Targeted Delivery of Chemotherapeutics to Tumors: Design Principles, Barriers, and Future Directions

Journal:	*The Innovation Drug Discovery*
Manuscript ID	TIDD-2026-0146.R3
Manuscript Type:	Review
Keywords:	Chemotherapy, Targeted delivery, Target expression, Payload, Release mechanism

Targeted delivery of chemotherapeutics to tumors: Design principles, barriers, and future directions

Huarui Zhang,[1,2,6] Zhuoheng Pan,[1,6] Meishen Ren,[3,6] Yufei Pan,[3] Zefeng Chen,[1] Yihao Zhang,[2] Hang Luo,[2] Xue Xue,[1] Yuan Ma,[2] Junlin He,[1] Wei Kang,[4,*] Baoting Zhang,[2,*] Aiping Lu,[1,5,*] Sifan Yu[1, 5,*] and Ge Zhang[1,5,*]

1. *Law Sau Fai Institute for Advancing Translational Medicine in Bone and Joint Diseases (TMBJ), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR 999077, China*
2. *School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR999077, China*
3. *Aptacure Therapeutics Limited, Hong Kong SAR 999077, China*
4. *Department of Anatomical and Cellular Pathology, State Key Laboratory of Translational Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong 999077e, China*
5. *Shenzhen Institute for Research and Continuing Education (IRACE), Hong Kong Baptist University, Shenzhen 518057, China*

[6] These authors contributed equally to this work.

* Correspondence: weikang@cuhk.edu.hk (W.K.); zhangbaoting@cuhk.edu.hk (B.Z.); aipinglu@hkbu.edu.hk (A.L.); yusifan@hkbu.edu.hk (S.Y.); zhangge@hkbu.edu.hk (G.Z.)

PUBLIC SUMMARY

- Effective targeted delivery requires balancing exposure, penetration, and drug release.
- Evaluates major targeting platforms by comparing their size, pharmacokinetics, and drug efficacy.
- Programmable aptamer designs enable precise payload loading and controlled release.
- Future designs should match delivery platforms to specific tumor barriers using AI.

Abstract

Conventional chemotherapy frequently causes uneven drug distribution and systemic toxicity due to inadequate in vivo selectivity. Passive targeting strategies, such as the enhanced permeability and retention effect, can no longer guarantee effective drug accumulation within tumor tissues. The success of active targeted chemotherapy cannot be simplified to a basic "ligand-drug" binding model, but relies on the coordinated regulation of multiple processes, including drug distribution, tumor penetration, cellular internalization, and intracellular processing. From a design-oriented perspective, this review elaborates on the core design logic of targeted chemotherapy delivery and highlights that target expression and accessibility, pharmacokinetic characteristics of targeting moieties, payload compatibility, and drug release mechanisms serve as critical determinants of therapeutic outcomes. Furthermore, this review summarizes and evaluates current mainstream targeted chemotherapy delivery platforms, including antibody-based, aptamer-based, small-molecule, peptide, and hybrid delivery systems. Finally, future research directions for targeted chemotherapy development are prospected. Rather than pursuing a single optimal delivery platform, a problem-oriented design strategy is proposed. The design of next-generation delivery systems requires an optimal balance among targeting construct size, *in vivo* drug exposure, and tissue permeability, as well as payload release profiles, based on the dominant transport limitations of specific tumor microenvironments.

Keywords

Chemotherapy, Targeted delivery, Target expression, Payload, Release mechanism

1. INTRODUCTION

Chemotherapy remains an important component of cancer treatment, and most conventional chemotherapeutic agents are low-molecular-weight molecules. However, their clinical benefits are still fundamentally constrained by one persistent problem: inadequate selectivity *in vivo*.[1] Because these drugs are generally administered systemically and exhibit limited intrinsic tumor specificity, they tend to distribute broadly throughout the body rather than accumulating exclusively in malignant tissues. As a result, drug exposure within tumors is often insufficient, heterogeneous, or short-lasting, whereas normal proliferative tissues are simultaneously exposed to toxic drug concentrations.[2] This mismatch between the intended site of drug action and the actual in vivo drug distribution remains one of the central reasons for the tight coupling between therapeutic efficacy and systemic toxicity in conventional chemotherapy. This issue is particularly prominent in solid tumors, where abnormal vasculature, stromal barriers, elevated interstitial pressure, and spatially heterogeneous cellular composition all restrict effective drug penetration and retention.[3,4] In this context, the core limitation of conventional chemotherapy lies not merely in the inherent toxicity of chemotherapeutic drugs, but in their poorly regulated biodistribution profiles.

