributes, clinical translation of peptide-loaded polymeric micelles remains limited, with most approved or late-stage micellar formulations developed for small-molecule drugs rather than peptides. Limitations such as relatively low peptide-loading capacity and potential instability upon dilution in vivo continue to pose challenges for systemic peptide delivery. Nevertheless, ongoing advances in polymer design, including core cross-linking and co-delivery strategies, are actively addressing these constraints and may improve the robustness of peptide-based micellar systems.[69,71,73]

The clinical success of small-molecule micelle formulations, such as Genexol® PM, a polymeric nanoparticle micelle formulation of paclitaxel, highlights the translational potential of this platform and suggests that further optimization could support the broader application of polymeric micelles for peptide therapeutics.[74]

Inorganic-Based Nanoparticles

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are inorganic nanocarriers with tunable pore structures that allow high peptide loading and controlled release.[75] Peptides can be physically adsorbed into the mesopores or chemically conjugated to the silica surface, while the rigid framework protects cargo from enzymatic degradation and environmental stress.[76,77] Functionalization with PEG, targeting ligands, or stimuli-responsive gatekeepers enables site-specific release in response to internal (pH, redox, enzymes) or external (light, temperature) triggers, supporting both therapeutic and theranostic applications.[78,79]

MSNs have been investigated for delivering anticancer peptides, antimicrobial peptides (eg., LL-37), and peptide-based vaccines.[80–82] For example, LL-37-loaded MSNs improve direct bactericidal activity and promote macrophage polarization toward the pro-inflammatory M1 phenotype, demonstrating synergistic antimicrobial and immunomodulatory effects.[81] Preclinical studies also show enhanced bioavailability, sustained release, precise targeting, and reduced off-target toxicity for peptide cargos.[80–82]

While MSNs generally exhibit favorable biocompatibility, their non-biodegradable nature raises concerns about long-term accumulation and toxicity. Ongoing work on biodegradable silica formulations and surface engineering aims to address these issues, positioning MSNs as a versatile platform for peptide-based nanomedicine.[83]

Hybrid and Stimuli-Responsive Nanocarriers

Hybrid Nanocarriers

Hybrid nanocarriers integrate complementary features of different materials to overcome the limitations of individual organic or inorganic nanoparticles. Organic carriers, such as liposomes and polymeric micelles, may suffer from limited structural stability and premature drug leakage, whereas inorganic systems can face challenges with biocompatibility, biodegradability, or immune recognition. By combining organic (eg., lipids, polymers) and inorganic (eg., silica, gold) components, hybrid nanocarriers enhance peptide protection, loading capacity, and controlled release. They also allow targeted delivery through surface functionalization with ligands or peptides, improving therapeutic efficacy while minimizing systemic toxicity. Examples include lipid–polymer hybrid nanoparticles (LPHNs), inorganic-based hybrid systems, metal–organic frameworks (MOFs), and carbon-based hybrid nanostructures.[37,84]

LPHNs feature a polymeric core providing mechanical strength and controlled drug release, encapsulated by a lipid shell that enhances biocompatibility and stability. This structure improves peptide encapsulation, protects peptides from enzymatic degradation, facilitates controlled and sustained release, and allows surface functionalization for site-specific targeting. LPHNs have been explored for peptide delivery in cancer therapy, metabolic disorders, and immunomodulation.[84,85]

Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers release therapeutic agents in response to physiological or externally applied triggers such as pH, enzymes, redox conditions, or temperature. They improve site-specific peptide release, reduce systemic toxicity, and protect peptides from degradation.[37]

Enzyme-responsive systems use overexpressed enzymes in specific environments, such as tumors, to trigger peptide release. Peptides are incorporated via covalent or physical methods and released when the target enzyme degrades the carrier.[37] For example, collagenase-responsive PEG hydrogels release antimicrobial peptides on demand at infection sites, preventing methicillin-resistant *Staphylococcus aureus* (MRSA)-induced osteomyelitis in SD rats.[87]

Thermo-responsive systems release peptides in response to elevated temperatures, slightly above physiological levels (~40–42 °C). Polymers or lipids undergo reversible phase transitions, enabling controlled, site-specific delivery.[37] Cao et al[88] developed a thermoresponsive hydrogel by combining poly(N-isopropylacrylamide) (PNIPAM) with the self-assembling peptide I3K, which forms nanofibrils and undergoes reversible sol–gel transition above 33 °C, enabling sustained, linear release of the antibacterial peptide $G(IIKK)_3I\text{-}NH_2$ for injectable, minimally invasive applications.

Peptide Selection and Incorporation Strategies

The incorporation of peptides into nanocarrier-based delivery systems has emerged as a pivotal strategy to enhance the clinical applicability of therapeutic peptides. While peptides exhibit high specificity, potent bioactivity, and favorable safety profiles, their utility is often compromised by poor stability, rapid enzymatic degradation, and short systemic half-life.[26–30] Careful selection of peptide candidates is therefore essential to ensure their suitability for delivery and therapeutic effectiveness.[86,89] Depending on the intended application, peptides can be physically encapsulated within nanocarriers, chemically conjugated to their surfaces, or co-designed as functional building blocks in self-assembled nanosystems. The combination of appropriate peptide selection and incorporation method critically determines the pharmacokinetics, targeting efficiency, and therapeutic performance of the nanocarrier system. Therefore, a comprehensive understanding of both peptide selection and incorporation strategies is essential for the rational design and optimization of peptide-based nanotherapeutics.[90]

Selection Criteria for Peptides

Before incorporating peptides into nanocarrier systems, the successful design of peptide-based nanocarriers begins with the careful selection or engineering of peptides that fulfill the functional and physicochemical requirements of the intended delivery system. This process forms part of a broader developmental trajectory that includes the discovery of therapeutic peptides from diverse biological or synthetic sources, followed by scalable production and systematic optimization. These steps are essential to generate peptides with properties suitable for clinical and pharmaceutical

applications. Optimization strategies often rely on structure–activity relationship (SAR) studies to identify functionally critical residues, enabling the substitution of non-essential ones to enhance bioactivity and physicochemical performance. Additionally, chemical modifications, such as cyclization or D-amino acid substitution, can be employed to stabilize peptide secondary structures like helices, turns, and β-sheets, thereby improving metabolic stability and target affinity.[91,92]

Throughout this development, several key criteria must be carefully evaluated, including stability, specificity, and immunogenicity. Stability ensures that peptides resist proteolytic degradation and remain active during formulation and in vivo circulation. Specificity is critical for achieving selective interactions with the intended molecular or cellular targets, thereby minimizing off-target effects and enhancing therapeutic efficacy. This can be achieved by designing peptides that recognize disease-specific receptors, antigens, or microenvironments through high-affinity binding motifs or ligand–receptor pairing. Meanwhile, immunogenicity is an important aspect of biopharmaceutical safety, determining whether a peptide will trigger an unwanted immune response. Therefore, to address immunogenicity, de-immunization techniques such as epitope mapping with targeted residue substitutions, sequence humanization, or incorporation of D-amino acids are employed to reduce MHC binding and T-cell activation. Together, these strategies ensure that peptides incorporated into nanocarriers are not only functionally effective but also stable, target-specific, and safe for in vivo applications.[91,92] The key selection criteria and representative optimization strategies are summarized in Table 2.

Table 2 Key Selection Criteria for Peptides in Peptide-Based Nanocarrier Systems

Selection Criterion	Design Objective	Design & Optimization Strategies	Representative Examples	Refs.
Stability	Improve resistance to enzymatic degradation and prolong in vivo activity	**Cyclization**: formation of closed-loop peptide structures that mask terminal protease sites and restrict flexibility, stabilizing bioactive conformations (head-to-tail, side chain–side chain, backbone cyclization); **PEGylation**: attachment of PEG chains to increase molecular weight, reduce renal clearance, provide steric protection from proteases, and enhance solubility; **D-amino acid substitution**: replacement of L-amino acids at protease-sensitive sites to reduce enzymatic degradation and extend plasma half-life	Cyclic peptides with increased conformational rigidity and protease resistance; selepressin with prolonged circulation time; DA7R–GICP conjugate retaining target binding with enhanced protease stability	[91–95]
Specificity	Enable selective binding to disease-relevant cells or tissues and reduce off-target effects	**Targeting peptide design**: selection of peptides that bind disease-specific receptors or molecular markers; **Organ-targeting peptides**: peptides that recognize tissue-specific surface markers to direct nanocarriers to designated organs; **Cell-penetrating peptides**: peptides that facilitate cellular internalization across diverse cell types via surface conjugation to nanocarriers	Liver-targeting peptides for hepatocellular carcinoma; adipose homing peptide (AHP) for adipose tissue imaging; RGD peptides targeting integrins; TAT peptides facilitating cellular uptake	[91, 96]

(*Continued*)

Table 2 (Continued).

