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REVIEW

Tumor Targeting with Peptide-Drug Conjugates: Showcasing Key Progress and Hurdles

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Abstract: Peptide-drug conjugates (PDCs) are modular, targeted therapeutics composed of a homing peptide linked to a cytotoxic or modulating drug payload via a cleavable/non-cleavable linker. PDCs utilize peptide targeting to enhance the delivery of potent drugs to tumors, providing advantages such as superior tissue penetration, reduced immunogenicity, and simpler manufacture compared to antibody-drug conjugates (ADCs). A comparison of PDCs versus ADCs highlights that PDCs' small size (~1-3 kDa) enables deeper tumor penetration and faster clearance, whereas ADCs (~150 kDa) benefit from prolonged circulation but suffer from limited tissue diffusion. This review surveys recent advances in PDC design and application. We discuss key design elements (targeting peptides, cleavable/non-cleavable linkers, and payloads) and how these drive mechanisms of tumor delivery and intracellular drug release. Mechanistically, PDCs bind receptors or translocate across membranes, undergo endocytosis, and exploit stimuli-responsive linkers or cell-penetrating peptides to release drugs. Many PDCs can self-assemble into nanoscale structures in aqueous environments. We illustrate PDC concepts through specific instances, such as the brain-penetrant paclitaxel trevatide (ANG1005, paclitaxel-Angiopep-2), the radiotherapeutic lutetium (^{177}Lu)-DOTATATE (Lutathera), and the LyP-1-conjugated doxorubicin-loaded liposomes (LyP-1-doxorubicin conjugate) for triple-negative breast cancer. Persistent challenges include in vivo stability (premature drug release and metabolic clearance), tumor heterogeneity (variable receptor expression), and manufacturing scale-up. We also address regulatory hurdles that have limited PDC clinical success; for example, currently, only lutetium (^{177}Lu)-DOTATATE is FDA-approved (others, like melphalan flufenamide (melflufen), have faced setbacks). Finally, we outline future directions, including theranostic PDCs, AI-assisted peptide optimization, dual-stimuli linkers, and integration with nanomaterials, to further enhance targeting and efficacy. This comprehensive review integrates findings from recent literature and provides an in-depth perspective on the design, advantages, limitations, and future prospects of PDCs in cancer therapy.

Keywords: antibody-drug conjugate, cancer, drug delivery, linker chemistry, nanotechnology, peptide-drug conjugate, targeting peptide, theranostics, tumor penetration

Introduction

Peptide-drug conjugates (PDCs) have emerged as a powerful class of targeted therapeutics that combine the high potency of small-molecule cytotoxic agents with the specificity of peptide homing ligands. In a typical PDC, a tumor-targeting peptide is covalently linked to a cytotoxic or modulating drug (payload) via a linker that can be cleavable or stable. The peptide directs the drug to cancer cells or the tumor microenvironment, enhancing local uptake and sparing normal tissues. Once the PDC reaches its target, the conjugate is internalized by the tumor cell, where intracellular environmental triggers such as pH or elevated enzyme concentration specifically cleave the linker, ensuring precise drug release.

PDCs are structurally simpler and much smaller than antibody-drug conjugates (ADCs); this allows deeper tumor penetration and rapid tissue diffusion.[1] Unlike antibodies, peptides are typically <5 kDa and can be synthesized chemically on a large scale. As a result, PDCs offer advantages over ADCs in manufacturability and cost, while retaining targeted delivery.[1] Compared to ADCs, PDCs offer benefits like deeper tumor penetration. PDCs generally show faster systemic clearance, which can reduce off-target toxicity, and can be engineered for improved stability and release kinetics.[2]

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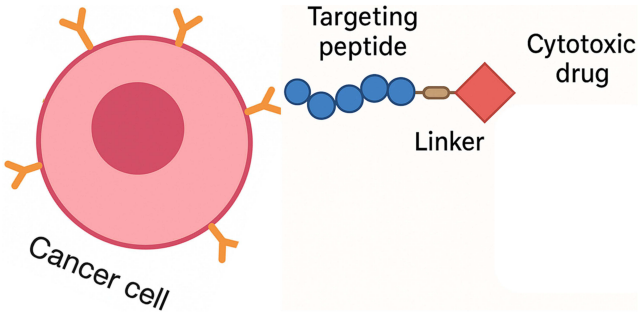
Graphical Abstract



To date, a few PDCs have advanced into the clinic. Notably, ^{177}Lu-DOTATATE lutetium (^{177}Lu)-DOTATATE (Lutathera®), a PDC of a somatostatin analogue and radiolabel, was FDA-approved in 2018 for gastroenteropancreatic neuroendocrine tumors.[3,4] This agent utilizes peptide receptor radionuclide therapy (PRRT) to selectively target somatostatin receptor-positive tumors, resulting in a significant improvement in progression-free survival compared to high-dose octreotide. Other examples include paclitaxel trevatide (ANG1005, paclitaxel-Angiopep-2), a PDC currently under investigation for treating brain metastases, including those from breast cancer, due to its ability to cross the blood-brain barrier via low-density lipoprotein receptor-related protein 1 (LRP1)-mediated transport.[5] However, despite hundreds of preclinical studies, only a handful of PDCs have reached late-stage trials, and the field still lags behind ADCs in clinical success. This review discusses the critical elements of PDC design (peptides, linkers, payloads), their mechanisms of action (including self-assembly behavior), and compares PDCs to ADCs in structure, pharmacokinetics, and clinical performance. We also examine instances (e.g., paclitaxel trevatide, lutetium (^{177}Lu)-DOTATATE, LyP-1-conjugated doxorubicin-loaded liposomes (LyP-1-doxorubicin (Dox)) to illustrate key principles. Finally, we analyze current challenges (stability, heterogeneity, and production) and outline future directions, including theranostic applications, AI-guided design, multi-trigger linkers, and combination with nanotechnology.

Design Elements of PDCs

A PDC consists of three modular components: a targeting peptide, a linker, and a payload drug[1] (Figure 1). More specifically, the PDC comprises a homing peptide for target binding, a cleavable or non-cleavable linker, and a therapeutic payload (drug, imaging agent, or radionuclide). PDCs can use various linkers (eg, non-cleavable thioethers or cleavable hydrazones) and payloads (small-molecule drugs or isotopes). PDCs with well-matched components offer enhanced tumor targeting and reduced off-target toxicity. Chemical conjugation approaches, such as PEGylation, lipid modification, or attachment to hydrophilic polymer scaffolds, expand the hydrodynamic radius of peptide conjugates, shield them from proteolytic degradation, and finely tune their pharmacokinetics, resulting in extended circulation times and reduced systemic toxicity.[1,6,7] Tumor-homing peptides direct drugs to specific receptors, while a small linker ensures on-site release. The tumor microenvironment is exploited for precision release.[8]

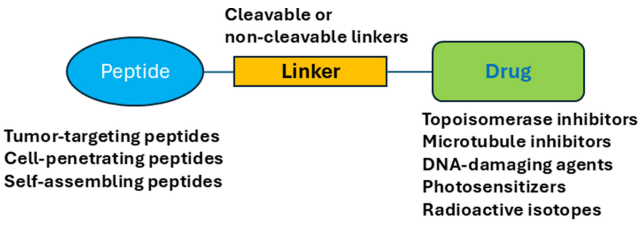


Figure 1 Schematic of a peptide-drug conjugate (PDC).

He et al (2019) described the therapeutic potential of PDCs in achieving both high efficacy and improved safety profiles.[9] Peptide moieties are designed to target specific receptors or cellular markers, significantly enhancing the localization of small molecule payloads to disease sites. Furthermore, the incorporation of stimuli-responsive linkers, sensitive to enzymatic activity, pH, or redox conditions, enables site-specific drug release, thereby reducing off-target toxicity. This tailored response to the tumor microenvironment minimizes the risk of premature drug activation in circulation, ultimately lowering systemic toxicity and enhancing therapeutic indices compared to less selective delivery systems.

Targeting Peptide

Figure 2 illustrates the types of multifunctional peptides utilized in PDCs, including cell-penetrating peptides, tumor-targeting peptides, and self-assembling peptides, which facilitate cellular entry through either direct membrane penetration or endocytosis.[6]

PDCs utilize peptides (typically 5–30 amino acids) that bind to tumor-associated receptors or microenvironmental markers. Table 1 summarizes some of the peptides discovered for tumor targeting. Common targeting motifs include RGD (integrin-binding), NGR (aminopeptidase N), iRGD (neuropilin-binding), LyP-1 (p32/NRP1-binding), somatostatin analogues (SSTR2-binding), SDT7 (statistically designed transcellular peptide), EGFR-binding peptide (EGF receptor binding), HER2 (HER2 receptor binding), rL-A9 (HER2 receptor binding), and many cell-penetrating peptides (CPPs) for broadly enhanced uptake.[10–20]

Short peptides, such as di- and tripeptides, play a crucial role in this respect, as they are small in structure, biocompatible, and can be easily modified. Peptides, such as cyclic, α-helical, linear, and amphiphilic ones, can self-assemble to form various nanostructures, including nanorods, nanospheres, nanotubes, and nanofibers.[21–23] These peptides confer specificity and can also facilitate the translocation of proteins across cell membranes or biological barriers.

RGD (arginine-glycine-aspartic acid) recognizes and binds to RGD-binding integrins (e.g., αvβ3, αvβ5) upregulated in tumor vasculature and tumor cells. This motif has been exploited across imaging and therapeutic platforms in oncology.[10] The **C**-end Rule (CendR) refers to a specific peptide motif that becomes functionally active only when

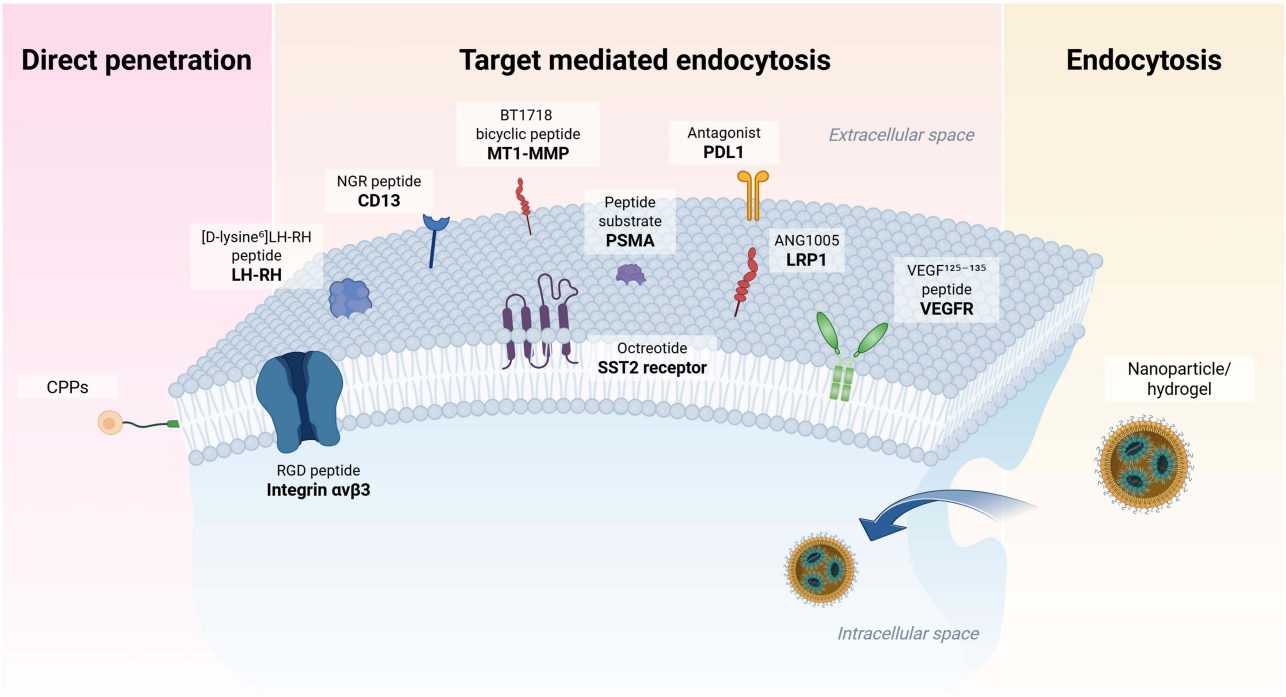


Figure 2 Peptides employed in PDCs include cell-penetrating peptides, tumor-targeting peptides, and self-assembling peptides. Blue arrows illustrate the transport of nanoparticles or hydrogels from the extracellular environment into the intracellular space.