Historically, this systemic challenge has driven extensive research efforts to improve tumor selectivity of chemotherapeutic drugs. For decades, passive tumor accumulation, predominantly mediated by the enhanced permeability and retention effect, was expected to address this limitation.[5] However, accumulating evidence has demonstrated that passive delivery alone cannot fully account for or guarantee robust drug accumulation in human tumors.[6] Delivery efficiency varies substantially across different tumor types, distinct clinical stages of tumor progression, and even discrete regions within a single tumor lesion.[7] Furthermore, even if a delivery system successfully

reaches tumor tissues, its intratumoral distribution often remains highly heterogeneous, resulting in insufficient drug exposure in poorly perfused or low-antigen tumor regions.[8] These inherent limitations have advanced the development of actively engineered drug delivery strategies, which improve tumor selectivity via targeting moiety recognition, controlled drug release, or a combination of both mechanisms. From this perspective, targeted chemotherapy is no longer defined merely as a strategy to deliver drugs to tumor sites, but as a coordinated approach to remodel drug biodistribution, tumor penetration, cellular internalization, and intracellular drug processing.

Importantly, targeted chemotherapy should not be reduced to a simple "ligand-plus-drug" strategy. Its success is determined by a much broader set of variables that encompass target expression level, the physicochemical properties of the targeting moiety, payload compatibility, the mode of drug release, as well as the pharmacokinetic fate of the entire construct. The above-mentioned factors are closely interconnected. A highly expressed target may still be therapeutically suboptimal if it is poorly accessible or heterogeneously distributed; a potent payload may still underperform if it cannot be released in an active form; and a well-designed targeting moiety may still fail if the overall system is cleared too rapidly or penetrates tumor tissue inefficiently.[9–11] Accordingly, therapeutic performance cannot be predicted by target binding alone, as an effective delivery system must also penetrate tumor tissue, maintain sufficient stability in circulation, and release its payload in a pharmacologically productive manner. It is noteworthy that successful targeted delivery should simultaneously achieve tumor penetration, construct stability in circulation, and productive intracellular or extracellular payload release.

These considerations are particularly pertinent at present, as targeted chemotherapy has evolved into a far broader design landscape compared with earlier generations of drug conjugates. Antibody-based systems have demonstrated significant clinical benefits through the selective delivery of cytotoxic payloads via antibody-drug conjugates (ADCs); similarly, aptamer-based systems have evolved into aptamer-drug conjugates (ApDCs) with analogous structures and mechanisms of action, which exhibit clear potential for clinical translation. Furthermore, owing to the chemical nature of nucleic acids, aptamer platforms offer superior chemical programmability in molecular design, the regulation of targeting specificity, and the sites and methods of payload conjugation. Meanwhile, small-molecule ligands, peptides, and hybrid delivery architectures have further expanded the repertoire of available formats, each presenting distinct trade-offs in terms of size, exposure, penetrability, loading capacity, and structural precision. As the field has matured, it has become increasingly evident that no single platform can resolve all delivery-related problems comprehensively. Instead, each format demonstrates a unique balance among selectivity, pharmacokinetics, release control, and translational feasibility.[12] This review examines targeted chemotherapy from a design-centered perspective. Section 2 outlines the core design logic of targeted chemotherapy delivery, focusing on the major factors that determine therapeutic performance, including target selection, targeting moieties, payload compatibility, release control, and translational feasibility. Sections 3 to 5 subsequently introduce representative delivery systems categorized by targeting format, including antibody-based systems, aptamer-based systems, and small-molecule, peptide, and hybrid systems. The final section discusses the broader challenges and future directions of targeted chemotherapy, with a particular focus on the size-exposure-penetration trade-off, tumor heterogeneity, and the significance of productive payload release in the design of next-generation delivery systems.