Selection Criterion	Design Objective	Design & Optimization Strategies	Representative Examples	Refs.
Immunogenicity	Minimize immune recognition and support safe repeated administration	**Epitope mapping and residue substitution**: identification and modification of immunodominant B-cell and T-cell epitopes to reduce immune activation; **Sequence humanization**: alignment of peptide sequences with human proteins guided by epitope prediction tools to reduce MHC binding and T-cell activation; **PEGylation**: steric masking of immunogenic epitopes to reduce proteolysis and immune detection	De-immunized peptide variants with reduced MHC binding; humanized peptide sequences; PEGylated peptides with reduced immune recognition	[97, 98]

Methods of Peptide Incorporation

Peptides can be incorporated into nanocarriers using several well-established strategies, including physical encapsulation, chemical conjugation, and self-assembly. Each strategy influences the overall performance of the delivery system, including stability, release profile, and targeting precision. Within these strategies, a variety of common fabrication approaches, such as emulsification, nanoprecipitation, microfluidics, spray drying, and ionic gelation, can be used to create carrier structures that enable effective peptide loading and delivery. The choice of fabrication method depends on the type of nanocarrier, the physicochemical properties of the peptide, and the intended therapeutic application.[99] This overview provides context for the subsequent discussion of each incorporation strategy and its compatibility with specific nanocarrier platforms.

Physical encapsulation involves entrapping peptides within the core or matrix of nanocarriers such as liposomes, polymeric nanoparticles, or hydrogels, protecting them from degradation and enabling sustained release. Chemical conjugation covalently links peptides to nanocarrier surfaces or structures via functional groups, enhancing stability and site-specific targeting.[100] A specific form of this is surface grafting, in which peptides are tethered to the external surface of nanocarriers to present bioactive ligands or targeting motifs. Additionally, self-assembly enables peptides, either alone or in combination with other amphiphilic molecules, to form nanostructures such as micelles or nanofibers, serving as either delivery vehicles or structural components. Each strategy offers unique advantages depending on the desired release profile, targeting precision, and application.[101] Figure 3 provides an overview of these incorporation mechanisms. The compatibility between peptide incorporation strategies and specific nanocarrier platforms is closely linked to the carrier architecture and surface chemistry discussed in Nanocarrier Platforms for Peptide Encapsulation Section. These relationships are highlighted for each method below.

Physical Encapsulation

Over the past decade, there has been substantial progress in the development and evaluation of carrier delivery systems for the encapsulation of bioactive agents[35,36,102–108] (Table 3). This approach involves the non-covalent incorporation of peptides into carrier matrices to protect them from degradation, enhance solubility, and enable controlled release, all while preserving their structural integrity and biological activity. Such encapsulation relies on fundamental interactions, including hydrophobic forces, van der Waals forces, hydrogen bonding, and electrostatic interactions, that allow peptides to be stably loaded without chemical modification.[35,36] A wide range of nanocarriers has been employed, such as emulsions, solid lipid nanoparticles (SLNs), liposomes, and biopolymer microgels. Selection is guided by the peptide's physicochemical properties (hydrophilicity, charge, molecular weight) and the desired release profile, which together influence loading capacity and encapsulation efficiency.[35]

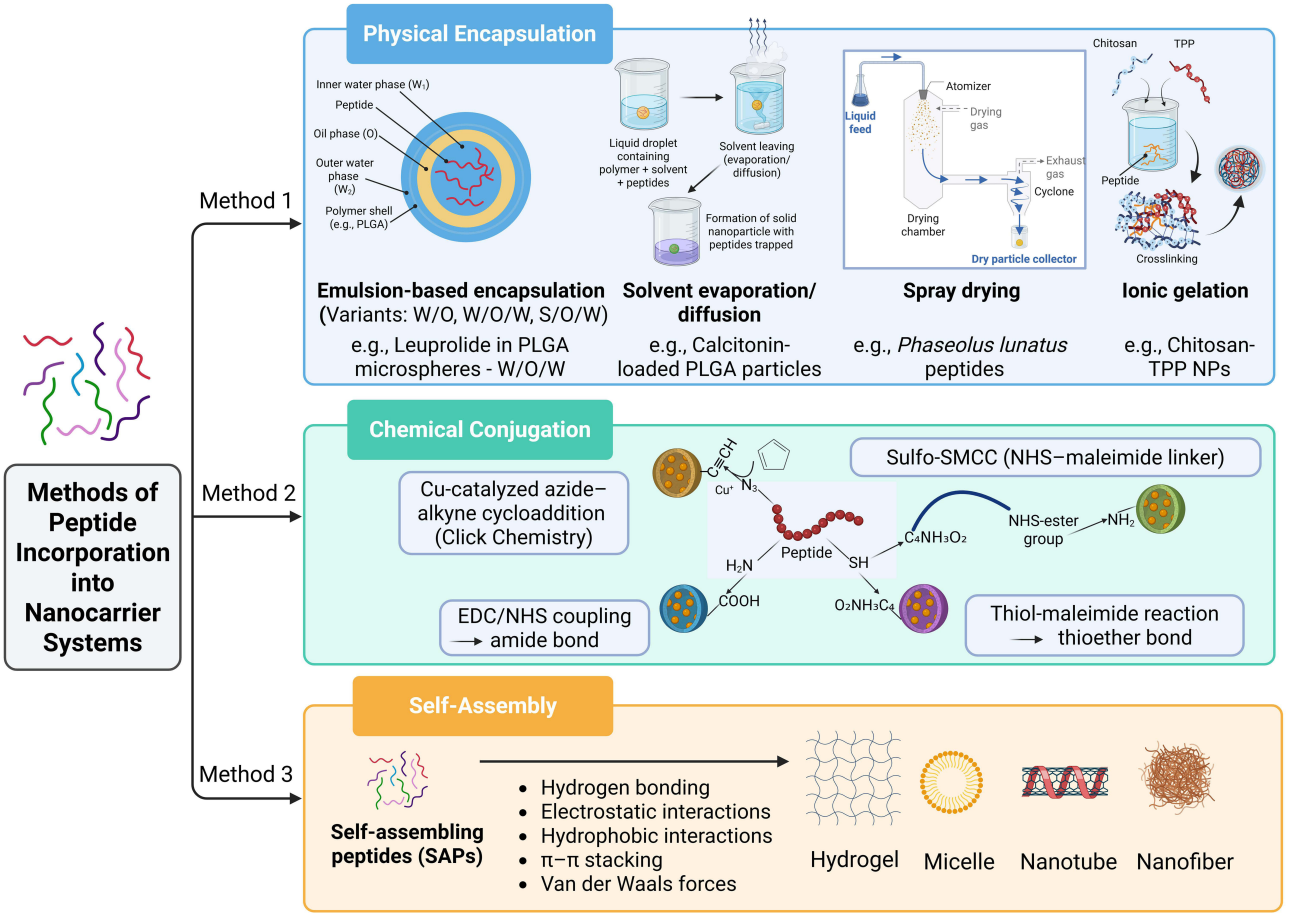

Figure 3 Peptides can be incorporated into nanocarrier systems through three major strategies: (1) physical encapsulation, including emulsion-based methods, solvent evaporation or diffusion, spray drying, and ionic gelation; (2) chemical conjugation, using reactions such as EDC/NHS coupling, thiol–maleimide chemistry, sulfo-SMCC linkers, or copper-catalyzed azide–alkyne cycloaddition (CuAAC); and (3) self-assembly of peptides into nanostructures such as hydrogels, micelles, nanotubes, or nanofibers.