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Table 1 Peptides for Tumor Targeting

Peptide Motif	Target/Mechanism	Key Application	References
RGD	Integrins (αvβ3, αvβ5)	Tumor vasculature targeting	[10]
iRGD (CRGDKGPDC)	Integrins → NRP-1 via CendR motif	Tumor-penetrating delivery	[11]
Angiopep-2 (TFFYGGSRGKRNNFKTEEY)	LRP1 (receptor-mediated transcytosis across BBB)	CNS delivery enhancement	[12]
NGR	Aminopeptidase N (CD13)	Tumor vasculature homing (literature-known)	[13,14]
LyP-1 (CGNKRTRGC)	p32 (mitochondrial protein), tumor lymphatics	Hypoxic/macrophage targeting (literature-known)	[15–17]
Somatostatin analogues	$SSTR_2$	Clinically used in PRRT (eg, ^{177}Lu-DOTATATE)	[18]
SDT7 (LARLLTGYHWYGYTPQNVI)	Enhancing skin penetration and drug delivery	Barrier-penetrating delivery peptide	[19]
rL A-9 (WAVATNVDQ)	HER2-expressing breast cancer	Tumor receptor targeting peptide	[20]

exposed at the C-terminus of a peptide chain. This motif, typically characterized by a sequence such as R/KXXR/K (where R or K are positively charged amino acids arginine or lysine, and X can be any amino acid), is crucial for binding to neuropilin-1 (NRP-1), a receptor involved in vascular and tissue penetration. A well-known example of a peptide utilizing this mechanism is iRGD (CRGDKGPDC), a disulfide-cyclized peptide. Initially, iRGD binds to αvβ3 or αvβ5 integrins, which are overexpressed on tumor vasculature. Upon this binding, tumor-associated proteases cleave the peptide, exposing an RGDK sequence at the new *C*-terminus. This exposed sequence matches the CendR motif and activates it. The activated CendR motif then engages NRP-1, triggering an active transport process that allows both the peptide and any attached or co-administered therapeutic cargo to deeply penetrate the tumor tissue.[11]

The NGR motif, composed of asparagine-glycine-arginine, functions as a tumor-homing sequence by selectively targeting aminopeptidase N (APN), also known as CD13, an enzyme highly expressed on the endothelial cells of tumor vasculature but largely absent in normal blood vessels. This specificity allows NGR-containing peptides to serve as effective vectors for delivering imaging agents or therapeutics directly to tumor sites, thereby enhancing localization and minimizing off-target effects.[13,14] Pasqualini et al[13] first demonstrated that peptides displaying the NGR motif could home to tumor vasculature by binding to CD13, validating this receptor as a promising target for tumor-selective delivery systems. Subsequent work expanded on this discovery, confirming that the NGR motif facilitates internalization into tumor cells via receptor-mediated endocytosis, which is key for therapeutic uptake. Wang et al[14] reviewed the development of NGR-conjugated imaging agents, showing that NGR-functionalized probes significantly improve the contrast and specificity of tumor imaging. These studies collectively established the foundation for using NGR-targeted platforms in both diagnostics and targeted therapy, including radiolabeled agents and nanoparticle-based delivery systems.

Peptide TFFYGGSRGKRNNFKTEEY) (Angiopep-2) specifically binds to the low-density lipoprotein receptor-related protein 1 (LRP1) and facilitates receptor-mediated transcytosis across the blood-brain barrier, enhancing delivery of therapeutic agents to the central nervous system.[12] Peptide CGNKRTRGC (LyP-1) is a disulfide-cyclized tumor-homing peptide that targets tumor lymphatics and mitochondrial p32 and is used for targeting hypoxic tumors and tumor-associated macrophages.[15–17]

Somatostatin analogues specifically target somatostatin receptor subtype 2 ($SSTR_2$), a G-protein-coupled receptor overexpressed in many neuroendocrine tumors. These analogs form the basis of peptide receptor radionuclide therapy (PRRT), such as with ^{177}Lu-DOTATATE, a radiolabeled somatostatin analogue approved for clinical use in treating gastroenteropancreatic neuroendocrine tumors.[18]

Statistically designed transcellular peptide 7 (SDT7) is a transcellular peptide that facilitates drug delivery across cellular and epithelial barriers. SDT7 was conjugated with 6-Paradol (PAR), forming TM5. TM5 demonstrated significantly improved cellular uptake and therapeutic effects compared to free PAR in keratinocyte assays and mouse psoriasis models.[19]

rL-A9 (WAVATNVDQ), a retro-analog of the L-A9 peptide, targets the HER2 receptor overexpressed in certain cancers. Conjugated to doxorubicin (DOX) via a succinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker, rL-A9–DOX interacted strongly with HER2, was internalized by $HER2^+$ cells, and delivered Dox intracellularly. It showed higher cytotoxicity in $HER2^+$ cells (SK-OV3) than in $HER2^-$ cells (MDA-MB-231), highlighting its potential as a selective therapy for HER2-expressing cancers with reduced off-target toxicity.[20]

In addition to targeting, anticancer peptides (ACPs) also demonstrate strong potential in both cancer diagnosis and therapy by selectively targeting and killing cancer cells through multiple mechanisms, including apoptosis induction, membrane disruption, DNA damage, immune system modulation, and the suppression of angiogenesis, cell survival, and proliferation pathways.[24,25] Recent advances in ACP engineering incorporate structural and chemical modifications that improve stability, refine pharmacokinetic behavior, and enable the targeting of previously undruggable proteins or resistance-associated pathways, thereby expanding their therapeutic potential.[26,27] Peptides can also be combined with imaging agents and advanced molecular imaging techniques, such as MRI, PET, CT, and near-infrared (NIR) imaging, to enhance tumor detection, classification, and monitoring of treatment effectiveness.[28–30]

Linkers

The linker is a critical design element in PDCs, bridging the targeting peptide and the cytotoxic or modulating drug payload and orchestrating controlled drug release. The linker's design is crucial for maintaining stability in circulation and enabling controlled release of the drug at the target site.[31] It is a chemical or biological moiety that covalently connects a therapeutic peptide to another molecule, such as a drug, polymer, or targeting ligand, enabling improved stability, controlled release, or targeted delivery of the peptide.[32] Broadly, linkers fall into two categories of non-cleavable and cleavable linkers[1] (Figure 3). A range of cleavable and non-cleavable linkers utilized in ADC design has been previously reviewed.[33]

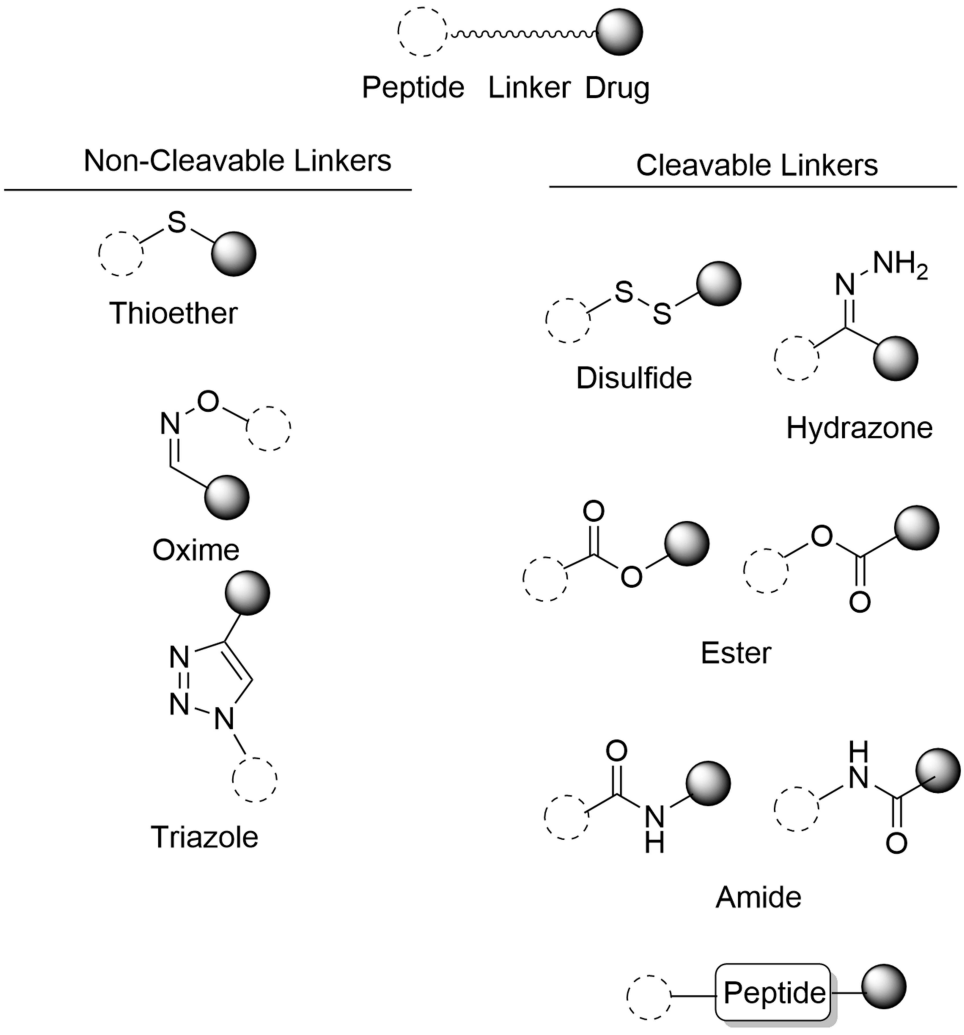

Figure 3 The cleavable and non-cleavable linkers used in PDCs.

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Non-cleavable linkers (e.g., thioether, oxime) remain intact during systemic circulation. These require complete proteolytic degradation of the peptide to liberate the drug, offering enhanced plasma stability but generally resulting in slower payload release. Common chemistries include succinimidyl thioethers and oxime bonds.[1,34]

Cleavable linkers are designed to respond to tumor-specific stimuli, releasing the payload selectively within the tumor microenvironment. An ideal cleavable linker should be robust during blood circulation yet cleavable upon reaching or entering target cells, thereby maximizing therapeutic efficacy and minimizing off-target toxicity.[1] Linkers that respond to pH changes, enzymatic activity, or redox conditions enable the selective release of the small molecule payload at the target site, thereby minimizing systemic toxicity.[9] Overly labile linkers risk premature cleavage during circulation, potentially diminishing tumor selectivity and increasing systemic side effects.[35] The specificity of drug release is governed by the chemical stability of the linker. While the conjugate remains intact during systemic circulation, it undergoes cleavage upon encountering the acidic microenvironment or elevated enzymatic activity of tumor tissue. This controlled activation ensures that the cytotoxic or modulating drug payload is released predominantly at the tumor site, improving therapeutic precision and minimizing off-target toxicity.

Acid-labile linkers (e.g., hydrazones) exploit the acidic milieu of tumors or endosomes, enabling pH-triggered release.[36] Redox-sensitive linkers (e.g., disulfide bonds) are cleaved by high intracellular concentrations of glutathione, permitting intracellular drug release in a reducing environment.[37] A prime example of this is the P14LRR-kanamycin conjugate, which delivers the antibiotic kanamycin in a targeted manner through its conjugation with the peptide P14LRR via a disulfide bond.[38]

Enzyme-cleavable linkers (e.g., valine-citruline dipeptides cleaved by cathepsin B, matrix metalloproteinase [MMP]-sensitive sequences) activate release only in enzyme-rich tumor regions, enhancing precision.[39–41] For example, the incorporation of a maleimidocaproyl-valine-citrulline (Mc-Val-Cit) linker in HER2-targeting ADCs has been shown to significantly enhance the selectivity and efficacy of intracellular drug release. Following receptor-mediated endocytosis, this cleavable linker is specifically recognized and cleaved by cathepsin B, an enzyme enriched in lysosomes of $HER2^{+}$ tumor cells. This enzymatic cleavage triggers the intracellular release of the potent cytotoxin monomethyl auristatin E (MMAE), enabling targeted cytotoxicity while sparing healthy, antigen-negative tissues. In contrast to non-cleavable linkers, which rely on slower or less specific degradation pathways, the Mc-Val-Cit linker facilitates more efficient payload release and improved antitumor activity, offering a strategic advantage in ADC design for precision oncology.[41]

Dual-cleavable linkers, incorporating two cleavable elements (e.g., a combination of a disulfide and a matrix metalloproteinase (MMP)-sensitive peptide), offer hierarchical activation mechanisms that enhance specificity and reduce premature drug release.[37]

The choice of linker depends on the required stability. The ideal linker strikes a balance between systemic stability and efficient release in the target tissue (Table 2). The choice of linker has a profound impact on the pharmacokinetic profile and therapeutic performance of PDCs. Non-cleavable linkers, such as thioethers, create exceptionally stable conjugates with minimal premature release, improving systemic safety and half-life. In contrast, cleavable linkers such as hydrazones (pH-sensitive) or disulfides (redox-sensitive) engineer a "smart" drug release mechanism, selectively activated within tumor environments while maintaining stability in the circulation.[42] A study exemplifies this principle: a DOX conjugate leveraging the 18–4 peptide, which targets keratin-1 (K1) receptors, was linked via an acid-sensitive hydrazone. In vivo, this PDC achieved 1.4 times higher tumor accumulation, 1.3–2.2 times lower off-target organ exposure, and significantly reduced toxicity compared to free Dox in a mouse triple-negative breast cancer model, clearly demonstrating enhanced specificity and an improved therapeutic index.[43]

Table 2 Linker Impact on PDC Performance

Linker Type	Stability in Circulation	Payload Release Trigger	Pros	Cons
Thioether (non-cleavable)	High	Requires proteolytic degradation	Excellent systemic stability	Slower drug release, which depends on intracellular degradation
Hydrazone (pH-sensitive)	Moderate	Acidic tumor/endosomal pH	Cued, site-specific release, enhanced efficacy	Potential premature cleavage in circulation
Disulfide (redox-sensitive)	Moderate	High intracellular glutathione	Tumor-specific release	Possible extracellular cleavage or instability

Payload

Table 3 and Figure 4 summarize some of the commonly used payloads in PDCs.[44–47] In PDCs, the payload is commonly referred to as the biologically active molecule or drug (e.g., typically a highly potent chemotherapeutic or radionuclide) that is attached to the peptide carrier, intended to exert its therapeutic effect once delivered to the target site.[32] These payloads alone often face challenges related to poor selectivity or solubility, which PDC delivery systems aim to overcome. Common payloads include Dox, paclitaxel, and camptothecin derivatives. These agents are highly effective but inherently nonspecific, often leading to systemic toxicities such as myelosuppression and organ damage. PDCs can mitigate this through targeted delivery.[48,49]

Topoisomerase Inhibitors

Dox, a potent anthracycline, is frequently associated with severe cardiotoxicity and myelosuppression due to its lack of tumor specificity.[67] Dox is often linked via acid-sensitive hydrazone or amide bonds to facilitate drug release in acidic tumor compartments. The hydrazone linker is among the earliest used for Dox, allowing pH-triggered release.[44–46] Camptothecin derivatives are highly active topoisomerase I inhibitors; however, their clinical use is hindered by poor solubility and systemic toxicity.[68]

Microtubule Inhibitors

Vinca alkaloids, such as vinblastine, and maytansine derivatives, including DM1 (mertansine), are among the most potent cytotoxic payloads used in targeted cancer therapies. These agents disrupt microtubule dynamics, arresting mitosis and inducing apoptosis. Maytansine derivatives,[69] including DM1, exhibit extremely high potency and are prominently featured in ADCs like trastuzumab-emtansine (T-DM1/Kadcyla®) for HER2-positive breast cancer.[70]

Paclitaxel, a microtubule-stabilizing agent widely used to treat a range of solid tumors (including breast, ovarian, and lung cancers), is associated with several significant toxicities. These include bone marrow suppression (particularly neutropenia), peripheral neurotoxicity, and hypersensitivity reactions, often necessitating premedication.[71]

DNA-Damaging Agents

Cisplatin and melphalan disrupt DNA integrity and trigger cancer cell death by induction of DNA crosslinks and adducts.[52,53] Though specific PDC studies on these are limited, they are recognized as potential payload classes.