2. DESIGN LOGIC OF TARGETED CHEMOTHERAPY DELIVERY

2.1 Target expression, accessibility, and biological characteristics

A valid target for chemotherapy delivery is more than a molecule simply overexpressed in tumor cells. For targeted delivery to yield therapeutic significance, the target should ideally exhibit sufficient abundance on the tumor cell surface, restricted expression in normal tissues, and high accessibility to circulating targeting moieties. Clinical experience shows that target value depends not only on whether a receptor is present, but on whether its expression reaches a level that is therapeutically actionable. This is evident for common targets in solid tumors that cover human epidermal growth factor receptor 2 (HER2) and folate receptor alpha (FRα).[13] Moreover, a similar principle applies to the rapidly emerging therapeutic target Claudin 18.2 in gastric and gastroesophageal junction adenocarcinoma, where higher tumor expression is correlated with greater clinical benefits from zolbetuximab.[14–16] As highlighted by the above-mentioned clinical precedents, target selection must go beyond simple abundance for integrating selectivity and specific clinical contexts.

Notably, whether the target supports efficient cellular internalization or local pharmacological action should be considered.[17,18] Some targets are more advantageous because they facilitate internalization or help position the payload for effective release, while others offer limited benefits even when detected on the cell surface.[7] Besides, intratumoral heterogeneity can weaken single-target strategies, since a receptor with strong expression in one tumor region may be sparse or absent in others. Target selection in targeted chemotherapy should therefore be regarded not as a simple receptor-identification procedure, but as a comprehensive assessment of expression level, surface accessibility, normal-tissue liability, trafficking behavior, and spatial heterogeneity. Thus, target selection should combine quantitative expression thresholds, spatial heterogeneity, internalization kinetics, and normal-tissue expression profiles to maximize the therapeutic index.

2.2 Physicochemical and pharmacokinetic properties of targeting moieties

The choice of targeting moiety exerts significant effects on the role of a delivery system *in vivo*. Antibodies, aptamers, peptides, and small molecules all provide viable pathways for tumor recognition, but they vary greatly in particle size, circulation half-life, tissue penetration capacity, and chemical modification feasibility. This can be clearly observed by comparing antibody-based systems such as trastuzumab emtansine (T-DM1), which benefit from extended systemic exposure, with smaller targeting formats such as aptamer-based constructs. These smaller constructs often possess higher synthetic flexibility and better penetration ability yet are more prone to rapid in vivo clearance.[19,20] Thus, the targeting moiety should not be viewed simply as a recognition element; it also defines the pharmacokinetic and transport context within which tumor delivery must occur.

Binding affinity also needs to be considered together with transport behavior. Strong binding may improve retention at accessible tumor sites, but it does not necessarily guarantee uniform tumor penetration.[21] In particular, larger targeting systems tend to accumulate predominantly in perivascular regions, while smaller targeting moieties diffuse more readily within tumor tissues but exhibit shorter retention time.[22] Accordingly, effective targeting relies not only on the binding affinity of targeting moieties but also on how their size and systemic in vivo fate modulate tumor tissue access and drug exposure (**Figure 1**).

2.3 Payload properties and delivery compatibility

Payload selection is a core design variable since different chemotherapeutic agents impose distinct requirements on delivery systems. This phenomenon is well illustrated by clinically approved ADCs including trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG), in which variations in payload classification, drug loading efficiency, and drug release profiles are closely correlated with overall therapeutic efficacy.[23,24] These clinical examples indicate that payloads are not interchangeable auxiliary components. Their chemical and pharmacological properties determine the maximum drug loading capacity, drug release kinetics, and the ultimate antitumor efficacy of delivery systems.