Multiple fabrication techniques are available, each offering distinct advantages. Emulsion-based methods (including single water-in-oil (W/O), double water-in-oil-in-water (W/O/W), and solid-in-oil-in-water (S/O/W) emulsions) are widely used to entrap peptides within polymeric matrices. For instance, W/O/W double emulsions enable the sustained release of hydrophilic peptides such as leuprolide from PLGA microspheres,[103] while S/O/W techniques improve encapsulation efficiency for peptides with low aqueous solubility.[35] Advanced variants like solvent diffusion and microfluidic emulsification further allow precise control of particle size and morphology, as demonstrated with calcitonin and exenatide.[35,104] Solvent evaporation builds on emulsion methods by solidifying particles through organic phase removal.[35,105]

Other techniques include spray drying, a scalable and cost-effective process that converts peptide-containing solutions into stable dry powders.[105] For example, Cian et al[126] showed that spray-dried *Phaseolus lunatus* peptides retained or enhanced bioactivity after simulated digestion, demonstrating improved stability and potential bioavailability. Ionic gelation offers a mild, aqueous-based alternative, forming peptide-loaded nanoparticles through electrostatic interactions between oppositely charged polymers such as chitosan and tripolyphosphate.[35,105]

Although challenges such as premature leakage, low encapsulation efficiency, and burst release remain, they can often be mitigated through formulation optimization, including adjustments to carrier composition, particle size, surface charge, and loading technique. Overall, physical encapsulation remains a versatile, non-invasive strategy for peptide delivery, offering enhanced protection, stability, and controlled release.[35] Physical encapsulation is most compatible with liposomes, SLNs, dendrimers, polymeric micelles, and hybrid nanocarriers (see Table 1 and Nanocarrier Platforms for

Table 3 Strategies of Peptide Incorporation into Nanocarrier Systems: Methods, Features, and Applications

Incorporation Method	Description	Advantages	Challenges	Common Applications	Examples		Refs.
					Peptide-based Nanocarrier System	Applications	
Physical Encapsulation	Entrapment of peptides inside carriers like liposomes or polymeric particles	Protects peptides from degradation, enhances solubility and bioavailability, enables controlled/sustained release, offers versatile fabrication methods, and preserves biological activity	Risk of premature leakage, low encapsulation efficiency, and occurrence of burst release	Enables controlled peptide delivery for chronic diseases (eg., cancer, diabetes), stabilizes enzymes, and enhances functional ingredients in nutraceutical and food formulations	Leuprolide encapsulated in PLGA microspheres via W/O/W emulsion	To achieve sustained drug release for prostate cancer and hormone-sensitive conditions	[35, 36, 102–108]
					Calcitonin encapsulated in monodisperse PLGA particles via solvent diffusion/microfluidics to deliver calcitonin	To treat osteoporosis and hypercalcemia	
					Exenatide encapsulated in monodisperse PLGA particles via solvent diffusion/microfluidics	To treat Type 2 diabetes	
Chemical Conjugation	Covalent attachment of the peptide to the carrier surface or core	Stable covalent bonding, preserved peptide structure and functionality, high specificity and control, resistance to changes in pH, temperature, and ionic strength	High peptide density can lead to steric hindrance that limits receptor accessibility	Targeted delivery, imaging	Andersonin Y1 + silver nanoparticles (AgNPs)	Enhanced antimicrobial efficacy with reduced dosage	[109–113]
					KT2 peptide + PEGylated gold nanoparticles (AuNPs)	Anticancer therapy with improved nanoparticle stability	
Self-Assembling Peptides (SAPs)	Peptides form nanostructures through non-covalent forces	High drug loading efficiency, prolonged circulation, high stability and biodegradability, low immunogenicity, tunable multifunctional designs, and reversible, stimuli-responsive assembly	Sensitive to environmental conditions, unstable in physiological fluids, variable between batches, difficult to scale and purify, challenging to standardize regulatory compliance, and prone to structural disassembly in vivo	Drug delivery (especially for cancer), tissue engineering and regeneration, and gene delivery	Crosslinked ultrashort peptide (LIVAGKC) hydrogels	Wound healing	[90, 91, 114–125]
					pH-responsive L5 peptide hydrogel delivering endolysin LysSYL	Antibacterial delivery and wound healing	
					PuraMatrix™ SAP hydrogel	Biomimetic 3D scaffold for cell culture and tissue regeneration	
					Peptide–siRNA co-assembled nanospheres	Gene silencing therapy for cancer (via siRNA delivery)	

Peptide Encapsulation Section). These platforms provide internal domains or cores that allow peptides to be loaded non-covalently, protecting them from degradation and enabling controlled or sustained release.

Chemical Conjugation

Chemical conjugation is a robust and widely used method for assembling peptide–nanoparticle conjugates (PNCs), enabling stable covalent attachment, which is critical for targeted delivery, imaging, and therapeutic applications. Reactive functional groups on peptides, such as amine ($–NH_2$), carboxyl (–COOH), hydroxyl (–OH), and thiol (–SH), can be covalently linked to functionalized nanoparticle surfaces, with the choice of chemistry guided by the physico-chemical properties of both components.[109–111] Common bioconjugation reactions include carbodiimide-mediated coupling using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) to form stable amide bonds. Thiol-specific reactions using maleimide or iodoacetamide reagents generate thioether linkages with high specificity and low cross-reactivity. Heterobifunctional cross-linkers such as sulfosuccinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) enable controlled, sequential attachment with minimal side reactions. Click chemistry, particularly copper-catalyzed azide–alkyne cycloaddition (CuAAC), offers a bio-orthogonal alternative that preserves peptide structure and activity. Reaction efficiency is further enhanced when copper catalysts are incorporated into nanoparticle systems.[111]

Surface grafting further enables precise control of peptide presentation. In the "grafting-to" approach, pre-synthesized peptides react directly with surface groups but may face steric limitations. The "grafting-from" strategy initiates peptide growth from reactive sites, enhancing spatial control and surface coverage. Incorporating flexible linkers or spacers can also improve ligand accessibility and receptor recognition.[29,30] Peptide–nanoparticle conjugates have shown enhanced therapeutic performance. For example, Pal et al[112] linked the antimicrobial peptide Andersonin Y1 to silver nanoparticles via thiol–silver bonds, increasing potency and reducing dosage requirements. Maraming et al[113] conjugated KT2 peptides to PEGylated gold nanoparticles using thiol–gold chemistry, improving colloidal stability and maintaining anticancer activity.

Challenges remain, including steric hindrance from high peptide density, which can reduce receptor accessibility, and potential bond instability during circulation or storage. These can be addressed through linker design, reaction condition optimization, and careful tuning of peptide multivalency. Ultimately, successful conjugation requires balancing efficiency, specificity, and structural integrity to produce stable, functional PNCs.[109–111] Overall, covalent attachment of peptides to nanoparticles allows precise control over peptide orientation, surface density, and binding strength. In targeted drug delivery, this precision is critical, as peptides act as ligands that guide nanoparticles to specific cells or tissues by recognizing overexpressed receptors, thereby enhancing therapeutic accumulation at disease sites while minimizing off-target effects. Chemical conjugation thus plays a key role in improving the specificity, bioavailability, and systemic stability of nanoparticle-based delivery platforms used in cancer therapy, inflammatory diseases, and other precision medicine applications (Table 3). Chemical conjugation is particularly well suited to liposomes, SLNs, dendrimers, polymeric micelles, and MSNs, which offer accessible surface chemistries for covalent peptide attachment and precise control over peptide orientation, surface density, and targeting (see Table 1 and Nanocarrier Platforms for Peptide Encapsulation Section).

Self-Assembly & Peptide Nanocarrier Co-Design

Self-assembling peptides (SAPs) are short sequences that spontaneously form ordered nanostructures through non-covalent interactions. Incorporating peptides through self-assembly or co-design offers a distinct strategy compared to encapsulation or surface conjugation, as peptides directly form or stabilize the nanocarrier. SAPs can assemble into micelles, nanotubes, nanofibers, or hydrogels to encapsulate therapeutic agents, with structures driven by hydrogen bonding, electrostatic forces, π–π stacking, and hydrophobic interactions.[90,91,114]

SAPs may act as standalone carriers or co-assemble with polymers, lipids, or inorganic nanoparticles to introduce properties such as stimuli responsiveness, targeting capability, and enhanced biocompatibility.[90,114] Through co-design strategies, nanocarrier characteristics, including size, surface charge, rigidity, and release kinetics, can be precisely tuned by modifying peptide sequence, amphiphilicity, or conjugation motifs. Chemical modifications further expand structural

diversity and functional complexity, enabling multifunctional systems capable of co-delivering therapeutics, responding to environmental cues (eg., pH, enzymes), and promoting selective cellular uptake.[90,91,114]