Photosensitizers

These agents, which are used in photodynamic therapy (PDT), can serve as powerful phototherapeutic payloads when conjugated to targeting peptides, enabling localized, light-triggered cytotoxicity. These peptide-photosensitizer conjugates improve tumor specificity and accumulation, mitigating systemic side effects and improving therapeutic outcomes in cancer treatment.[72] Kamarulzaman et al[72] demonstrated peptide-conjugated chlorin-type photosensitizers targeting

Table 3 Payload Types in PDCs

Payload Category	Examples	Advantages	Reference
Dox (hydrazone/amide)	Hydrazone- and amide-linked Dox	Enables pH-triggered release for tumor selectivity	[44–46]
Paclitaxel	Paclitaxel trevatide	Paclitaxel moieties are attached via cleavable ester bonds	[47]
Camptothecin	diCPT-PLGLAG-iRGD	Glutathione reduction triggers the release of CPT	[50]
Microtubule inhibitors	Vinblastine, DM1	Interrupts mitotic spindle formation; potent payloads	[51]
DNA-damaging agents	Cisplatin, Melphalan	Directly causes DNA damage, leading to apoptosis	[52,53]
Radionuclides	^{177}Lu-DOTATATE	Combines therapy and imaging in one conjugate	[54,55]
Phototherapeutic agents (PDT)	Photosensitizers	Enables spatially controlled activation via light	[56]
Fluorescent dyes	BODIPY fluorophore	Imaging	[57]
Fluorescent dyes	BODIPY-based near-infrared (NIR) fluorescent probes	Imaging	[58]
TDP1 inhibitor	Usnic acid derivatives (hydrazinothiazole-benzylidene furanone–modified)	Inhibit DNA repair. Enhanced apoptosis	[59]

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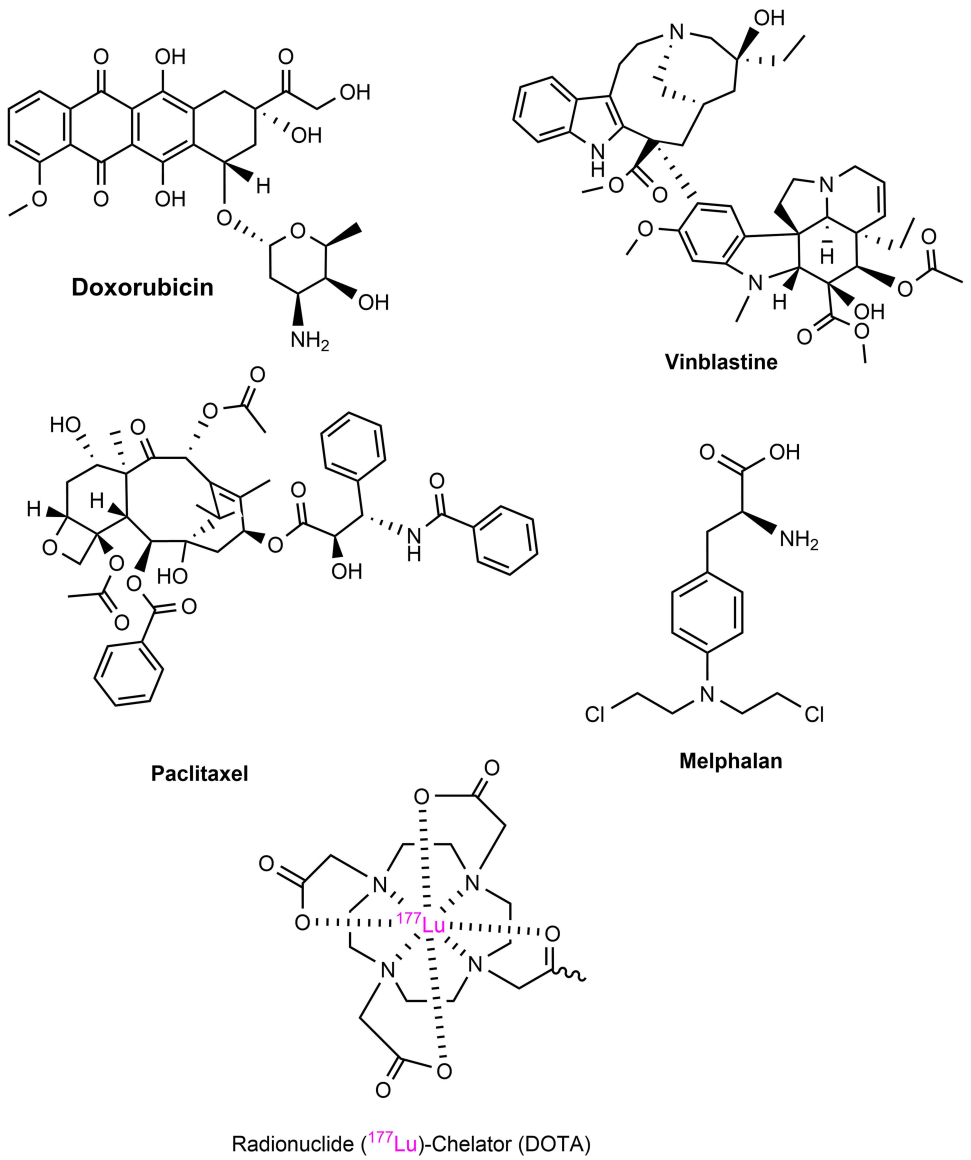

Figure 4 Chemical structures of payloads used in designing PDCs.

NRP-1 to enhance tumor selectivity in PDT applications. Vale et al[56] reviewed peptide-conjugated photosensitizers for photodynamic cancer therapy, detailing various designs and advantages of PDC-based PDT strategies. Nagatani et al[73] described innovative chlorophyll-peptide conjugates that self-assemble and selectively activate under acidic tumor environments, thereby enhancing PDT specificity and reducing phototoxicity in normal tissues.

Verteporfin, an FDA-approved benzoporphyrin derivative, is particularly attractive as a photosensitizer payload owing to its strong absorption at 690 nm, which lies within the tissue optical window, enabling deep light penetration with minimal scattering and autofluorescence. Moreover, its chemical structure allows facile conjugation to the *N* terminus of peptides without loss of photophysical activity. In a recent study, *Arias* et al[74] reported a Verteporfin-conjugated cyclic peptide that targets SNAP25, a synaptic vesicle-associated protein aberrantly externalized on the surface of glioblastoma (GBM) cells. The resulting SNAP25-Verteporfin PDC demonstrated high selectivity for GBM, with minimal binding to normal neurons or astrocytes. Upon activation by 690 nm light, the conjugate generated reactive oxygen species, inducing localized cytotoxicity and significantly suppressing tumor growth in orthotopic GBM models without off-target toxicity.

Radioactive Isotopes

Lutetium-177 (^{177}Lu) integrated into PDCs enables both therapeutic and diagnostic capabilities, known as theranostics. A canonical example is ^{177}Lu-DOTATATE, a radiolabeled somatostatin analogue approved by the FDA in 2018. Used in peptide receptor radionuclide therapy (PRRT), it delivers targeted radiation to somatostatin receptor-positive tumors, providing both imaging and cytotoxic treatment in one conjugate.[54,55] Its regulatory approval was driven by the Phase III NETTER-1 trial, which demonstrated that patients with well-differentiated, metastatic midgut neuroendocrine tumors who received ^{177}Lu-DOTATATE every 8 weeks (four doses) plus best supportive care with long-acting octreotide had significantly improved progression-free survival, overall response rates, and overall survival compared with those treated with octreotide alone. Beyond improving outcomes in this patient population, ^{177}Lu-DOTATATE also validated peptide receptor radionuclide therapy as a clinically effective strategy for PDCs.[75] The Phase III NETTER-1 trial demonstrated that treatment with ^{177}Lu-DOTATATE lowered the risk of death by about 60% compared with octreotide LAR.[2]

Fluorescent Dyes

These dyes absorb light and emit fluorescence, serving as probes to track biomolecules. In PDCs, they enable visualization of uptake and localization, confirm receptor targeting, assess stability, and, in modified forms, provide theranostic potential by combining imaging with therapy. Williams et al (2021) reported the synthesis and evaluation of BODIPY–peptide conjugates using *click chemistry* to couple fluorescent BODIPY dyes to peptides targeting the epidermal growth factor receptor (EGFR). The peptides used include both linear and cyclic forms, designed for high specificity and stability. The resulting conjugates showed strong fluorescence and receptor-specific binding, highlighting their utility in bioimaging and targeted delivery applications.[57]

Kaufman et al (2019) synthesized a series of BODIPY-based near-infrared (NIR) fluorescent probes conjugated to the EGFR-targeting peptide PEG–LARLLT.[58] These bioconjugates were rigorously characterized using molecular modeling, surface plasmon resonance (SPR), fluorescence microscopy, and competitive binding assays. The findings revealed high specificity for EGFR, minimal cytotoxicity, and selective tumor accumulation in HT-29 xenograft mouse models. Only conjugates bearing the LARLLT peptide localized to tumors, demonstrating the utility of peptide-targeted fluorophores for non-invasive cancer imaging.

Tyrosyl-DNA Phosphodiesterase 1 (TDP1) Inhibitors

Topoisomerase I temporarily nicks DNA to relieve supercoiling but can become trapped on DNA, forming TOP1-DNA covalent complexes. TDP1 hydrolyzes the 3′-phosphotyrosyl bond between TOP1 and DNA, thereby resolving these complexes and restoring DNA integrity. TDP1 inhibitors block this repair enzyme that removes stalled topoisomerase I–DNA complexes and helps cancer cells survive DNA damage. Inhibiting TDP1 leaves breaks unrepaired, driving replication stress and tumor cell death. O'Flaherty et al (2024) utilized usnic acid-derived TDP1 inhibitors conjugated to the peptide L-K6, resulting in PDCs with dual action. L-K6 induced DNA damage, while the inhibitor blocked repair, resulting in synergistic cytotoxicity, particularly in glioblastoma, while sparing normal cells.[59]

PDCs in Cancer Therapy

Traditional chemotherapies lack specificity, leading to systemic toxicity and narrow therapeutic indices. PDCs aim to improve the therapeutic index by selectively delivering cytotoxic agents to tumor cells. Coupling therapeutic payloads to peptides capable of recognizing resistant tumor cells enables PDCs to directly access malignancies that evade conventional drugs. This targeted strategy overcomes many resistance-associated barriers and is further strengthened when combined with immunotherapies or monoclonal antibodies, potentially yielding more robust and durable cancer responses.[6,39,76] These modular constructs consist of three key components: (1) a tumor-targeting peptide that provides specificity, (2) a potent cytotoxic payload, and (3) a cleavable linker (Figure 1) that ensures controlled release within the tumor microenvironment. This design enables precise drug delivery to tumors while minimizing off-target effects and systemic toxicity.[8]

Table 4 and Figure 5 summarize representative PDCs in clinical development, showing the peptide sequence, linker chemistry, target receptor, and indication for each. These examples highlight diverse payloads (chemotherapeutics, radionuclides) and targets (eg, GPCRs, receptors, enzymes), demonstrating the versatility of PDCs in precision oncology.

Paclitaxel trevatide (Figure 5) is a PDC that exemplifies advanced tumor-targeting strategies designed to overcome the challenges of penetrating the blood-brain barrier (BBB) in metastatic cancers. This conjugate links three molecules of paclitaxel, a potent microtubule-stabilizing chemotherapeutic, to Angiopep-2, a 19-mer amino acid peptide (TFFYGGSRGKRNNFKTEEY) that specifically binds to low-density lipoprotein receptor-related protein 1 (LRP1). LRP1 is highly expressed on the BBB endothelium and facilitates receptor-mediated transcytosis into brain tissue. The paclitaxel moieties are attached via cleavable ester bonds, allowing the drug to be released at tumor sites.

Preclinical studies demonstrated that paclitaxel trevatide achieved an 86-fold higher influx across the BBB and up to 161-fold greater brain parenchymal delivery of paclitaxel compared to the free drug, alongside substantial accumulation in brain metastases.[77] In clinical trials involving breast cancer patients with brain metastases or leptomeningeal disease, paclitaxel trevatide administered at 600 mg/m^2 every 3 weeks achieved clinical benefit rates of 77% intracranially and 86% extracranially, with a median overall survival of ~8 months in patients with leptomeningeal disease, significantly outperforming historical benchmarks. These findings position paclitaxel trevatide as a promising candidate for brain-targeted cancer therapy via a PDC mechanism, exploiting both BBB penetration and tumor-specific release of cytotoxic agents.[5,47] Paclitaxel trevatide is in Phase II trials for brain metastases and leptomeningeal carcinomatosis (NCT02048059, NCT01480583).