This compatibility issue is further pronounced in sequence-integrated aptamer delivery systems. Fully drug-constituted aptamer architectures constructed from clinically approved nucleoside analogues verify that certain payloads exhibit superior compatibility with sequence-defined scaffolds, whereas others are more suitable for post-synthetic conjugation strategies.[25,26] Payload compatibility, therefore, depends on more than cytotoxic potency. It also encompasses structural matching with delivery scaffolds and appropriate drug release patterns for sustaining pharmacological activity. The complete workflow for targeted chemotherapy delivery system design is depicted in Figure 2. To be specific, target identification, payload selection, carrier design, formulation, preclinical testing, and final translation are carried out sequentially.

2.4 Release mechanisms and drug activation

Targeted chemotherapy exerts therapeutic efficacy only when drug release achieves both selectivity and productivity **(Figure 2)**. In drug conjugate systems, linkers govern the temporal and spatial activation of loaded payloads. Recent clinical advances, particularly regarding T-DXd and datopotamab deruxtecan (Dato-DXd), demonstrate that release chemistry is tightly associated with overall therapeutic performance.[27,28] As validated in ADC research and development, overly stable linkers may impair antitumor efficacy, while premature payload release may diminish tumor selectivity and induce systemic toxicity equivalent to that of free cytotoxic drugs.[29] Release control is therefore regarded as a core pharmacological function rather than a minor auxiliary chemical property.

This design principle is also applicable to systems independent of traditional ADC-style linkers. In programmable aptamer delivery systems, payload release relies on scaffold degradation or enzyme-mediated processing instead of individual synthetic linkers.[26] In such cases, simple chemical cleavage is insufficient; the key determinant lies in whether scaffold processing can generate pharmacologically active drug moieties.[30] Productive drug liberation thus acts as a more practical design criterion than mere molecular cleavage, especially for delivery systems with highly integrated targeting and payload architectures (**Figure 2**).

Taken together, these design principles indicate that targeted chemotherapy should not be evaluated by a single parameter such as binding affinity, payload potency, or drug loading capacity. A delivery system with high target affinity may still fail if the target is poorly accessible, if the construct cannot maintain sufficient systemic exposure, or if the payload is not released in a pharmacologically active form. Conversely, moderate target affinity may be therapeutically sufficient when it is coupled with favorable tumor penetration, productive release, and appropriate payload diffusibility. Therefore, the central design question is not how to maximize each individual parameter independently, but

how to coordinate these parameters according to the dominant delivery barrier in a specific tumor setting. This provides the conceptual basis for comparing antibody-, aptamer-, small molecule-, peptide-, and hybrid-based platforms in the following sections.

3. ANTIBODY-BASED TARGETED CHEMOTHERAPY SYSTEMS

Among current targeted chemotherapy platforms, antibody-based systems are the most extensively developed and clinically established. Their importance lies not only in the number of approved products, but also in the range of design variables they have helped define, including target selection, linker chemistry, payload class, drug loading, and biomarker-guided patient stratification. In the following sections, representative clinically applied ADCs and recent advances in antibody-based design are summarized, with an emphasis on how these systems have been optimized for diverse therapeutic scenarios (**Table 1**).

3.1 Representative clinically used ADCs

ADCs constitute the most extensively developed class of targeted chemotherapy systems and offer multiple clinically validated examples for solid tumor treatment. In the HER2-targeted setting, ado-T-DM1 established the clinical utility of HER2-directed ADC therapy, while T-DXd has expanded HER2-directed delivery to additional clinical scenarios, including tumors with low and heterogeneous HER2 expression.[19,31,32] For trophoblast cell-surface antigen 2 (TROP2)-targeted therapy, SG and Dato-DXd represent two ADCs targeting the same antigen family but incorporating distinct linker-payload systems.[33,34] Other clinically approved regimens include mirvetuximab soravtansine (MIRV) for FRα-positive ovarian cancer and telisotuzumab vedotin (Teliso-V) for mesenchymal-epithelial transition factor (c-Met)-overexpressing non-squamous non-small cell lung cancer.[35,36] Collectively, these clinical agents show wide applicability of antibody-guided chemotherapy across various target classes. Clinical outcomes rely on the combination of target expression level, delivery mode, linker performance and payload property, rather than target recognition alone.