Recent studies highlight the therapeutic versatility of SAP-based systems.[127,128] For example, Seow et al,[115] developed crosslinked ultrashort peptide (LIVAGKC) hydrogels that accelerated re-epithelialization in full-thickness wound models. Liu et al[116] designed a pH-responsive hydrogel using the peptide L5 for the sustained release of the phage-derived enzyme endolysin LysSYL, which demonstrated potent antibacterial activity against MRSA and significantly improved wound healing outcomes. Clinically, SAP technologies are advancing toward translation, as exemplified by PuraMatrix™, a commercially approved SAP hydrogel that mimics the extracellular matrix for 3D cell culture, tissue engineering, and regenerative medicine.[117]

Self-assembled peptide nanocarriers typically exhibit high stability and biodegradability, as well as low immunogenicity, which are features essential for clinical application.[91,114] They offer unique advantages over conventional polymers, including stimuli-responsive behavior, structural tunability, reversible assembly, and precise bottom-up fabrication. The convergence of self-assembly and co-design continues to enhance the performance of peptide-based delivery systems and is expected to advance further with innovations in computational modeling, peptide synthesis, and high-throughput screening.[114,118,119]

Despite their advantages, SAP-based nanocarriers face several challenges, including sensitivity to environmental conditions, instability in physiological fluids, batch-to-batch variability, difficulties in scaling peptide synthesis and ensuring purity, regulatory standardization issues, and susceptibility to structural disassembly in vivo.[120–122] Addressing these challenges is essential for the successful translation of SAP-based nanocarriers from the laboratory to clinical applications (Table 3). Self-assembly and co-design strategies align with polymeric micelles, hybrid nanocarriers, and stimuli-responsive systems, where peptides function as structural or functional components, enabling bottom-up fabrication and precise tuning of nanocarrier properties (see Table 1 and Nanocarrier Platforms for Peptide Encapsulation Section).

Table 3 summarizes the major strategies for peptide incorporation into nanocarrier systems, including physical encapsulation, chemical conjugation, and self-assembling peptides. The table compares their mechanisms, advantages, challenges, common applications, representative examples, and relevant references.

Mechanisms of Precision Targeting

A key objective in nanomedicine research is the targeted delivery of drugs to specific organs, cells, or organelles to enhance therapeutic efficacy while minimizing dosage and toxic side effects. Incorporating peptides into nanoparticle-based drug delivery systems provides an advanced way to achieve this. Peptides offer high specificity, tunable functions, and good biocompatibility, enabling nanoparticles to cross biological barriers, recognize disease-related molecular markers, respond to local microenvironments, and release therapeutic agents directly at diseased sites or inside target cells. These combined capabilities enhance biodistribution, cellular uptake, and overall therapeutic performance while limiting off-target effects. Peptide-mediated targeting typically works through several complementary mechanisms: passive accumulation due to physiological differences between healthy and diseased tissues,[91,129] active targeting via ligand–receptor interactions, and stimuli-responsive release triggered by pathological conditions.[91] Together, these strategies enable the development of intelligent nanocarrier systems that offer improved pharmacokinetics, reduced systemic toxicity, and enhanced treatment outcomes, particularly in oncology, infectious diseases, and regenerative medicine.[91,129] These targeting mechanisms are summarized in Figure 4, and are discussed in detail below.

Passive Targeting & Enhanced Permeability Retention (EPR) Effect

Passive targeting is a drug delivery strategy that relies on the body's inherent physiological characteristics, particularly systemic circulation, to guide therapeutics toward diseased tissues. Central to this mechanism is the enhanced permeability and retention (EPR) effect, a phenomenon wherein macromolecules or nanoparticles preferentially accumulate in tumor tissues due to the abnormal features of tumor vasculature, namely, increased permeability and defective lymphatic drainage. This pathophysiological hallmark serves as the foundational principle behind passive tumor targeting in nanomedicine. Tumor angiogenesis, driven by rapid tumor growth, leads to abnormal blood vessels with incomplete

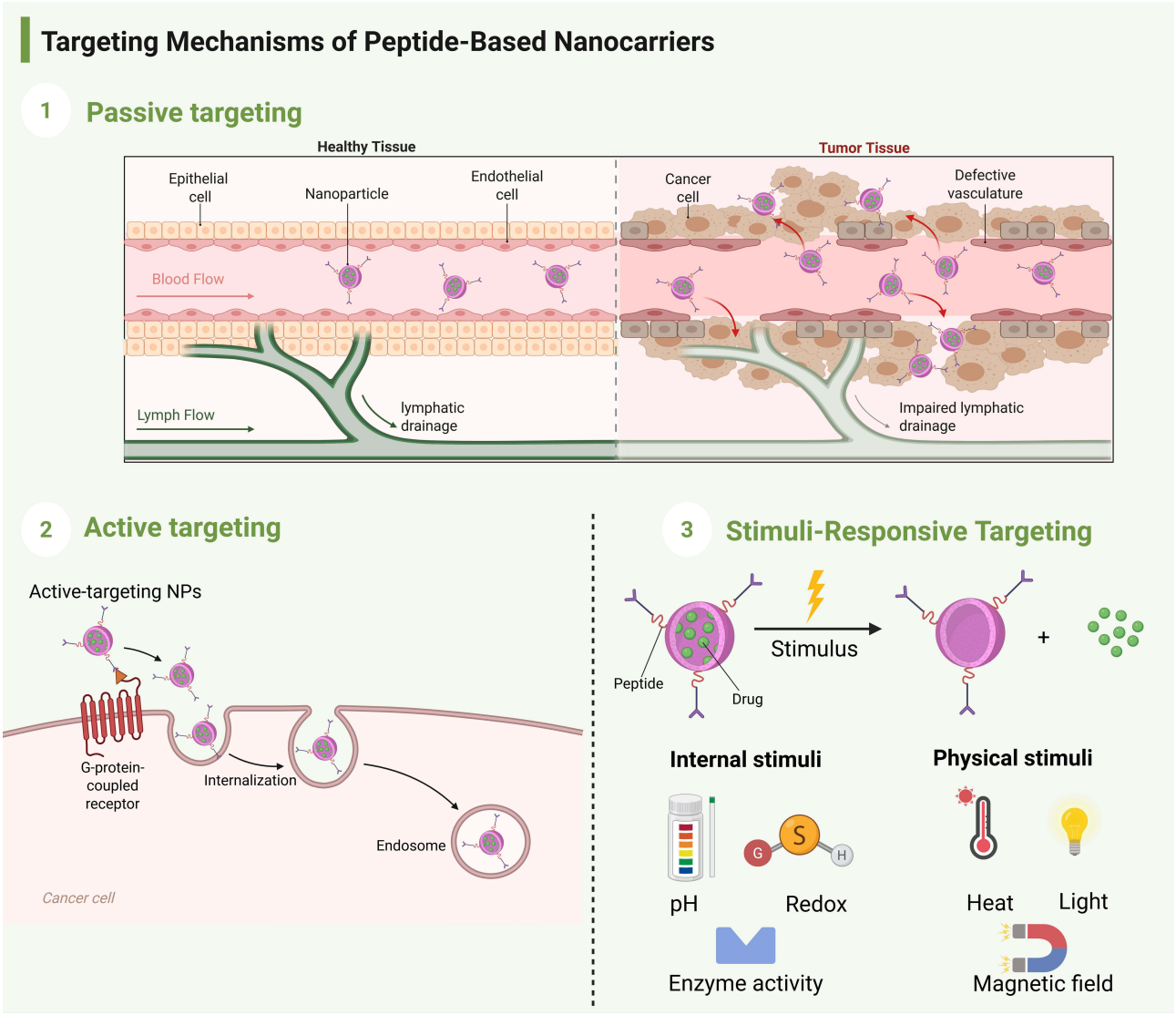

Figure 4 Targeting mechanisms of peptide-based nanocarriers: 1) passive targeting, illustrating preferential accumulation in tumor versus healthy tissue, 2) active targeting via ligand–receptor interactions, and 3) stimuli-responsive targeting triggered by chemical (pH, enzymes, redox) or physical (heat, light, magnetic field) cues.

endothelial linings and large pores (0.1–3 μm), resulting in high vascular permeability and hydraulic conductivity. Nanoparticles, liposomes, and macromolecular drugs smaller than these pores can penetrate tumor tissue via the EPR effect. Optimal delivery requires nanocarriers to be larger than 6–8 nm or 40 kDa to prevent renal clearance and ensure effective tumor accumulation. Nanoparticles engineered within the optimal size range of approximately 10–200 nm can effectively take advantage of the EPR effect, promoting preferential accumulation at tumor sites while minimizing distribution to healthy tissues.[129,130]