Only two PDCs have been in broad clinical use: (approved) and melphalan flufenamide (melflufen) (a peptidase-activated melphalan prodrug, briefly approved for myeloma). ^{177}Lu-DOTATAT (Figure 5) is a landmark marketed PDC, a peptide receptor radionuclide therapy (PRRT) designed for targeted treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). It employs a somatostatin analogue (octreotate) that specifically binds to somatostatin receptor subtype 2 (SSTR2), which is highly expressed in these tumors.[78] The peptide is conjugated via a DOTA chelator, which securely coordinates the β-emitter radioactive isotope lutetium-177 (^{77}Lu), ensuring stability in circulation. After binding to SSTR2 on tumor cells, the conjugate is internalized, delivering localized beta radiation that induces DNA double-strand breaks and tumor cell death.[55] This targeted radioactivity ensures that non-cancerous tissues are spared, while the tumor receives a concentrated therapeutic dose, explaining the significant increase in progression-free survival observed in clinical trials. Clinically approved by the FDA in 2018, (^{177}Lu)-DOTATATE has proven effective in patients with SSTR-positive GEP-NETs, offering a favorable therapeutic option amid limited alternatives.

Melphalan flufenamide is a peptidase-activated melphalan prodrug, recently approved for the treatment of myeloma. Melphalan flufenamide, also known by its brand name Pepaxto, is a PDC designed as a peptidase-activated derivative of melphalan, intended to enhance drug delivery and selectivity in multiple myeloma. The drug received accelerated FDA approval in February 2021 for relapsed/refractory multiple myeloma under stringent conditions.[79] However, the

Table 4 Examples of PDCs Investigated or Under Investigation in Clinical Development

PDC (Name)	Peptide (Target)	Payload	Linker	Molecular Target	Indication	Reference
Paclitaxel trevatide	TFFYGGSRGKRNNFKTEEY) (Angiopep-2) (LRP1)	Paclitaxel	Ester (cleavable)	LRP1 receptor (BBB)	Breast cancer with brain metastases	[47]
^{177}Lu-DOTATATE	Octreotate (SSTR2)	^{177}Lu (radiation)	DOTA chelator (stable)	Somatostatin receptor 2	Neuroendocrine tumors (GI tract)	[55]
LyP-1–Dox	LyP-1 (p32/NRP1)	Dox	Thioether or hydrazone	p32/NRP1 on tumor cells	Triple-negative breast cancer (preclinical)	[60]
Sudocetaxel zendusortide	BPR1H (SORT1)	Docetaxel	Peptide (enzymatic)	Sortilin (SORT1 receptor)	Solid tumors (SORT1+)	[61]
Zoptarelin doxorubicin	LHRH peptide (GnRHR)	Dox	Maleimide (stable)	Luteinizing hormone-releasing hormone receptor	Endometrial/ovarian cancer	[62]
BT1718	Bicycle peptide (MT1-MMP)	DM1 (maytansinoid)	Thioether (non-cleavable)	MT1-MMP (matrix metalloprotease)	Advanced solid tumors	[63]
^{212}Pb-NG001	PSMA-targeting peptide (PSMA)	^{212}Pb (alpha-emitter)	Chelator (DOTA)	Prostate-specific membrane antigen	Prostate cancer (metastatic)	[64–66]

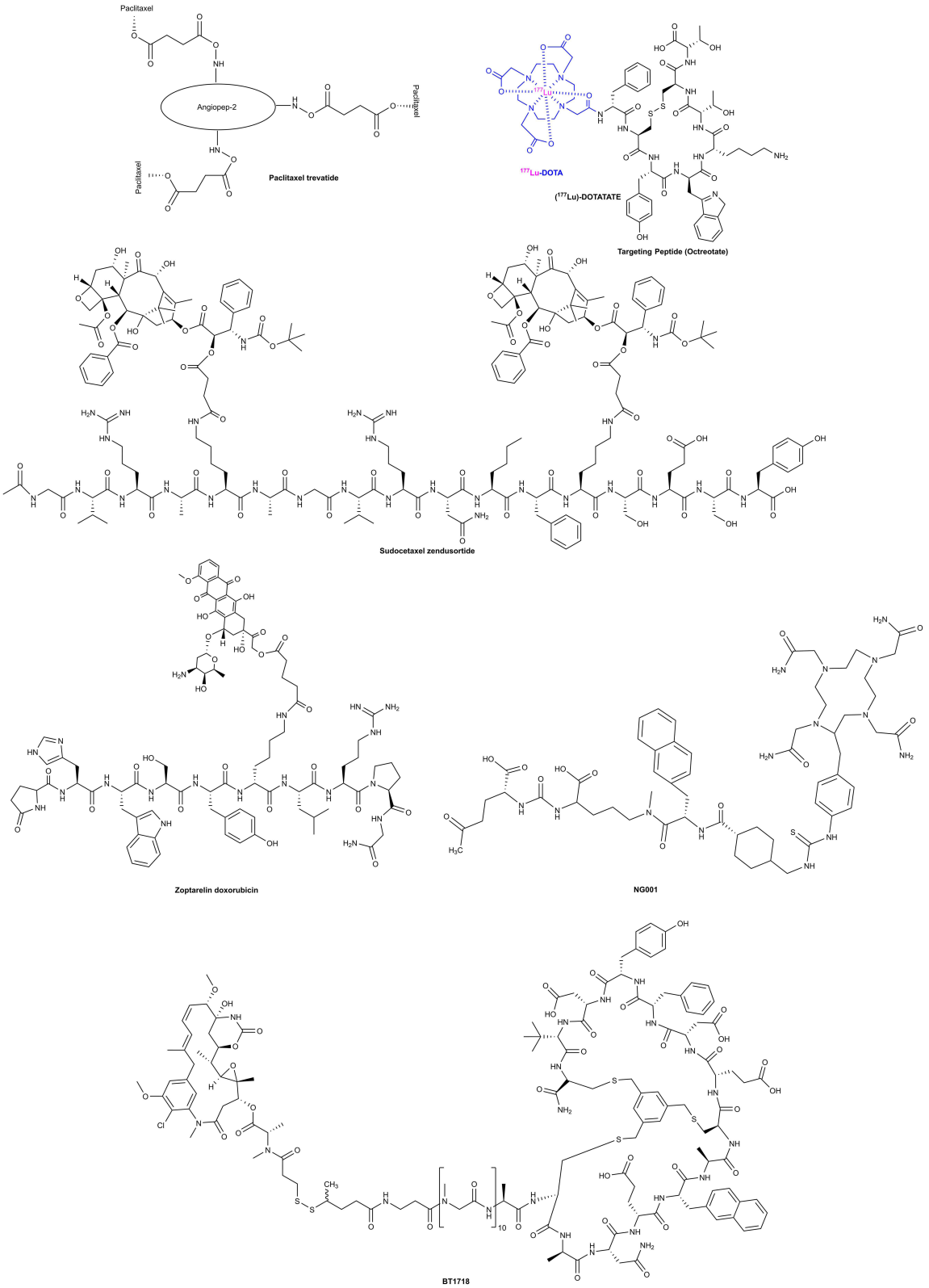

Figure 5 Chemical structure and synthetic scheme for paclitaxel trevatide, (^{177}Lu)-DOTATATE, Sudocetaxel zendusortide, Zoptarelin doxorubicin, BT1718, and NG001.

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confirmatory phase III OCEAN trial failed to demonstrate a clinical benefit and raised serious safety concerns, including a detrimental signal in overall survival. Consequently, the FDA issued a final decision in February 2024 to withdraw Melphalan flufenamide's approval due to concerns about its lack of efficacy and safety.

Other PDCs include Sudocetaxel zendusortide (TH1902, peptide-targeted docetaxel, Sortilin-targeted for solid tumors), bicyclic drug conjugate BT1718 (MT1-MMP-targeted DM1 conjugate for solid tumors), Zoptarelin doxorubicin (AEZS-108, LHRH peptide-Dox for endometrial/breast cancer), and ^{212}Pb-NG001 (PSMA-targeted peptide–radioisotope for prostate cancer).

Sudocetaxel zendusortide (Figure 5) is a PDC targeting sortilin (SORT1), a receptor overexpressed in various solid tumors, including triple-negative breast cancer (TNBC) and ovarian and endometrial cancers. It comprises the TH19P01 peptide (Ac-GVRAKAGVRN(Nle)FKSESY), which requires SORT1 for internalization, linked to docetaxel via enzyme-cleavable ester bonds. In vitro studies confirmed that Sudocetaxel zendusortide's efficacy is SORT1-dependent, its uptake was abrogated by SORT1 silencing or competition with known ligands, and that it induced significantly greater apoptosis and anti-migration effects than free docetaxel in TNBC-derived MDA-MB-231 cells.[61] In vivo, Sudocetaxel zendusortide demonstrated significant tumor regression in murine xenograft models of TNBC and ovarian cancer, outperforming standard docetaxel without inducing neutropenia and overcoming chemoresistance mediated by cancer stem cells (CSCs).[80] Additionally, the conjugate significantly inhibited growth of ovarian and endometrial tumor xenografts, yielding enhanced efficacy and safety, both as monotherapy and in combination with carboplatin.[81]

Zoptarelin doxorubicin (Figure 5) is a targeted cytotoxic analog of luteinizing hormone–releasing hormone (LHRH),[82] engineered to improve the precision delivery of chemotherapy to cancers expressing LHRH receptors. In this construct, Dox is conjugated to a D-Lys^6–LHRH peptide, harnessing the peptide's ability to bind the LHRH receptor, which is overexpressed in approximately 80% of endometrial and ovarian cancers but is minimal in most normal tissues. Upon binding, Zoptarelin doxorubicin undergoes receptor-mediated endocytosis, directing Dox into tumor cells and thereby limiting off-target toxicity. Preclinical xenograft studies demonstrated that Zoptarelin doxorubicin achieved superior tumor growth inhibition with reduced systemic side effects compared to free Dox. In clinical Phase II trials involving women with advanced or recurrent LHRH receptor-positive endometrial or ovarian cancers,[62] Zoptarelin doxorubicin showed promising efficacy and tolerability, marking it as a receptor-directed chemotherapeutic strategy.

BT1718 (Figure 5)[83] is a Bicycle-Drug Conjugate (BDC®) that leverages a constrained bicyclic peptide targeting membrane-type 1 matrix metalloproteinase (MT1-MMP or MMP14), a protease commonly overexpressed in various solid tumors. This peptide was conjugated through a thioether (non-cleavable) or hindered disulfide linker to the potent microtubule inhibitor DM1 (maytansinoid).[63] A Phase I/IIa clinical trial (NCT03486730), led by Cancer Research UK, assessed BT1718's pharmacokinetics, safety, and preliminary efficacy in patients with advanced solid tumors. In this multicenter dose-escalation study, the recommended phase II dose (RP2D) for the twice-weekly schedule was established at 7.2 mg/m^2, with dose-limiting toxicities (DLTs) such as grade 3 fatigue and elevated GGT observed at 9.6 mg/m^2. Importantly, pharmacokinetic analysis confirmed favorable tumor-specific delivery: drug levels in patient tumor biopsies matched those achieved in preclinical xenograft models. The plasma half-life (~0.3 h) and volume of distribution (~0.2 L/kg) reflect the molecule's small size and rapid clearance, reducing systemic exposure and potential toxicity.[84]

^{212}Pb-NG001 is a novel PDC that combines a prostate-specific membrane antigen (PSMA)-targeting peptide (NG001) (Figure 5) with the alpha-emitting radionuclide ^{212}Pb, chelated via the bifunctional chelator *para*-isothiocyanatobenzyl-1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamoylmethyl)cyclododecane (p-SCN-Bn-TCMC). Designed for precision alpha therapy, it targets prostate-specific membrane antigen (PSMA), a cell surface protein overexpressed in metastatic castration-resistant prostate cancer (mCRPC). In preclinical studies, ^{212}Pb-NG001 demonstrated efficient radiolabeling with high purity (>94%) and sustained stability in serum for up to 48 h.[64] Biodistribution studies in C4-2 tumor-bearing mice revealed strong tumor uptake and significantly lower renal retention compared to PSMA-617-based analogs, a key feature given the concerns about nephrotoxicity associated with radiolabeled PSMA ligands. In multicellular tumor spheroids and xenograft models, ^{212}Pb-NG001 produced potent antitumor effects, with a favorable therapeutic index (~3.5), especially when administered in repeated doses.[65,66] These findings support ongoing translational efforts in radiopharmaceutical oncology by using PDCs.

LyP 1 (sequence: CGNKRTRGC) (Figure 6) is a tumor-homing cyclic peptide with a cryptic CendR motif, that first targets the p32 receptor, an overexpressed cell-surface marker on tumor lymphatics, hypoxic tumor regions, and certain

cancer cells. In one study, LyP-1 was conjugated to Dox-loaded liposomes to create a targeted delivery system (LyP-1-Dox liposome) designed to suppress lymphatic metastasis. In triple-negative breast cancer models, these LyP-1-modified liposomes exhibited significantly enhanced accumulation in metastatic lymph nodes, increased cytotoxicity in MDA-MB-435 cells, and effective destruction of tumor lymphatics, outperforming non-targeted liposomal Dox in both in vitro and in vivo assessments.[60]

CPPs, particularly those rich in arginine or lysine residues, significantly enhance cellular uptake beyond traditional receptor-mediated mechanisms. There are many other PDCs reported for Dox. Nasrolahi Shirazi et al (2013) developed both cyclic ([W(RW)$_4$]-Dox) and linear ((RW)$_4$-Dox) PDCs (Figure 7), using a three-carbon linker at Dox's 14-hydroxyl position to enhance cellular delivery and retention.[85] The study demonstrated notably higher antiproliferative effects of the cyclic conjugate compared to the linear form across several cancer cell lines, including CCRF-CEM, SK-OV-3, HCT-116, and MDA-MB-468, achieving 50–79% inhibition at 1 μM after 72–120 h. Crucially, cyclic [W(RW)$_4$]-Dox showed 3.6-fold higher uptake in SK-OV-3 cells than free Dox at 24 h, and an intracellular hydrolysis profile with 99% of the conjugate releasing Dox by 72 h post-uptake. These results show its potential as a sustained-release prodrug with enhanced retention and potency, supporting the promise of peptide-Dox conjugation strategies for overcoming efflux-mediated resistance and improving intracellular delivery.