Side-by-side evaluation of approved ADCs also reveals that structural differences lead to varied pharmacological behaviors. T-DM1 possesses an average drug-to-antibody ratio (DAR) of approximately 3.5 and uses a non-cleavable linker to deliver DM1, a maytansinoid microtubule inhibitor, making payload release closely associated with cellular internalization and lysosomal processing.[37] T-DXd, on the other hand, adopts a cleavable tetrapeptide linker and a higher DAR of around 8.[38] In the TROP2-targeted treatment, SG makes use of a hydrolyzable CL2A linker independent of enzymatic cleavage to deliver the SN-38 payload. This structure bears a short polyethylene glycol chain, which improves the water solubility of ADC molecules and prevents antibody aggregation under high drug loading conditions, with a mean DAR of roughly 7.6. In contrast, Dato-DXd applies a cleavable tetrapeptide linker identical to T-DXd and carries a DXd payload with a DAR of about 4.[39, 40] These structural discrepancies indicate that the comprehensive performance of ADCs stems from target selection, drug loading status, linker properties and payload pharmacological characteristics. Notably, payloads (e.g., DXd in T-DXd) exhibit potent bystander cytotoxic effects, which can enable activity in tumors with heterogeneous or low target expression.[41]

The currently applied FRα- and c-Met-directed ADCs further illustrate the role of biomarker-defined patient selection in antibody-based chemotherapy delivery. MIRV is applied in FRα-positive platinum-resistant ovarian cancer, whereas Teliso-V has been developed for tumors with

high c-Met expression.[35,36] These cases indicate that ADC application often depends on expression thresholds or companion diagnostic frameworks rather than on broad target positivity alone. In this regard, antibody-based chemotherapy systems are typically linked not only to molecular design, but also to patient stratification strategies that define when a given target is sufficiently expressed to support therapeutic application.

Recent mechanistic studies have also expanded the understanding of ADC release behavior. In the case of T-DXd, extracellular protease-mediated linker cleavage within the tumor microenvironment has been reported to contribute to antitumor activity in HER2-low and even HER2-negative settings.[42] As indicated the above-mentioned findings, for some ADCs, therapeutically viable payload liberation may not be restricted to internalization-dependent pathways, but may involve extracellular or pericellular cleavage events. Accordingly, ADC activity may depend on target binding and the spatial context in which payload liberation occurs.

3.2 Recent directions in ADC design

Beyond clinical approvals, recent ADC design has focused on addressing key limitations (e.g., tumor heterogeneity and suboptimal payload release) through innovations in DAR, conjugation chemistry, and linker technology.[43] One ongoing direction in ADC development is the adoption of higher drug loading in more controlled molecular formats. Early ADC design often regarded high DAR as potentially problematic because increased hydrophobicity could induce aggregation, instability, and faster clearance. However, clinically applied examples such as T-DXd and SG show that relatively high loading can be compatible with therapeutic efficacy when linker chemistry, payload properties, and overall construct behavior are appropriately balanced.[38,39] These examples indicate that the effect of DAR depends on the broader molecular context rather than on loading number alone.

This point has also been explored in preclinical studies. Cysteine-engineered THIOMAB-based platforms combined with XTEN polypeptides have been utilized to generate homogeneous high-DAR constructs, including ADCs with DAR values up to 18 named “TXCs”.[44] In a related direction, self-immolative phosphoramidate linker chemistry has been utilized to generate homogeneous DAR8 ADCs carrying payloads (*e.g.*, SN-38, DXd, and gemcitabine).[45] These developments indicate that current ADC design is extending not only toward more controlled loading, but also toward broader payload compatibility, including agents that have historically been more difficult to conjugate and release in a well-defined manner.