However, while passive targeting enhances initial localization within the tumor microenvironment, it does not inherently guarantee efficient cellular uptake or precise intracellular delivery, which may be attributed to the complex tumor microenvironment. To address this, the integration of peptides into nanoparticle systems introduces additional functional advantages. Peptide-based nanoparticles combine the structural benefits of nanocarriers, such as improved stability and extended circulation time, with the inherent bioactivity of peptides, which can facilitate tumor targeting, membrane penetration, receptor-mediated uptake, or even exert direct therapeutic effects. This synergistic design improves both the biodistribution profile and therapeutic precision, making peptide-based nanocarriers a promising platform for enhancing the efficacy of cancer treatments.[91,114,129,131]

Owing to the tumor selectivity offered by the EPR effect, numerous nanomedicines employing this mechanism have been extensively explored for cancer treatment. For instance, Bian et al developed a novel nanocarrier composed of paclitaxel (PTX)-loaded silk fibroin nanoparticles conjugated with an iRGD-EGFR nanobody recombinant protein (anti-EGFR-iRGD) for the treatment of cervical cancer. These nanoparticles, termed A-PTX-SF-NPs, demonstrated efficient tumor penetration and enhanced cytotoxicity against cancer cells. In HeLa tumor-bearing nude mice, the A-PTX-SF-NPs showed superior tumor accumulation and antitumor efficacy in vivo, driven by the EPR effect. This study highlights how peptide-functionalized nanoparticles utilize the EPR effect for passive tumor accumulation, while the peptide component facilitates active targeting to improve therapeutic efficiency.[131]

Active Targeting via Ligand-Receptor Interactions

Active targeting involves the use of specific ligand–receptor interactions to direct therapeutic agents to diseased or abnormal cells with high precision. In this strategy, ligands such as peptides, antibodies, or small molecules are designed to selectively bind to receptors that are overexpressed or uniquely expressed on target cells, such as those in tumors or sites of inflammation. This targeted binding facilitates cellular uptake through receptor-mediated mechanisms, enhancing the accumulation of therapeutics at the desired site while minimizing effects on healthy tissues. By recognizing disease-specific molecular markers, active targeting significantly improves the efficacy and specificity of various drug delivery approaches.[132,133]

In nanomedicine, active targeting through ligand–receptor interactions is a powerful strategy to improve the specificity and therapeutic index of drug-loaded nanocarriers. This approach involves modifying the surface of nanocarriers, such as liposomes, polymeric nanoparticles, or micelles, with ligands that have a high binding affinity for receptors overexpressed on target cells. These ligands may include monoclonal antibodies, aptamers, or, more commonly, peptides due to their favorable biocompatibility, small size, low immunogenicity, and ease of synthesis. Upon systemic administration, the ligand-functionalized nanocarriers circulate through the body and selectively bind to target cells through specific receptor–ligand recognition, such as integrin–RGD, EGFR–GE11, or transferrin–TfR interactions.[132,134] This binding promotes receptor-mediated endocytosis, enabling internalization of the nanocarrier and efficient intracellular release of its therapeutic payload, thereby enhancing treatment efficacy while minimizing damage to healthy tissues.[96,132,135]

One promising approach within this framework is the use of peptide-encapsulated nanocarrier systems. These systems combine the therapeutic potential of bioactive peptides with the precision of targeted delivery. By encapsulating therapeutic peptides within a nanocarrier and functionalizing its surface with targeting ligands, such systems can protect peptides from enzymatic degradation, prolong circulation time, and ensure site-specific delivery.[90] For example, tumor-homing peptides such as iRGD or liver-targeting peptides can be conjugated to the nanocarrier surface, guiding the encapsulated peptides to their intended cellular targets, enhancing specificity and improving treatment outcomes. This dual-function design, therapeutic payload plus targeting capability, makes peptide-encapsulated nanocarriers an attractive platform for precision therapy, especially in cancer and inflammatory diseases.[135–138]

Environment-Responsive Release Strategies

Peptides can be engineered to respond to specific internal or external stimuli within the pathological microenvironment, enabling spatiotemporally controlled drug release. This is particularly important for the treatment of diseases such as malignancy, as the stimuli-responsive DDSs can react to endogenous cues within the tumor microenvironment eg., acidic pH, elevated enzyme levels, and redox imbalances, or external triggers like heat, light, or temperature. In response, these systems may transform, including changes in surface charge or particle size reduction, which enhance cellular uptake and internalization by cancer cells. This dynamic behavior promotes more effective targeted delivery and deeper tumor penetration, while also enabling controlled drug release at the diseased site.[26]

Enzyme-Stimulated Responsive Peptide DDSs

Elevated levels of extracellular enzymes, such as matrix metalloproteinases (MMPs) and proteolytic hydrolases, within tumor tissues can trigger peptide-based DDSs to regulate the release of anticancer agents. For instance, cathepsin

B (CTSB), a histone protease abundantly expressed in the cytosol of bladder cancer cells, specifically targets the GFLG peptide sequence and cleaves it at the bond between the phenylalanine (F) and leucine (L) residues.[26] Song and Choi[139] developed enzyme-responsive nanoparticles, RH-$(GFLG)_3$, featuring a cathepsin B-sensitive GFLG oligopeptide core. As a novel drug delivery platform, these nanoparticles demonstrated excellent biocompatibility, biodegradability, and enzyme-triggered controlled drug release. Comprising arginine, histidine, and the enzyme-sensitive peptide core, RH-$(GFLG)_3$ formed stable nanoscale structures with strong enzyme-responsive behavior. Compared to non-responsive controls, the nanoparticles exhibited significantly enhanced cellular uptake. Furthermore, cytotoxicity assays, including MTT, LDH, and hemolysis, confirmed their minimal toxicity in HeLa cells. When loaded with doxorubicin (LL-Dox), the nanoparticles showed potent anticancer activity. LL-Dox achieved superior therapeutic outcomes compared to isomer-containing control groups, attributed to its improved enzyme-triggered release profile. Notably, LL-Dox also demonstrated strong anticancer efficacy in both 3D tumor spheroid models and zebrafish cancer models.[139] These findings highlight the potential of enzyme-responsive peptide-based nanocarriers as efficient and biocompatible DDSs for biomedical applications.

pH-Stimulated Responsive Peptide DDSs

In most cancerous tissues, acidic conditions (lower pH) arise due to the buildup of lactic acid and a decrease in oxidative phosphorylation. This pH gradient between cancerous and healthy tissues can be exploited to develop DDSs that release medication in response to the acidic environment of tumors. Tumor tissues and inflamed sites typically exhibit a slightly acidic extracellular pH (~6.5–6.8) compared to normal physiological pH (~7.4), while endosomes (~pH 6.0–6.8) and lysosomes within cells are even more acidic (~pH 4.5). Peptide-based nanocarriers are engineered with pH-sensitive motifs that undergo conformational changes, charge reversal, or cleavage under acidic conditions, triggering drug release at the target site. The pH responsiveness can be achieved through the incorporation of acid-labile linkers, such as hydrazone, cis-aconityl, or acetal bonds, or through the use of ionizable amino acids like histidine, which respond to protonation under acidic conditions. These mechanisms enable nanoparticles to remain stable in the bloodstream but rapidly release their therapeutic payloads upon exposure to the acidic tumor microenvironment or intracellular organelles.[140–142]

Additionally, some pH-responsive peptides facilitate endosomal escape by adopting membrane-disruptive conformations under acidic conditions, enhancing cytosolic delivery of drugs or biomacromolecules. This pH-triggered delivery strategy improves spatial precision, minimizes premature drug release, and enhances intracellular delivery efficiency, offering significant potential for improving the safety and efficacy of cancer therapeutics and other disease treatments characterized by acidic microenvironments.[140–142] Wang et al[143] designed an ultra pH-responsive peptide nanocarrier engineered for targeted gene therapy in cancer. The system is constructed from self-assembling peptides that maintain stable nanostructures at physiological pH (7.4) but undergo progressive assembly–disassembly transitions in response to moderately acidic tumor environments (pH 6.5–6.8) and more acidic lysosomal interiors (pH 5.0–6.0). This dynamic pH-triggered behavior enables highly efficient delivery of nucleic acids, eg., siRNA, pDNA, and mRNA, with transfection efficiencies reaching 87.1% for pDNA and 74.9% for mRNA, surpassing previously reported peptide carriers. Moreover, cancer cell-targeting motifs on the nanocarrier surface facilitate uptake, causing up to 96% cancer cell death in vitro. The system also demonstrates excellent biocompatibility and low toxicity, positioning it as a promising platform for precision cancer gene and immunotherapy.[143]