Darwish et al (2019) synthesized novel Dox conjugates containing thiol and disulfide linkers: Dox-SH, Dox-SS-Pyridine, and a cyclic peptide conjugate Dox-SS-[C(WR)$_4$K] (Figure 7).[86] All conjugates displayed equal or superior cytotoxicity compared to free Dox in HEK-293, HT-1080, and CCRF-CEM cells across 24- and 72-h assays, likely owing to improved cellular retention and activity. Fluorescence microscopy confirmed nuclear localization of these

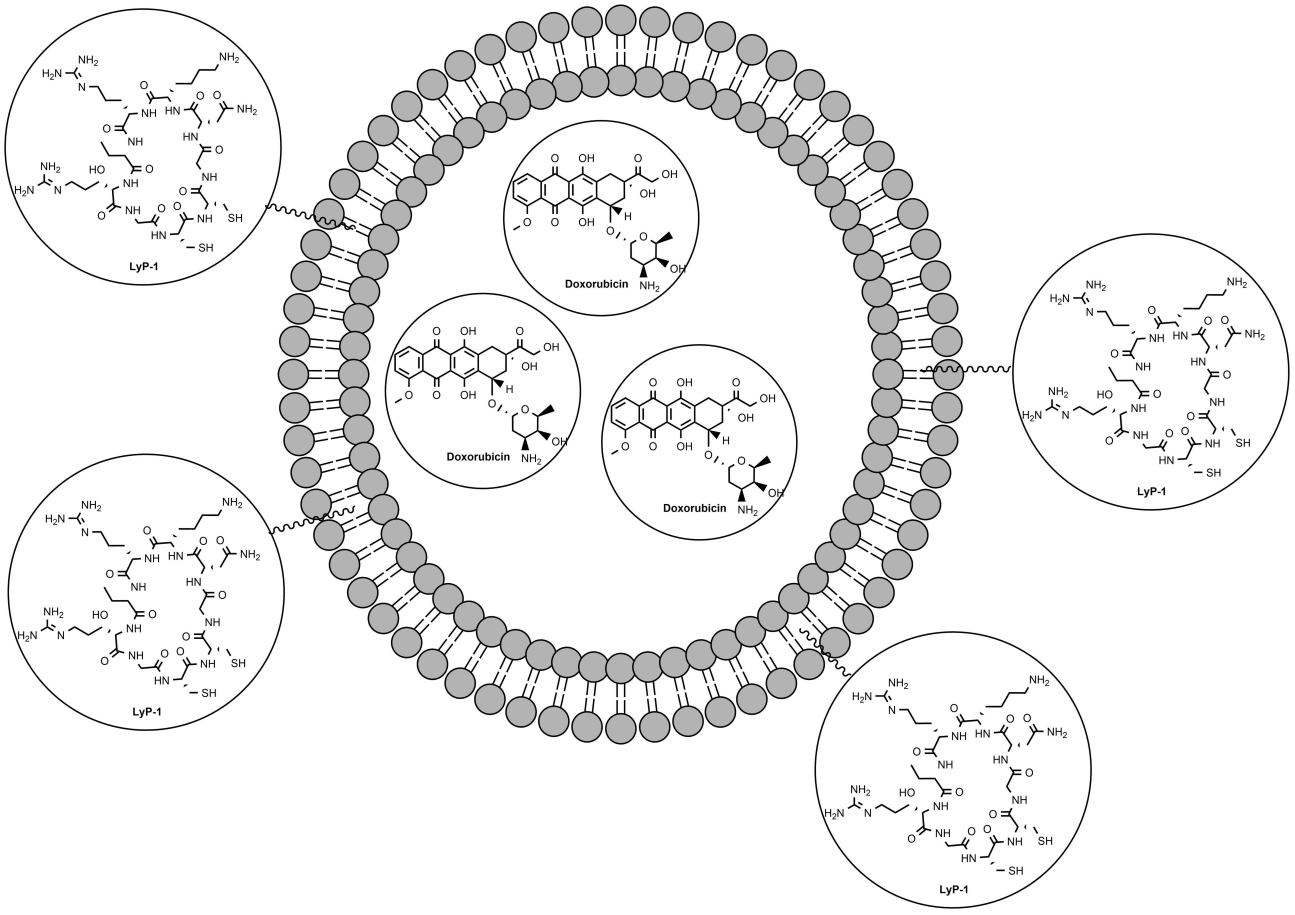

Figure 6 A schematic illustration of LyP-Dox liposome.

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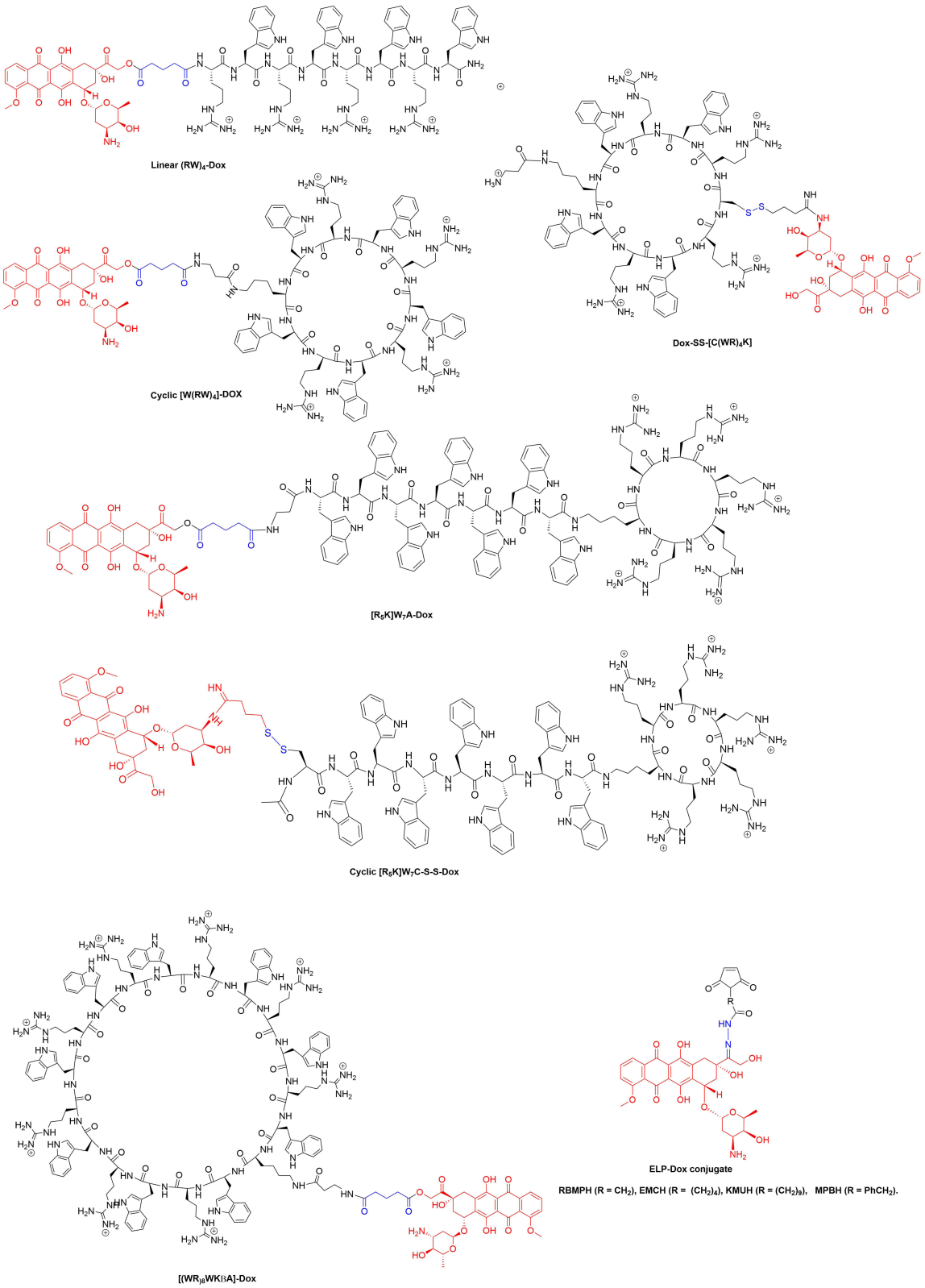

Figure 7 Chemical structures of linear $(RW)_4$-Dox, cyclic $[W(RW)_4]$-Dox, Dox-SS-$[C(WR)_4K]$, $[R_5K]W_7A$-Dox, $[C(WR)_4K]$-S-S-Dox, $[(WR)_8WK\beta A]$-Dox, and ELP-Dox conjugate. The linker is shown in blue, and the drug cargo is shown in red.

conjugates in multiple cancer cell lines (HT-1080, SK-OV-3, MDA-MB-468, MCF-7), indicating efficient nuclear delivery.

Mozaffari et al (2021) designed hybrid cyclic-linear and disulfide-linked PDCs, including $[R_5K]W_7A$-Dox (glutarate linker) and $[R_5K]W_7C$-S-S-Dox (Figure 7), to tackle both Dox resistance and toxicity issues.[87] The hybrid cyclic-linear conjugate $[R_5K]W_7A$-Dox (Figure 7) displayed potent antiproliferative activity: at 5 μM, 72 h incubation resulted in 84% inhibition in CCRF-CEM cells, 39% in SK-OV-3, and 73% in AGS, matching or closely approximating the effects of free Dox (85%, 33%, and 87%, respectively). Comparative analysis revealed that $[R_5K]W_7A$-Dox was roughly twice as efficient as its linear counterpart (R_5KW_7A-Dox) and the disulfide-linked $[R_5K]W_7C$-S-S-Dox in inhibiting proliferation in human leukemia cells (CCRF-CEM).

Zoghebi et al (2022) synthesized a cyclic peptide-Dox conjugate, $[(WR)_8WK\beta A]$-Dox (Figure 7), via a glutarate linker, aiming to surmount Dox resistance in cancer cells.[88] The conjugate demonstrated substantially greater antiproliferative potency across multiple cancer cell lines: at 5 μM after 72 h, viability reductions reached 59% in SK-OV-3, 71% in MDA-MB-231, and 77% in MCF-7 cells, significantly outperforming free Dox (35%, 63%, and 57%, respectively). In the Dox-resistant MES-SA/MX2 cells, the conjugate reduced viability by 92% at 5 μM, whereas free Dox had a minimal effect (only 15% reduction), demonstrating its potential to overcome multidrug resistance mechanisms. Confocal microscopy confirmed efficient nuclear delivery and retention of the conjugate, while uptake in the presence of endocytosis inhibitors suggested a predominantly endocytosis-independent internalization mechanism. Stability assays revealed a plasma half-life of approximately 6 h, with over 80% degradation by 12 h, and near-complete intracellular release of Dox from the conjugate by 72 hours.

Mechanisms of Action

After systemic administration, a PDC continues to circulate until the peptide moiety recognizes and binds to its target receptor in the tumor, triggering receptor-mediated endocytosis. Non-CPPs enable this process, while some CPPs can facilitate passive uptake across cell membranes. Once internalized, the PDC is trafficked through endosomal compartments, where specific tumor-associated triggers, such as acidic pH, elevated glutathione (GSH), or proteolytic enzymes, cleave the linker and release the active drug intracellularly.

In certain PDC constructs, the peptide component performs more than just tumor targeting; it can be engineered with secondary functionalities such as facilitating cell penetration, triggering immune activation, or acting as therapeutic molecules themselves. As a result, peptides within PDCs can be engineered to do far more than guide delivery; they can actively modulate the tumor microenvironment by breaking down immunosuppressive barriers or attracting immune effector cells, effectively converting immunologically "old"tumors into "ot", responsive lesions. This multifunctionality transforms the peptide into a dual-purpose agent, enhancing both delivery and therapeutic impact.[9,89]

A recent review[1] notes that homing peptides mediate receptor-mediated endocytosis, followed by intracellular release of the drug, primarily within endo-lysosomal compartments responsive to low pH and specific enzymes like cathepsins or MMPs. Another review emphasizes[90] that receptor binding initiates endocytosis, after which stimuli-responsive linker cleavage (due to pH, redox state, or enzymatic activity in the tumor microenvironment) ensures the release of the payload in the intended cellular compartment.