A growing focus has also been placed on conjugation precision and molecular definition. Early ADC drugs mainly adopt random coupling, which can result in high product heterogeneity. It is noteworthy that higher DAR exhibits greater instability *in vivo*.[46] Current ADC platforms concentrate on boosting homogeneity via site-specific conjugation strategies. As a result, payload placement can be better controlled, and more interpretable structure-activity relationships can be achieved.[47] Meanwhile, linker design has continued to diversify, covering non-cleavable, protease-cleavable, and self-immolative chemistries, each linked with distinct release behaviors and pharmacological consequences. These findings suggest that ADC optimization is no longer centered merely on target selection. It also focuses on the coordinated design of loading density, conjugation precision, linker behavior, and payload diffusibility.[48]

Recent preclinical and early clinical studies have also broadened the architectural scope of ADCs beyond single-payload, single-target formats. Bispecific ADCs cover HER2 biparatopic constructs

such as zanidatamab zovodotin (ZW49) and MEDI4276, as well as dual-target structures including BL-B01D1, which targets epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 3 (HER3) and has proceeded into clinical evaluation.[49–51] At the same time, dual-payload ADCs have been investigated to integrate two cytotoxic mechanisms within the same construct. Typical examples include HER2-directed monomethyl auristatin E (MMAE)/monomethyl auristatin F (MMAF)-co-loaded ADCs and other homogeneous dual-payload designs with tunable payload ratios, as well as early clinical candidates such as the TROP2-directed dual-payload ADC KH815.[52,53] Though these formats are still less mature than approved single-target ADCs, they demonstrate how antibody-based delivery is being adjusted to tackle antigen heterogeneity, incomplete uptake, and payload-specific resistance mechanisms.

In general, current ADC development not only involves the expansion of approved products, but also continuous optimization of delivery architecture and release design. In both clinically applied and emerging systems, key design variables consist of DAR optimization, conjugation homogeneity, linker behavior, payload diffusibility, biomarker-defined patient selection, and the spatial biology of tumors. These characteristics show that antibody-based chemotherapy delivery is developing as a multivariable design system, rather than a simple extension of antibody binding alone.

A critical insight from antibody-based targeted chemotherapy is that the success of ADCs is not solely attributable to antibody specificity. Instead, clinically effective ADCs are those in which antibody binding, linker cleavage, payload potency, bystander activity, and biomarker-defined patient selection are properly matched. This also explains why ADCs targeting the same antigen may display markedly different clinical behaviors when their linker-payload systems differ. From this perspective, ADC development has shifted from a target-centered model to an integrated release- and exposure-centered model. The major strength of antibody-based systems lies in their prolonged circulation and clinically validated translational framework, whereas their major limitation remains restricted tissue penetration and incomplete coverage of heterogeneous tumors. Therefore, future ADC optimization should focus less on simply expanding target repertoires and more on tailoring release chemistry, payload diffusibility, and patient-selection criteria to the spatial biology of tumors.

Table 1. Clinical approved ADCs

ADC Name	Targets	Linker Type	Payload Mechanism Class	Disease
Ado-trastuzumab emtansine (T-DM1)	HER2	Non-cleavable	Maytansinoid (DM1)	HER2-directed therapy.
Trastuzumab deruxtecan (T-DXd)	HER2	Cleavable (tetrapeptide)	Deruxtecan (DXd)	HER2-directed delivery, including tumors with lower and more heterogeneous HER2 expression.
Sacituzumab govitecan (SG)	TROP2	Cleavable (CL2A)	SN-38	Solid tumors.
Datopotamab deruxtecan (Dato-DXd)	TROP2	Cleavable (tetrapeptide)	Deruxtecan (DXd)	Solid tumors.
Mirvetuximab soravtansine (MIRV)	FRα	Cleavable (sulfo-SPDB)	Maytansinoid	FRα-positive platinum-resistant ovarian cancer.
Telisotuzumab vedotin (Teliso-V)	c-Met	Cleavable (mc-val-cit-PABC)	Vedotin	c-Met-overexpressing non-squamous non-small cell lung cancer.