Redox Stimuli-Responsive Peptide DDSs

Redox-responsive peptide DDSs are emerging as promising tools in biomedicine due to their ability to release drugs in response to changes in the cellular redox environment, particularly the concentration of glutathione (GSH). These systems offer targeted drug delivery, enhanced efficacy, and reduced side effects, making them attractive for treating diseases like cancer and inflammation, where redox imbalances are often present. In the context of cancer pharmacotherapy, redox-responsive peptides are designed to sense the redox potential within the tumor microenvironment, primarily influenced by elevated levels of reactive oxygen species (ROS) and GSH. These peptides often incorporate disulfide bonds that remain stable in the bloodstream but are cleaved in the reductive, GSH-rich environment of tumor

cells. This cleavage triggers drug release or nanoparticle disassembly specifically at the tumor site while maintaining colloidal stability during circulation.[26,142] Xiao et al[144] created a redox-responsive peptide-based nanocarrier system designed for targeted and synergistic cancer therapy. The nanocarrier comprises a mesoporous silica nanoparticle (MSN) core loaded with chemotherapeutic drugs, encapsulated by a disulfide-linked therapeutic peptide shell ($(RGDWWW)_2$ KC). The RGD motif facilitates active tumor targeting by binding to integrin receptors, while the peptide shell acts as a gatekeeper, preventing premature drug release during circulation. Upon entering the tumor microenvironment, elevated intracellular GSH levels trigger the cleavage of disulfide bonds, disassembling the peptide shell and enabling controlled drug release. Simultaneously, the released tryptophan-rich peptide fragments contribute additional cytotoxicity by damaging DNA. Notably, this dual-functional system integrates active targeting, redox-responsive release, and synergistic therapeutic effects, offering a promising strategy for enhancing the efficacy and precision of cancer nanomedicine.[144]

Overall, the combination of these targeting strategies, ie., passive targeting, active targeting, and stimuli-responsive DDSs, enables peptide-functionalized nanoparticles to function as highly intelligent, precision-guided delivery systems. This multi-layered targeting approach addresses the key challenges in nanomedicine, including poor bioavailability, non-specific distribution, and off-target toxicity, ultimately enhancing treatment efficacy and safety in a range of diseases.[26,91,129]

Applications of Peptide-Based Nanocarriers for Targeted Delivery

Cancer Therapy

Conventional chemotherapy, including agents such as cisplatin, carboplatin, paclitaxel, and docetaxel, targets rapidly dividing cells but is inherently non-specific, damaging healthy tissues such as bone marrow, gastrointestinal tract, and hair follicles. These off-target effects lead to immunosuppression, gastrointestinal distress, and hair loss, often requiring dose reductions that compromise efficacy. Additionally, the development of drug resistance through mechanisms such as enhanced DNA repair, drug efflux, or altered cell death further limits long-term effectiveness. Overall, conventional therapies suffer from poor selectivity, systemic toxicity, and inadequate tumor accumulation.[15,145]

Peptide-based nanocarriers address these limitations by integrating the physicochemical advantages of nanoparticles with the molecular specificity of peptides. Nanoparticles can be engineered to fall within optimal size ranges to promote prolonged circulation and preferential accumulation in tumors, while peptide functionalization enables active targeting via ligand–receptor interactions. Tumor-homing peptides such as RGD (integrin-targeting), GE11 (EGFR-targeting), and transferrin-mimetic peptides facilitate receptor-mediated endocytosis, enhancing cellular uptake and intratumoral drug retention while minimizing off-target exposure.[135–138] These effects directly arise from the passive accumulation and active targeting mechanisms discussed in Mechanisms of Precision Targeting Section, which together improve biodistribution and therapeutic precision.[15,145]

In addition to improving targeting specificity, peptide-encapsulated nanocarriers offer effective strategies for overcoming multidrug resistance (MDR), a major obstacle in cancer treatment. These systems enable the co-delivery of chemotherapeutic agents alongside functional peptides, such as siRNA-conjugated peptides or cell-penetrating sequences, that inhibit drug efflux pumps or sensitize tumor cells to therapy. Peptide-mediated targeting further promotes preferential accumulation of therapeutic payloads in resistant tumor tissues, reducing premature drug clearance and enhancing intracellular drug availability. By combining tumor-specific targeting with mechanisms that bypass resistance pathways, peptide-based nanocarriers significantly improve therapeutic efficacy and show strong potential for treating aggressive and treatment-resistant cancers.[145,146]

Despite these advances, challenges remain for clinical translation, including heterogeneity of the tumor microenvironment, variability in receptor expression, and inconsistent exploitation of the EPR effect across tumor types. Addressing these factors will be critical for maximizing the clinical impact of peptide-based nanocarrier systems in oncology.

Neurological Disorders

The effective treatment of neurological disorders is severely constrained by the blood–brain barrier (BBB), a highly selective physiological barrier that restricts the transport of most systemically administered therapeutics into the CNS. As

a result, many conventional drugs fail to achieve therapeutic concentrations in the brain, limiting treatment options for neurodegenerative diseases, brain tumors, and other CNS disorders.[147,148] Peptide-functionalized nanocarriers provide a promising strategy to overcome BBB-associated delivery limitations by exploiting receptor-mediated transport mechanisms. BBB-penetrating peptides, such as transferrin-derived peptides, TAT, and angiopep-2, can be conjugated to nanocarrier surfaces to facilitate transcytosis across brain endothelial cells. These strategies directly expand upon the active targeting mechanisms discussed in Mechanisms of Precision Targeting Section, allowing selective interaction with BBB transport receptors and enhanced CNS delivery.[149] Encapsulation within nanocarriers further protects peptide and small-molecule therapeutics from enzymatic degradation and allows controlled release once within the brain parenchyma.[147,148]

While these systems substantially improve brain delivery, challenges remain, including limited targeting specificity within heterogeneous brain tissues, potential neurotoxicity, and the need for precise control over intracellular release. Continued optimization of peptide selection and carrier design will be essential to translate these approaches into effective neurological therapies.

Infectious Diseases

The treatment of infectious diseases is increasingly complicated by poor tissue penetration of conventional antibiotics, rapid drug degradation, non-specific distribution, and the emergence of antimicrobial resistance. These limitations reduce therapeutic efficacy and contribute to systemic toxicity and treatment failure. Peptide-based nanocarriers offer a multifunctional platform to address these challenges by improving drug stability, prolonging circulation time, and enabling targeted delivery to infection sites.[150,151]

Encapsulation of antimicrobial peptides (AMPs), either alone or in combination with antibiotics, enhances their bioavailability and protects them from proteolytic degradation. By co-delivering AMPs with conventional antibiotics within nanocarriers, these systems further improve drug stability, prolong circulation time, and reduce toxicity to healthy cells. In addition, functionalization with targeting peptides that recognize bacterial surface proteins, biofilm-associated components, or infection-specific microenvironments promotes selective accumulation at sites of infection.[150,151] These advantages arise from active targeting and environment-responsive release mechanisms, as outlined in Mechanisms of Precision Targeting Section, enabling spatiotemporally controlled drug release in response to pathological cues such as acidic pH, elevated enzyme activity, oxidative stress, or temperature changes.

Beyond their intrinsic membrane-disrupting and immune-modulatory activities, AMPs benefit significantly from nanocarrier-based delivery. Encapsulation improves AMP stability, enhances bioavailability, and facilitates targeted delivery to infection sites, collectively enhancing antimicrobial efficacy while reducing off-target damage to healthy host tissues.[150,152] The ability to engineer nanocarriers with stimuli-responsive properties further allows precise, on-demand therapeutic action within complex and dynamic infectious environments.[152]

Representative studies highlight the therapeutic potential of AMP-incorporating nanocarriers. Van der Weide et al encapsulated the AMP AA139 into polymeric nanoparticles and lipid-core micelles, demonstrating potent in vitro activity and effective biodistribution following aerosol delivery in models of multidrug-resistant *Klebsiella pneumoniae* pneumonia and septicemia.[153] In another study, a porous silicon-based nanocarrier co-loaded with silver nanoparticles and the AMP Tet-213 enabled pH- and ROS-responsive, on-demand release under infection-like conditions, resulting in synergistic antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. In vivo evaluation in an infected rat wound model demonstrated efficient bacterial clearance, accelerated healing, and minimal toxicity, highlighting the potential of this platform for targeted, antibiotic-free antimicrobial therapy and wound treatment.[154]

Overall, peptide-based nanocarriers represent a highly adaptable and promising platform for precision antimicrobial therapy, particularly in addressing drug-resistant pathogens and biofilm-associated infections. Despite these encouraging outcomes, challenges such as potential immunogenicity of AMPs, scalability of large-scale manufacturing, and long-term safety evaluation remain to be addressed to facilitate clinical translation.