An example of pH-triggered drug release involves an elastin-like polypeptide (ELP)-Dox conjugate (Figure 7), where the drug is attached via a hydrazone linker. This conjugate demonstrated a remarkable, nearly 80% release of Dox at pH 5.0 over 72 h, while under physiological pH (approximately 7.4), release was significantly impaired, with approximately 15% release at pH 7.4, illustrating selective acid-triggered release.[44]

Redox-sensitive disulfide-linked conjugates exploit the markedly higher intracellular glutathione (GSH) concentrations, typically 1–10 mM, versus extracellular levels (~2–20 μM) (Figure 8).[91,92] This contrast ensures that drug release is substantially accelerated inside cells, often up to 1000-fold faster, thereby ensuring intracellular-specific activation of the payload. Guo et al, 2018 and Zhao et al, 2017 detailed that intracellular GSH concentrations can reach 10 mM, compared to mere 2–20 μM in extracellular fluids, creating a strong redox gradient that favors selective cleavage of disulfide bonds within tumor cells.[91,92]

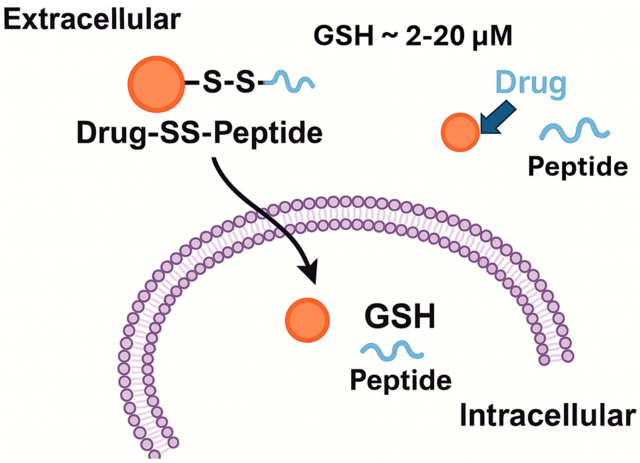

Figure 8 Redox-triggered intracellular cleavage of disulfide-linked PDCs via elevated intracellular GSH levels. The arrows indicate the direction of Drug-SS-Peptide uptake from the extracellular environment into the intracellular space.

An example of a redox-sensitive PDC is the RGD-Dox construct, in which a cyclic RGD peptide (cRGDfK), targeting integrin αvβ3 receptors overexpressed on tumor vasculature, is linked to Dox via a disulfide bond. This redox-sensitive linker design exploits the steep redox gradient between the extracellular environment (~2–20 μM GSH) and the intracellular milieu (~1–10 mM GSH) of tumor cells.[93] Upon systemic administration, the conjugate remains stable in circulation, minimizing off-target effects. Once internalized into cancer cells via receptor-mediated endocytosis, the elevated intracellular glutathione concentration cleaves the disulfide bond, releasing active Dox specifically within the tumor. This selective release mechanism results in significantly enhanced intracellular drug accumulation, reduced cardiotoxicity, and superior antitumor efficacy compared to free Dox.

Peptide-polymer conjugates combine peptides with synthetic polymers, merging the specificity of peptides with the stability and processability of polymers. This offers potential applications not just in targeted drug delivery but also in nanomedicine and hybrid material design. For instance, in vitro and in vivo studies of cyclic RGD-functionalized, disulfide-crosslinked polymersomal Dox (cRGD-PS-Dox) have demonstrated significantly enhanced tumor targeting (Figure 9).

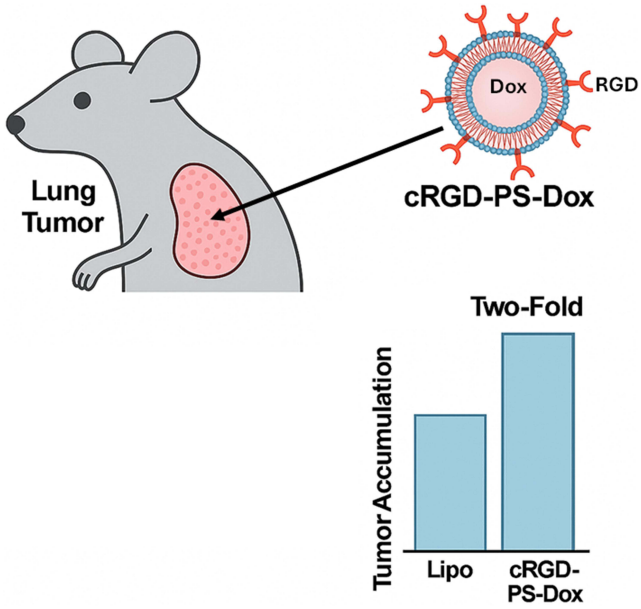

Figure 9 Targeted delivery of cRGD-functionalized polymersomal Dox for lung tumor chemotherapy in murine xenografts. Arrows depict the localization of cRGD-PS-Dox within lung tumors and the associated delivery of Dox.

Specifically, in murine xenograft models of human non-small cell lung cancer, tumor accumulation of Dox was approximately two-fold higher following cRGD-PS-Dox administration compared to PS-Dox and Lipo-Dox, accompanied by markedly improved therapeutic outcomes and minimal off-target toxicity.[94]

Many PDCs also exploit self-assembly. Hydrophobic drugs and amphiphilic peptide motifs can drive PDCs to form nanostructures (micelles, fibers, vesicles) in an aqueous milieu. For instance, a Camptothecin-peptide conjugate (diCPT-PLGLAG-iRGD) self-assembles into nanofibers that localize to tumors (Figure 10), where they respond to both MMP-2 protease activity (via the PLGLAG linker) and glutathione reduction, triggering the release of CPT for combined chemotherapy and immunotherapy applications.[50] The nanotube network is loaded with anti-PD-1 antibodies (aPD-1), which, once released into the tumor microenvironment, block the PD-1-1/PD-L1 immune checkpoint pathway and thereby enhance T cell activation (both $CD4^+$ and $CD8^+$) and antitumor immune responses. Self-assembly can protect the drug, prolong its circulation, and facilitate the co-delivery of multiple drugs. Designs like dual-responsive hydrogels (forming into the tumor microenvironment and slowly releasing payloads) are also emerging.

In some innovative PDC and nanoparticle systems, the peptide component transcends its traditional targeting function to provide immunomodulatory activity, thereby amplifying anticancer immune responses. A notable example is D-PPA1 (sequence: NYSKPTDRQYHF; identified through phage display), a D-peptide antagonist of PD-L1 that binds with high affinity ($K_d \approx 0.51$ μM), effectively blocking the PD-1/PD-L1 immune checkpoint and promoting T-cell activation. Chang et al (2015) first demonstrated that D-PPA1 significantly inhibited tumor growth and extended survival in murine models of cancer.[95]

Building upon this foundation, Zhu et al (2021) incorporated D-PPA1 (D-Cys-Pro-Pro-Ala) into a tumor extracellular pH-sensitive nanoparticle co-loaded with Dox, achieving dual-function chemo-immunotherapy.[96] A hydrophilic D-type polypeptide (D-PPA) and two hydrophobic stearyl chains were conjugated through a pH-sensitive CDM linker to form an amphiphilic molecule (DCS, where D = D-PPA, C = CDM cleavable linker, S = stearyl chains) capable of self-assembling into nanoparticles (NPs). The chemotherapeutic agent Dox was subsequently encapsulated to yield Dox@DCS NPs, which preferentially accumulated at tumor sites via the enhanced permeability and retention (EPR) effect and released D-PPA under acidic tumor extracellular conditions, enabling both targeted drug delivery and pH-responsive immune modulation. On this platform, D-PPA1 decoration facilitated selective binding and internalization into PD-L1-expressing tumor cells, while acidic pH-triggered Dox release enhanced localized cytotoxicity. Simultaneously, PD-1/PD-L1 blockade reactivated antitumor immunity, resulting in improved tumor accumulation, deeper intratumoral penetration, and reduced systemic toxicity compared to free Dox or non-targeted nanoparticles (Figure 11).

Moreover, peptide-guided reprogramming of tumor-associated macrophages (TAMs) has emerged as a promising therapeutic strategy. Nanoparticle-based systems and several PDC designs have been developed to specifically target

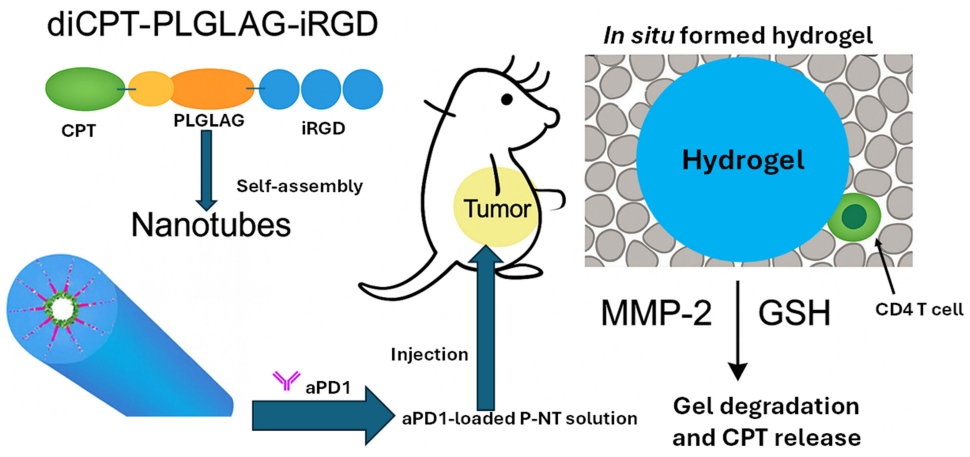

Figure 10 Schematic illustration of localized delivery of CPT and anti-PD1 (aPD1) via a diCPT-PLGLAG-iRGD-based supramolecular hydrogel. The diCPT-PLGLAG-iRGD conjugate undergoes self-assembly into nanotubes, which are co-loaded with aPD1. Upon intratumoral injection, the nanotubes form an in situ hydrogel within the tumor microenvironment. The hydrogel undergoes bioresponsive degradation in the presence of MMP-2 and elevated GSH, triggering the controlled release of CPT and aPD1.

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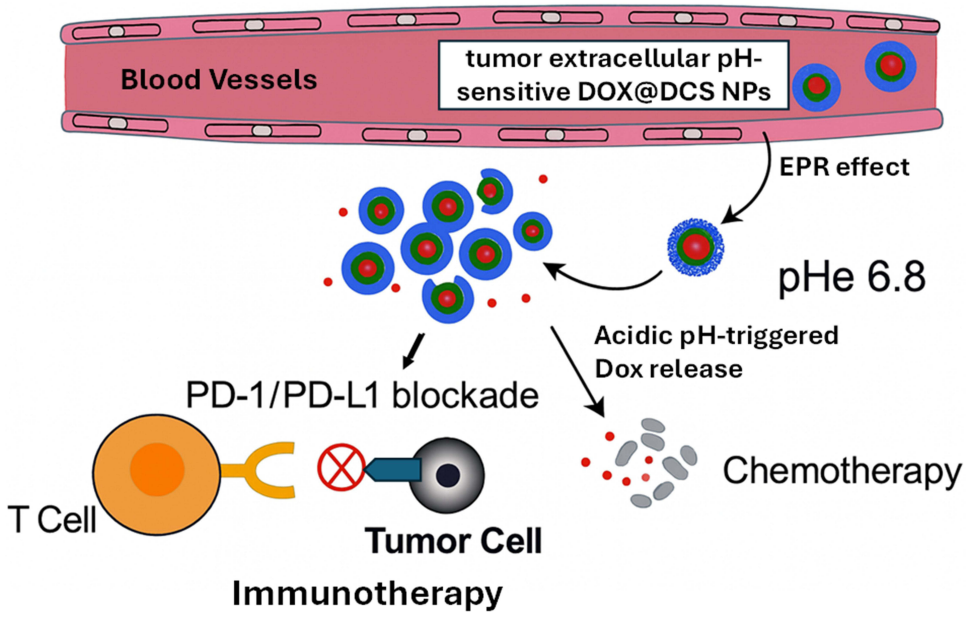

Figure 11 pH-Sensitive nanoparticle-mediated chemo-immunotherapy by Dox@DCS targeting PD-L1 for enhanced tumor accumulation and T cell activation in colon cancer.

TAMs. For example, M2pep (sequence: YEQDPWGVKWWY), a peptide that selectively binds M2-polarized TAMs, has been used to deliver CSF-1R siRNA via nanomicelles. This approach effectively reprograms TAMs toward a tumor-suppressive M1 phenotype, suppressing pancreatic tumor growth in preclinical models.[97]

M2pep was conjugated to the pro-apoptotic peptide KLAKLAK (M2pep-KLAKLAK) to selectively deplete protumoral M2-like TAMs.[98] This PDC selectively induces apoptosis in M2-polarized macrophages while sparing M1 macrophages. In vivo, systemic administration of M2pep-KLAKLAK in mice bearing MKN-45P gastric carcinoma significantly suppressed tumor growth. These findings suggested M2pep-KLAKLAK as a prototype of macrophage-targeted PDCs capable of remodeling the tumor immune microenvironment and suppressing tumor progression.[98]

More recently, a macrophage-targeting PDC termed MACTIDE-V has been developed for selective modulation of TAMs in breast cancer. This system employs the cyclic peptide MACTIDE, for its preferential binding to TAMs within the tumor microenvironment. In MACTIDE-V, MACTIDE is conjugated to Verteporfin, an FDA-approved photosensitizer and YAP/TAZ pathway inhibitor, enabling targeted delivery to macrophages in solid tumors. Upon internalization, the Verteporfin payload suppresses YAP/TAZ-mediated transcriptional activity, thereby reprogramming TAMs from an immunosuppressive M2 phenotype toward a proinflammatory M1 state. This macrophage reprogramming leads to remodeling of the immune microenvironment, reduced tumor growth, and suppression of metastasis in murine breast cancer models.[99] These two examples demonstrate the emerging potential of TAM-directed PDCs as an immunomodulatory approach to reshape the tumor microenvironment and enhance antitumor immunity.

In essence, incorporating multifunctional peptides into PDCs elevates their therapeutic sophistication, enhancing tumor penetration, overcoming drug resistance, and harnessing immune mechanisms alongside cytotoxic delivery. Overall, PDCs act as prodrugs whose activity depends on tumor-selective activation. The peptide increases the local concentration of the PDC in cancer tissue, while the linker ensures that the cytotoxic payload is liberated only after reaching the target site.