Inflammatory and Autoimmune Diseases

Peptide-encapsulated nanocarrier systems have shown growing potential in the treatment of inflammatory and autoimmune diseases due to their ability to enable precision targeting of dysregulated immune responses. Autoimmune conditions such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD),[155,156] multiple sclerosis (MS), and systemic lupus erythematosus (SLE)[156] have been widely investigated using this approach. Compared with conventional anti-inflammatory therapies, peptide-functionalized nanocarriers offer significant advantages by enabling targeted drug delivery to inflamed tissues, thereby reducing off-target effects and systemic toxicity.

Unlike traditional therapies that act broadly and are often associated with serious side effects, peptide-based nanocarriers can be engineered for site-specific binding and stimuli-responsive release, ensuring precise and sustained therapeutic action. These systems also enhance tissue penetration, prolong circulation time, and allow the co-delivery of multiple therapeutic agents for synergistic or theranostic applications, collectively improving efficacy, safety, and adaptability in managing inflammatory and autoimmune diseases.[155,157]

Peptide-functionalized nanocarriers can be designed to selectively deliver immunomodulatory agents, including AMPs, cytokine inhibitors, or siRNA, directly to inflamed tissues or to overexpressed immune cell receptors such as VCAM-1.[156,158] For example, nanocarriers functionalized with targeting peptides that recognize activated endothelium in inflamed joints have demonstrated enhanced drug accumulation and improved therapeutic outcomes in both in vitro and in vivo models of rheumatoid arthritis.[159,160] Similarly, in IBD, colon-targeting peptides have been employed to direct therapeutic payloads to the inflamed intestinal mucosa.[161] By improving site-specific delivery while minimizing systemic exposure, peptide-encapsulated nanocarriers offer a promising strategy for modulating immune dysfunction with greater efficacy and fewer side effects in autoimmune disorders.

Gene Delivery

Gene delivery represents a rapidly advancing therapeutic strategy for modulating gene expression in a wide range of diseases, including cancer, genetic disorders, and inflammatory conditions. Approaches such as siRNA-mediated gene silencing, mRNA-based protein replacement, and CRISPR-mediated gene editing require delivery systems that are both safe and efficient. Peptide-functionalized nanocarriers provide a versatile platform for gene delivery by protecting nucleic acid cargo from degradation, enhancing cellular uptake, and enabling receptor-mediated targeting to diseased tissues.[162,163]

Certain peptides further enhance intracellular delivery by facilitating endosomal escape and nuclear localization, which are critical steps for successful transfection. By enabling nucleic acids to avoid endosomal degradation and reach the nucleus, these peptides significantly improve transfection efficiency.[163,164]

A representative example is provided by Wang et al,[165] who developed a nanocarrier based on a cationic amphiphilic peptide ($(CR_3)_3C$) for targeted, stimulus-responsive delivery of CRISPR/Cas9 ribonucleoprotein (RNP) complexes in cancer models. This system exploited multiple cellular uptake pathways, including caveolae-mediated endocytosis and lipid raft-associated internalization, while endosomal escape was facilitated by the proton sponge effect and nuclear localization was driven by the intrinsic nuclear localization signal of Cas9. In HeLa-EGFP cells, the nanocarrier achieved a gene editing efficiency of 33.8% at 100 nM RNP while maintaining over 90% cell viability. These findings underscore the critical role of peptide-based nanocarriers in overcoming key barriers to gene therapy, including cellular uptake, endosomal escape, and nuclear delivery, while enabling precise, tumor-targeted genome editing through environmentally responsive design.[165] Figure 5 summarizes the therapeutic applications of peptide-based nanocarriers, highlighting their potential for achieving targeted delivery with reduced systemic toxicity.

Challenges and Limitations

Despite encouraging preclinical outcomes and growing interest, the clinical translation of peptide-based nanocarriers as DDSs remains a major challenge, with only a limited number advancing successfully through clinical trials and into routine clinical use. Peptide-based nanocarriers face significant stability challenges in vivo. Peptides are inherently susceptible to enzymatic degradation and rapid clearance, which can undermine their therapeutic efficacy.[90] Although strategies such as chemical modification, encapsulation, or the use of peptidomimetics can enhance peptide stability, they

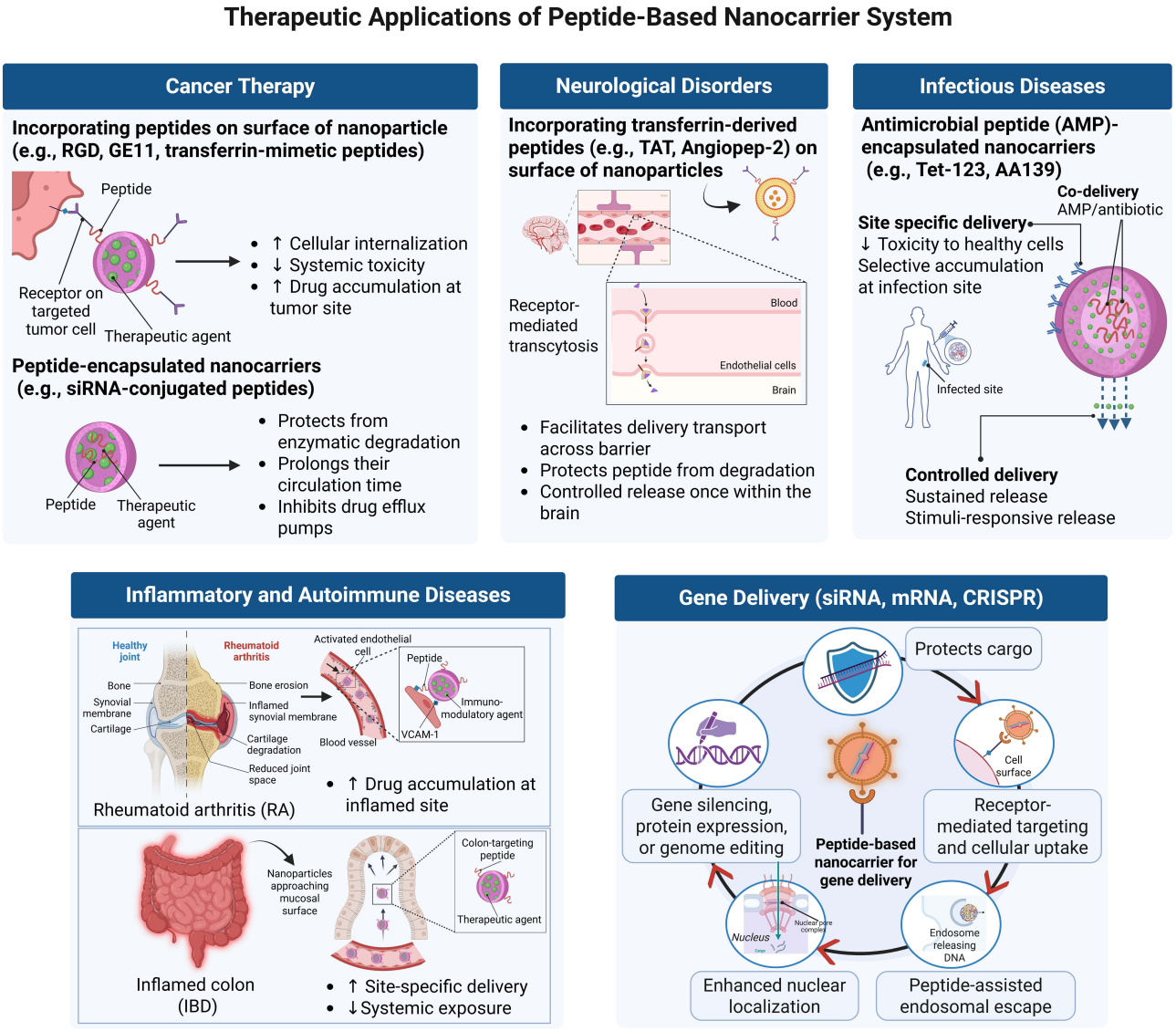

Figure 5 Therapeutic applications of peptide-based nanocarriers: Peptide-functionalized nanocarriers enable precision drug delivery in various biomedical contexts, including cancer, neurological, infectious, inflammatory, and gene-based therapies. They facilitate receptor-mediated targeting, protect therapeutic payloads, enhance cellular uptake, and allow stimuli-responsive or site-specific release. Their adaptability to small molecules, peptides, and nucleic acids highlights their potential as versatile next-generation delivery platforms. Upward arrows (↑) indicate an increase, downward arrows (↓) indicate a decrease.

may also affect bioactivity or introduce formulation complexities. Changes to the peptide's structure can affect its ability to bind to a target, its stability in solution, and its pharmacokinetic properties. This can be both beneficial, allowing for optimization of drug candidates, or detrimental, potentially leading to loss of activity or unexpected side effects. For instance, substituting D-amino acids can greatly enhance a peptide's resistance to enzymatic degradation, but may also reduce its biological effectiveness. Nevertheless, the strategic integration of various chemical modifications alongside suitable delivery platforms may lead to the development of peptides with markedly improved performance.[166] Additionally, while nanoparticle encapsulation offers protection for therapeutic payloads, maintaining the long-term structural integrity of the nanocarrier and preventing premature drug release within the body remain formidable challenges.[167] Following administration, these systems must also evade rapid renal clearance and recognition by the reticuloendothelial system (RES), both of which can significantly reduce circulation time and limit target site accumulation.[90] Thus, careful optimization of nanoparticle design, such as size, surface characteristics, and the incorporation of stealth features, is essential to ensure stability, prolong circulation, and enhance therapeutic outcomes.[90]

Another major concern is the potential immunogenicity and toxicity associated with both the peptides and the nanocarriers. Repeated administration of exogenous peptides may elicit immune responses, while certain nanocarrier materials may induce cytotoxic or pro-inflammatory effects. Ensuring biocompatibility and minimizing unintended immune activation remain key hurdles in clinical translation.[90,96] Biodistribution and off-target effects remain persistent limitations, particularly in complex biological environments. Even with targeting ligands, non-specific accumulation in organs such as the liver or spleen can reduce therapeutic efficiency and increase systemic toxicity. Comprehensive in vivo profiling is necessary to optimize distribution and minimize unintended interactions.[90] The manufacturing and scale-up of peptide-based nanocarriers also present considerable challenges. The need for precise control over particle size, peptide loading, and batch-to-batch consistency poses technical barriers to large-scale production. Moreover, incorporating multiple functional components, such as targeting ligands and stimuli-responsive linkers, not only increases the structural and formulation complexity but also substantially elevates manufacturing costs. From a regulatory perspective, peptide-based nanocarriers fall into a grey area between biologics and nanomedicines, complicating the approval pathway. Current regulatory frameworks are not fully adapted to address the unique pharmacokinetics, multifunctionality, and long-term effects of these hybrid systems. This leads to extended evaluation timelines and inconsistent global standards.[28,90,96] The current status of clinical trials involving peptide-functionalized nanocarriers remains limited, with most efforts still in preclinical or early-phase testing. Challenges in demonstrating clear therapeutic superiority, scalability, and safety at the clinical level have slowed progress toward market approval.[90,96] In summary, while peptide-based nanocarriers offer remarkable therapeutic potential, their translation into clinical and commercial success will depend on overcoming these critical scientific, technical, and regulatory challenges.

Future Perspectives

The advancement of peptide-based nanocarriers is increasingly driven by the emergence of smart delivery systems that integrate molecular specificity, structural stability, and responsiveness to biological stimuli. Advances in rational peptide design, informed by structural and functional analysis, allow precise modulation of binding affinity, biodegradation rates, and controlled release kinetics, thereby optimizing delivery efficacy and minimizing off-target effects. In particular, stimuli-responsive systems that react to environmental cues such as pH variations, redox potential, or enzymatic activity are gaining momentum as they offer precise spatiotemporal control over therapeutic release.[91] Moreover, progress in peptidomimetic engineering and synthetic peptide analogues has addressed key limitations associated with native peptides, such as enzymatic degradation and poor pharmacokinetics. The incorporation of D-amino acids and backbone-modified constructs not only enhances proteolytic resistance and in vivo stability but also enables fine-tuning of physicochemical and functional attributes without compromising biological activity.[168] Collectively, these innovations offer a promising avenue for the realization of robust, functionally versatile peptide-based nanocarriers, capable of meeting the stringent demands of modern targeted therapeutics.

One of the emerging technologies with great potential to revolutionize peptide-based nanocarrier development is microfluidics. Traditional fabrication methods for nanodrug delivery systems (NDDSs), such as homogenization, self-assembly, and nanoprecipitation, often result in a broad particle size distribution, poor dispersion, and high batch-to-batch variability due to inefficient mixing and mass transfer. These limitations hinder clinical translation. Microfluidics offers a promising alternative, enabling precise control over fluid dynamics at the microscale. This approach enables rapid mixing, reduced reagent consumption, and the consistent production of nanocarriers with well-defined properties. For peptide-based nanocarriers, microfluidics enhances formulation precision, facilitates the integration of targeting ligands or responsive linkers, and supports scalable, reproducible manufacturing, making it a key direction for advancing targeted drug delivery.[91,169]

The emergence of multifunctional and personalized nanocarriers marks a major shift toward precision medicine. Future platforms are envisioned to integrate multiple therapeutic and diagnostic functions ("theranostics") while being tailored to patient-specific molecular profiles. Personalized peptide ligands, engineered for individual biomarkers or genetic signatures, could significantly improve targeting accuracy and therapeutic outcomes.[109,170] Finally, the integration of artificial intelligence and predictive design tools is poised to revolutionize the discovery and optimization of peptide-nanocarrier systems. Machine learning algorithms can analyze vast datasets to predict peptide-receptor

interactions, optimize nanocarrier formulations, and simulate in vivo behavior. This data-driven approach will accelerate the development of next-generation peptide-based therapeutics with improved efficacy, safety, and translational potential.

Conclusion

Nanomedicine has emerged as a transformative approach for treating a wide range of diseases, including cancer,[53,80,113,134,143] infectious diseases,[153,154] inflammatory disorders,[156,159–161] and neurological conditions.[147–149] Its advantages, such as enhanced pharmacokinetics, controlled release, and precision targeting, have helped overcome many limitations of conventional therapies, with cancer therapy remaining the most widely explored application. Beyond oncology, nanomedicines are being increasingly investigated for tackling bacterial infections, as well as other complex conditions.[171] Within this evolving landscape, peptide-based nanocarriers stand out as a promising platform due to their biocompatibility,[45,46,54,56,71,83,172] molecular specificity,[37,39,91,92,96,145,173] ease of functionalization,[63,84,85,172] and responsiveness to biological stimuli.[26,37,69,78,90,114] These features make them particularly well-suited for targeted drug and gene delivery, enabling high selectivity, reduced systemic toxicity, and improved therapeutic efficacy.[90]

This review highlights that progress in peptide-based nanocarriers depends on their rational integration, where thoughtful peptide selection and incorporation strategies are aligned with nanocarrier design, forming rational design frameworks that remain an unmet need this review seeks to address. Challenges related to peptide instability and immunogenicity are being actively addressed through strategies such as D-amino acid substitution, backbone modification, cyclization, and protective nanocarrier encapsulation, which collectively enhance proteolytic resistance, circulation stability, and in vivo performance. Similarly, advances in nanocarrier design and controlled fabrication approaches are helping to mitigate issues related to premature drug release, biodistribution, and scalability.

Emerging technologies such as artificial intelligence, machine learning, high-throughput screening, and computational modeling are further accelerating the design, optimization, and prediction of peptide–nanocarrier behavior in biological systems. A particularly promising direction is the convergence of rational peptide engineering with stimuli-responsive nanocarriers and controlled fabrication technologies, offering a cohesive strategy to improve targeting precision, stability, and translational robustness. Realizing the full clinical potential of these systems will require sustained interdisciplinary collaboration to bridge the gap between laboratory innovation and clinical application, ultimately paving the way for more precise, effective, and personalized treatments. The scarcity of clinically approved peptide-functionalized nanocarriers highlights not a lack of promise, but a need for deeper mechanistic understanding and rational design frameworks.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors hereby declare that they have no conflict of interest.

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