PDCs vs ADCs

ADCs are first transported to tumor cells via the bloodstream. Upon reaching their destination, they bind to specific antigens on the surface of cancer cells and are internalized through antigen-mediated endocytosis. Inside the cell, ADCs accumulate in endosomes and are subsequently degraded in lysosomes, where the cytotoxic drug is released. The released payload then targets key intracellular components, ultimately leading to the destruction of the cancer cell (Figure 12).[100]

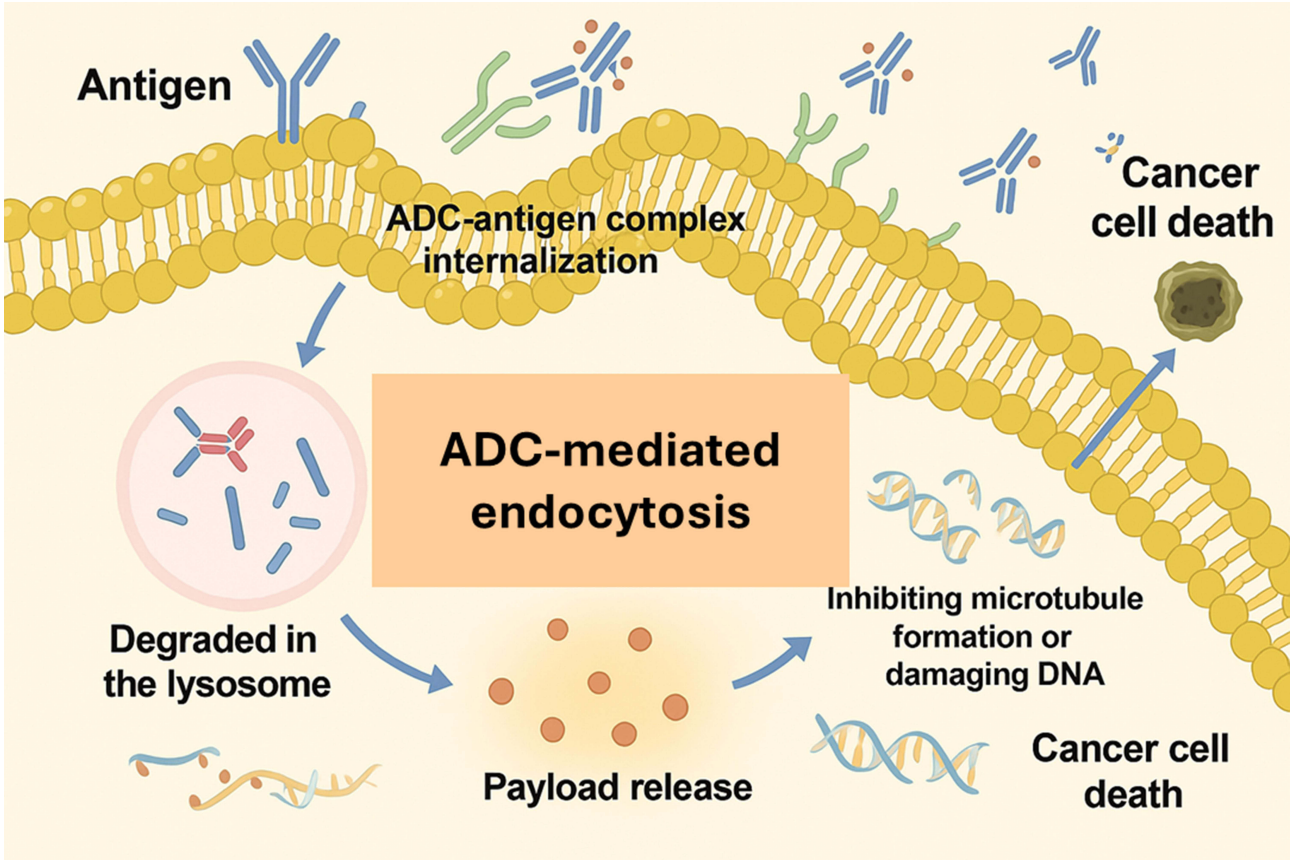

Figure 12 Mechanism of ADC-mediated endocytosis and intracellular cytotoxicity in cancer cells. ADCs bind selectively to surface antigens expressed on cancer cells, initiating antigen-mediated internalization via endocytosis. The ADC-antigen complex is trafficked into lysosomes, where it undergoes proteolytic degradation, releasing the cytotoxic payload. Once released into the cytosol, the payload interferes with key cellular components such as microtubules or DNA, leading to apoptotic cell death.

In contrast, ADCs often suffer from perivascular trapping and poor interstitial diffusion, a phenomenon known as the "binding site barrier". This effect occurs when high-affinity antibodies or ADCs bind rapidly to antigens on tumor cells near blood vessels, thereby limiting their penetration into deeper tissue and resulting in a heterogeneous intratumoral distribution. Delivering higher doses can saturate receptors in perivascular regions yet still fail to reach distal tumor cells.[101–103] In practice, PDCs can achieve more uniform tumor distribution, potentially overcoming one mechanism of drug resistance.[104]

Figure 13 provides a theoretical overview of the internalization process of PDCs via receptor-mediated mechanisms in cancer cells. Initially, the PDC specifically recognizes and binds to an overexpressed receptor on the surface of the cancer cell. This interaction triggers internalization of the complex (Step 1). Once inside the cell, cleavage of the linker facilitates the release of the cytotoxic drug, as symbolized by the red lightning bolt (Step 2). Following drug release, the receptor dissociates from the ligand and is recycled back to the cell membrane. The liberated payload then exerts its cytotoxic effect, ultimately leading to the death of cancer cells (Step 3).

PDCs and ADCs share the same conceptual framework (carrier-linker-drug), but differ fundamentally in terms of size, structure, and pharmacology.[1] PDCs use small peptides (~1–3 kDa) as carriers, whereas ADCs use ~150 kDa monoclonal antibodies. The small size of PDCs confers superior tissue penetration: PDC molecules readily diffuse through the dense tumor stroma, reaching cells deep from blood vessels.

These size and diffusion differences also affect pharmacokinetics. PDCs are cleared more rapidly via renal filtration, resulting in shorter circulation half-lives. This can reduce systemic exposure and off-target toxicity, but it may also require more frequent dosing. ADCs, by contrast, have long half-lives in the blood, allowing for sustained delivery, but at the expense of prolonged exposure to healthy tissues.[100]

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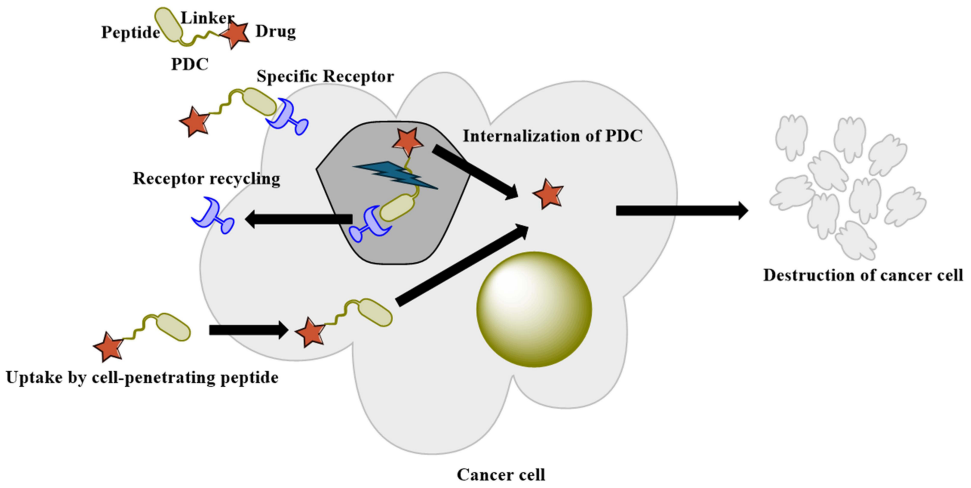

Figure 13 Conceptual framework of internalization of PDCs in cancer cells.

Moreover, PDCs generally have lower immunogenicity (small peptides are less likely to provoke neutralizing antibodies) and greater synthetic flexibility. Manufacturing PDCs is simpler and less expensive because they are chemically synthesized, whereas ADC production requires biologic expression and precise control of complex conjugation.[104]

Clinically, ADCs have seen more success to date, with >15 FDA approvals (eg, trastuzumab emtansine, brentuximab vedotin).[105] By contrast, only two PDCs have been in broad clinical use: (^{177}Lu)-DOTATATE and melphalan flufenamide (a peptidase-activated melphalan prodrug, briefly approved for the treatment of myeloma). However, the confirmatory phase III OCEAN trial failed to demonstrate clinical benefit and raised serious safety concerns, including a detrimental signal in overall survival. Consequently, the FDA issued a final decision in February 2024 to withdraw melphalan flufenamide on grounds of lack of efficacy and safety.

These outcomes reflect the stringent requirements for stability, potency, and reproducibility in the clinic. Nonetheless, several PDCs are in advanced trials or have been studied (Table 4). Mechanistically, both PDCs and ADCs rely on receptor targeting and controlled release, but PDCs often incorporate features learned from ADCs (eg, cathepsin-cleavable linkers) while exploiting the benefits of peptide biology (cell-penetration, alternative targets).

Challenges in Clinical Translation of PDCs

PDCs offer compelling promise as next-generation targeted therapeutics; however, their clinical translation remains constrained by several pharmacological hurdles. A major limitation is premature drug release in circulation, often driven by unstable linkers, such as certain hydrazones, and peptide proteolysis, which together contribute to off-target toxicity and weakened tumor delivery. Additionally, the small size of many peptides predisposes them to rapid renal clearance, significantly limiting their systemic half-lives. Achieving a delicate balance between optimal circulatory stability and efficient tumor-triggered payload release is therefore critical but nontrivial. For example, although disulfide linkers offer environmentally triggered release, they may be susceptible to cleavage by plasma glutathione (leading to off-target release), whereas thioether linkers, while stable, may impede effective drug release at the tumor site. Ensuring controlled "triggered" release without leakage underlies ongoing engineering efforts in PDC design.[106,107]

There are other factors that contribute to challenges in the successful development and effectiveness of PDCs, such as tumor heterogeneity, manufacturing, scale-up, and pharmacological challenges.

Tumor Heterogeneity as a Barrier to PDC Effectiveness

While PDCs can be exquisitely selective for a particular receptor or antigen, their efficacy may be limited by variable receptor expression across tumor subclones or metastatic sites. This often results in incomplete targeting and suboptimal tumor penetration. Tumor heterogeneity presents a major obstacle to the efficacy of PDCs. Mixed cell populations within

tumors often express varied levels, or even complete absence, of the targeted receptors, allowing some subpopulations to evade treatment entirely. This intra-tumor diversity is compounded by microenvironmental variability, such as heterogeneous pH levels and protease activity, which can influence linker cleavage and payload release. As a result, a PDC highly effective in a controlled cell line may underperform in the complex and variable contexts of clinical tumors. To mitigate these limitations, strategies include targeting broadly expressed markers (such as integrins or transporters) or engineering multifunctional PDCs, for instance, bispecific peptides or dual payload constructs that address heterogeneity through broader targeting while maintaining specificity and efficacy.[108,109]

Manufacturing and Scale-Up Challenges for PDCs

Despite their therapeutic potential, PDCs face substantial hurdles in manufacturing and scale-up for clinical use. Although solid-phase peptide synthesis (SPPS) is well-established and scalable, the conjugation of highly potent cytotoxic drugs demands precise control of reaction conditions to maintain consistent drug-to-peptide ratios and high purity. Complex linkers, especially those incorporating peptide sequences, further complicate the synthesis process, increasing the number of steps and the burden of quality control. These factors elevate production costs significantly. While peptide synthesis is chemically less expensive than antibody production, peptide conjugation to payloads remains relatively difficult and costly, thus slowing clinical translation. Regulatory-grade manufacturing, particularly for constructs featuring novel linkers or payloads, entails additional regulatory scrutiny, thereby increasing development costs.[106]

Other Pharmacological Challenges in PDC Development

PDCs often contend with multiple pharmacological barriers that hinder their clinical success. Small peptides are particularly susceptible to proteolytic degradation, and certain sequences can elicit immunogenic responses, thereby compromising stability and safety. Their rapid renal clearance, driven by low molecular weight, results in short systemic half-lives and limited tumor exposure. To address these limitations, strategies such as PEGylation or albumin-binding modifications are employed to prolong circulation time and shield against enzymatic degradation. A protein-G-derived albumin-binding domain (ABD) conjugated with Dox through a pH-sensitive linker demonstrated prolonged plasma half-life and a four-fold increase in tumor accumulation,[110] In another study, albumin-binding peptide (DICLPRWGCLW)-based bioconjugates also showed stability for enhanced tumor targeting.[111]

However, these modifications can sometimes reduce biological activity or introduce new immunogenicity concerns. Another obstacle involves off-target uptake, particularly in renal tissue, and non-specific distribution in normal organs. This is especially true for CPPs that lack inherent specificity. Additionally, after cellular internalization, ensuring efficient endosomal escape of the released drug is critical; without it, payloads often become trapped and degraded within endolysosomal compartments, limiting therapeutic efficacy.[112,113]

Conjugation of antimicrobial peptides with small-molecule antibiotics[114,115] or hydrophilic polymers has enhanced proteolytic stability, prolonged circulation time, and facilitated membrane permeabilization, resulting in synergistic antimicrobial effects that may inspire similar conjugation strategies in cancer-directed PDCs.[116]

In summary, the successful development of PDCs demands a delicate balance among competing design goals: stability versus triggered release, target selectivity versus tumor heterogeneity, and manufacturability versus chemical complexity. A common pitfall in PDC design is over-optimization for circulation stability, which can compromise the efficiency of drug release at the tumor site. Conversely, overly labile linkers or unprotected peptides may result in premature drug release, systemic toxicity, and diminished therapeutic benefit.

From a translational perspective, in vitro potency does not reliably predict in vivo efficacy. In preclinical studies, many PDCs demonstrate excellent cell-killing ability under controlled conditions; however, they often fail to replicate these results in animal models or clinical settings due to poor bioavailability, metabolic degradation, or immune clearance. Moreover, the manufacturing of PDCs remains challenging; site-specific conjugation, reproducible drug loading, and scalability under GMP conditions require stringent process control, especially when working with highly toxic payloads.

These hurdles explain why, despite decades of research and dozens of candidates in development, only a handful of PDCs have reached clinical approval. Still, the continued refinement of linker chemistry, peptide engineering, multi-targeting

strategies, and nanocarrier-assisted delivery promises to overcome these barriers and unlock the full potential of PDCs in targeted cancer therapy.

Artificial Intelligence (AI)-Powered Discovery of PDCs

The integration of AI is beginning to shape the development of PDCs, paving the way for more predictive and data-driven approaches to therapeutic design. While models like DRlinker have demonstrated the feasibility of using deep reinforcement learning for fragment-based linker generation,[117] dedicated resources such as PDCdb now provide structured, component-level data across over 2000 PDCs to facilitate AI-enabled pattern recognition and property prediction.[118] These advances align with a broader transformation in biomedical research, marked notably by the 2024 Nobel Prize in Chemistry awarded for breakthroughs in AI-based protein structure prediction, a milestone highlighting the growing impact of AI across all phases of drug development.

AI-driven approaches,[119,120] including deep learning, generative modeling, and molecular simulations, are transforming every stage of PDC design by overcoming traditional limitations like narrow peptide libraries, unoptimized linkers, and trial-and-error payload choices. The result is a shift from laborious trial-and-error workflows to in silico-guided design of more effective and selective PDCs.

Optimizing Tumor-Targeting Peptides

AI-powered deep learning and generative techniques enable the rapid development of peptides with superior tumor-targeting and stability properties. In silico sequence optimization enables high-throughput screening of peptide libraries, surpassing the speed and efficiency of conventional approaches, such as phage display.[121,122]

Template-based AI tools like AlphaFold2 (https://golgi.sandbox.google.com/) have revolutionized peptide-receptor modeling by predicting peptide-bound protein structures and identifying key binding interfaces. For example, Kosugi and Ohue (2023) employed a modified AlphaFold2 framework incorporating a cyclic-peptide complex offset to design cyclic peptide binders targeting protein-protein interaction sites, such as MDM2/p53. This demonstrated that these AI-designed peptides could achieve lower predicted binding energies than native ligands.[123] Similarly, Chen et al (2024) applied structure-conditioned generative modeling and refinement workflows to develop high-affinity linear peptide inhibitors, achieving nanomolar potency against therapeutic protein targets, further illustrating the expanding role of AI in rational peptide design for biomedical applications.[124] *De novo* computational design methods offer valuable alternatives to traditional discovery methods. Diffusion-based models such as RFdiffusion have produced cyclic tumor-targeting peptides exhibiting approximately 60% greater receptor affinity compared to those identified through phage display.[120] Similarly, reinforcement learning platforms enable the optimization of peptide attributes, including cyclization and the incorporation of non-canonical amino acids, to improve resistance to proteolytic degradation. For example, AI-guided strategies such as backbone cyclization and the integration of D-amino acids or non-natural residues are increasingly applied to extend peptide half-life and minimize enzymatic breakdown.[125,126]

Early successes in AI-guided peptide discovery tools, such as AlphaFold2 and RoseTTAFold, were utilized to model the interaction between kidney injury molecule-1 (KIM-1) and death receptor 5 (DR5), leading to the design of new peptides that block this interaction. These peptides showed strong protective effects against acute kidney injury in lab and animal studies.[127,128] In sum, AI-powered peptide engineering facilitates the creation of customized targeting ligands that exhibit enhanced tumor binding and improved stability in circulation compared to peptides discovered through traditional approaches.

Intelligent Linker Design

While generative AI has shown transformative potential in drug discovery, particularly in the design of small molecules, peptides, and biologics optimized through latent space exploration and multi-omics integration, its direct application to linker design in PDCs remains underexplored in current literature.[129] For instance, Link-INVENT (https://github.com/MolecularAI/Reinvent) builds upon the REINVENT generative-molecule design framework, employing reinforcement learning to generate novel linkers connecting two molecular subunits. The system enables the optimization of linker-specific objectives, such as effective length, graph length/branching, ring count, and flexibility (rotatable bonds), through a tailored scoring function for multi-parameter optimization.[130] Similarly, DRlinker builds on deep reinforcement learning to generate linkers tailored to

user-specified objectives, such as controlling linker length and log P (lipophilicity), and demonstrates that ~91% and ~93.9% of generated compounds met the respective design criteria. While DRlinker has demonstrated strong performance in fragment-linking tasks, including high success rates for physicochemical targets, its application in therapeutic conjugates, such as ADCs or PDCs, has not yet been demonstrated in published studies.[117]

AI-Guided Payload Selection

Selecting the most suitable payload for a PDC requires balancing potency, selectivity, and pharmacological liabilities. While this process has traditionally relied on empirical screening, AI-driven methods, particularly graph neural networks (GNNs) trained on large-scale chemical datasets, are increasingly being used to predict molecular properties, prioritize payloads, and guide early-stage decision-making.[131] While this approach has shown substantial promise across small-molecule and biologics pipelines, its direct application to PDCs has not yet been demonstrated in published studies. AI methodologies can similarly accelerate PDC development by screening extensive libraries of cytotoxic compounds and ranking those best suited for peptide-mediated delivery. Generative models, such as variational autoencoders and transformers, can even design novel payloads that are both highly potent and specifically released within target cells, thereby limiting systemic toxicity. Overall, by using machine learning to evaluate millions of candidate payloads (including those never synthesized before), scientists can systematically find PDC payloads with high tumor cell lethality, limited off-target effects, and even efficacy against resistant cancer cells, accelerating the discovery of next-generation payloads beyond the conventional set of Dox and taxanes.

Future Directions in PDC Development

Research continues to tackle key challenges in PDC therapeutics by embracing several promising innovation pathways:

Theranostics and Multimodal PDCs

Combining therapeutic and diagnostic functions in one PDC is a major trend. For example, attaching a radiolabel or fluorescent dye alongside a drug enables real-time tracking of distribution. Such theranostic PDCs could allow patient selection and monitoring of target engagement. While conventional reviews acknowledge this potential, several PET- or SPECT-labeled PDCs are already under preclinical investigation.[106]

AI-Guided Design

Machine learning is emerging as a tool to optimize peptide sequences and linkers for enhanced affinity, stability, and selectivity. In silico modeling can predict peptide-receptor interactions and cell-penetrating properties, accelerating the discovery of novel homing peptides. AI can also suggest linker chemistries tailored to tumor environments. Thus, powerful generative and predictive models may now help design peptides with enhanced binding, stability, and selectivity and tailor linkers for tumor-specific activation.[131–133]

Dual-Linker and Multi-Payload Systems

Inspired by bispecific antibodies, dual-trigger PDCs are being developed. For example, constructs with two different cleavable linkers (eg, one redox-sensitive and one enzyme-sensitive)[1] can ensure activation only in the precise tumor niche. Likewise, some designs incorporate two drugs (eg, a chemotherapy agent plus an immunomodulator) on a single peptide scaffold, allowing for synergistic therapy.

For example, Bargh et al[134] developed a dual-enzyme cleavable linker based on 3-*O*-sulfo-β-galactose, which requires sequential cleavage, first by arylsulfatase A and then by β-galactosidase, to activate the drug payload. This dual-trigger approach ensures highly selective activation within the target environment and could inspire similar designs for PDCs to enforce release only under precise tumor conditions.

Nanotechnology Integration and Self-Assembly

Innovative strategies are leveraging nanotechnology to improve PDC pharmacokinetics and therapeutic efficacy. One such approach involves designing PDCs that can self-assemble into nanostructures, such as fibers, micelles, or hydrogels,

thereby creating a drug depot effect and prolonged local release. An example is a camptothecin-based self-assembling prodrug (SAPD) hydrogel, which transforms into supramolecular filaments upon contact with brain tissue. This injectable hydrogel, used as an adjunct post-surgical treatment in a glioblastoma model, provided sustained release of camptothecin, suppressed tumor recurrence, and extended survival in mice.[135] The versatility of self-assembling PDCs in forming diverse nanostructures and prolonging drug release in targeted therapy contexts has been reviewed.[136,137] Additionally, co-delivery vehicles (such as liposomes and polymeric carriers) can encapsulate PDCs or utilize PDCs as targeting ligands, thereby merging the advantages of PDCs with nanoparticle delivery control.

Diversifying Targets Beyond Cell-Surface Receptors

Beyond traditional cell-surface receptors, PDCs are increasingly engineered to engage novel and context-specific tumor targets, including components of the tumor microenvironment (TME), such as fibronectin extra domain B (FN-EDB),[138] and matrix metalloproteinases (MMPs) like MT1-MMP,[139] both of which are overexpressed in many cancers and contribute to tumor invasion and metastasis. These targets offer opportunities for selective tumor localization independent of receptor heterogeneity. Additionally, intracellular targeting via CPPs[2] and activatable peptides responsive to tumor-specific enzymatic activity or pH present promising strategies for site-specific activation and payload release.[140] By integrating such stimuli-sensitive or environment-responsive elements, PDCs can achieve enhanced selectivity and overcome limitations of uniform receptor expression.[141]

Regulatory and Translational Efforts

To accelerate clinical adoption, further work is needed to standardize and optimize regulatory pathways for conjugates. Developing regulatory frameworks that encompass PDC-specific aspects, such as conjugate stability, batch-to-batch consistency, and safety profiling, is crucial. The complexity of conjugates poses distinct challenges for Chemistry, Manufacturing, and Controls (CMC), like those for ADCs,[142] demanding comprehensive characterization of each component to satisfy regulatory scrutiny.[6,143]

Improved understanding of pharmacokinetics through imaging studies and biomarkers will help optimize dosing. Leveraging imaging strategies (such as PET/SPECT) and biomarker-driven studies can help optimize dosing regimens and measure real-time distribution. Such techniques support safer and more effective clinical translation.

Finally, collaborative efforts (databases like ConjuPepDB)[144] and PDCdb[118] will guide smarter design. These databases are invaluable for the field, providing structured, annotated datasets of PDCs, including their chemical structures, biomedical applications, and pharmacological data. These open resources accelerate rational design and foster reproducibility.

By integrating cutting-edge advances in targeting, linker chemistry, payload diversity, and formulation technologies, the next generation of PDCs stands poised to redefine targeted therapy paradigms. These innovations aim to emulate the exquisite receptor selectivity of monoclonal antibodies, thereby ensuring tumor-specific recognition, while simultaneously preserving the favorable pharmacokinetics and tumor penetration capabilities characteristic of small molecules. For example, precision linker engineering allows for environmentally responsive drug release, self-assembling architecture enhances bioavailability, and peptide engineering supports resistance to proteolytic degradation and immunogenicity.

Moreover, PDCs offer a unique modularity that enables the simultaneous delivery of cytotoxic agents, immune modulators, and diagnostic payloads. This multi-functionality not only supports combination therapy strategies within a single molecule but also facilitates real-time monitoring of treatment efficacy through theragnostic applications. Artificial intelligence and data-driven design are further accelerating the development of bespoke PDC constructs optimized for individual tumor profiles, paving the way for truly personalized medicine.

Ultimately, as these technological, regulatory, and translational barriers are overcome, PDCs are likely to emerge as a class of therapeutics that bridges the best features of biologics and small molecules. Their ability to selectively kill tumor cells, modulate the tumor microenvironment, and guide immune responses, all while minimizing systemic toxicity, positions PDCs as a transformative platform in precision oncology. With increasing clinical momentum, robust databases, and interdisciplinary innovation, PDCs may soon join the ranks of mainstream targeted cancer therapies.

Conclusion

PDCs represent a versatile and rapidly evolving platform for targeted cancer therapy. They harness the specificity of peptides to deliver potent drugs deep into tumors, potentially overcoming some limitations of conventional chemotherapy and even ADCs. We have reviewed the key components of PDC design (homing peptide, linker, payload) and elucidated their mechanisms, including receptor binding, cell internalization, and triggered drug release. Compared to ADCs, PDCs have distinct pharmacokinetic and penetration profiles, which we highlighted. Through case studies such as paclitaxel trevatide, (^{177}Lu)-DOTATATE, and LyP-1-Dox, we illustrated how PDCs can successfully translate targeting strategies into therapeutic benefit.

Nonetheless, significant hurdles remain. Ensuring stability in circulation while achieving efficient drug release in tumors is a persistent challenge. Tumor heterogeneity and delivery barriers can compromise efficacy. The manufacturing and regulatory complexity of these hybrid molecules also slows progress. Addressing these issues will require integrated approaches: smarter peptide engineering (for affinity and stability), advanced linker chemistry (for dual triggers and controlled release), and leveraging technology (AI design, imaging, nanocarriers).

In conclusion, PDCs hold great promise as next-generation therapeutics. By integrating precise targeting peptides, optimized linkers, and potent drugs, PDCs can achieve high tumor-specificity with reduced side effects. Continued progress in understanding their design principles and overcoming translational challenges should propel more PDCs into the clinic, expanding the arsenal of targeted cancer treatments.

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

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