4. APTAMER-BASED CHEMOTHERAPY DELIVERY SYSTEMS

Aptamer-based chemotherapy delivery systems serve as a unique branch of targeted chemotherapy, as they integrate molecular recognition with sequence-defined chemical programmability. Compared with antibody-based platforms, aptamer platforms generally feature smaller molecular size, greater structural flexibility, and more direct regulation over payload placement. Certain aptamers possess superior affinity and target specificity toward specific proteins relative to monoclonal antibodies, and exhibit better safety profiles in in vivo tests, making them a viable alternative therapeutic platform to monoclonal antibodies.[54,55] However, their clinical translation is still limited by inherent obstacles including insufficient serum stability and rapid in vivo clearance.[56] The following sections summarize conventional ApDCs and novel programmable sequence-integrated designs, focusing on their typical formats and major design features (**Figure 3)**.

4.1 Conventional ApDCs

Aptamer-based chemotherapy delivery systems were established as an alternative targeted format that adopts nucleic acid ligands instead of protein-based recognition scaffolds. Their core characteristics cover sequence-defined synthesis, positional chemical modifiability, and the potential to integrate targeting and drug-loading strategies within a relatively compact molecular framework. Early designs of conventional ApDCs generally followed two mainstream development routes: covalent attachment of the payload to the aptamer, and noncovalent or structure-assisted loading of the drug onto the aptamer scaffold.[57]

Among the earliest documented cases, the protein tyrosine kinase 7 (PTK7)-binding DNA aptamer sgc8c was conjugated with doxorubicin (DOX) to form a covalent sgc8c-DOX construct for selective delivery to CCRF-CEM leukemia cells.[58] In a similar non-covalent binding strategy, the HER2-binding aptamer HB5 was applied to load DOX via intercalation, offering a typical model of aptamer-mediated chemotherapy delivery without direct covalent linkage between ligands and drugs.[59] These delivery systems verified that aptamers can serve not only as specific recognition ligands, but also as chemically tunable scaffolds for loading traditional chemotherapeutic drugs.

Another typical example is the nucleolin-binding aptamer AS1411, which has been utilized as a targeting backbone for DOX delivery in multiple formats, including intercalated AS1411-DOX complexes.[60] Moreover, apart from DOX delivery, aptamers have also been applied to transport other chemotherapeutic agents such as paclitaxel. For instance, the programmed death-ligand 1 (PD-L1) aptamer-paclitaxel conjugate improved anti-proliferative effects in PD-L1-overexpressing triple-negative breast cancer (TNBC) cells.[61] Recently, Zhang's research team fabricated fluorouracil-modified AS1411-paclitaxel conjugates with a thioether linker and verified markedly enhanced inhibitory effects on TNBC progression both *in vitro* and *in vivo*.[62] These studies demonstrate that aptamers originally explored as independent therapeutic ligands can also be repurposed as delivery scaffolds. In this context, the development of conventional ApDCs relies on both de novo delivery-oriented aptamer design and the reuse of existing tumor-targeting aptamers with validated biological functions.

Conventional ApDCs have also evolved beyond the simple one-ligand-one-drug structural mode. A representative case is the enzymatically cleavable aptamer-gemcitabine system reported by Qi and coworkers, in which the aptamer carried three gemcitabine molecules through a dendrimer-like design equipped with an enzyme-responsive release linker.[63] This type of construct proves that aptamer-guided chemotherapy has been further explored in designs with elevated payload density

and precise release regulation. In another direction, Sgc8c-M, the PTK7-targeted agent conjugating the microtubule inhibitor MMAE to the sgc8c aptamer, has been assessed in rodent models and non-human primates.[64] As revealed by the above-mentioned studies, conventional ApDCs are being studied with both classic chemotherapeutic agents and more potent payload categories.

Additional cases further expand the range of conventional ApDC designs. The P19-gemcitabine monophosphate (dFdCMP) system was constructed to deliver an active gemcitabine metabolite instead of the parent drug itself, revealing that aptamer-guided delivery can also be engineered based on intracellular activation mechanisms.[65] Collectively, these findings demonstrate that conventional ApDCs cover covalent conjugates, intercalated complexes, metabolite-based constructs, and enzyme-cleavable or high-potency payload-loaded architectures. Meanwhile, they also reflect several common limitations, including the coupling of payload attachment with aptamer folding, the sensitivity of most aptamer constructs to serum degradation, and the relatively short circulation time associated with smaller nucleic acid ligands (**Figure 3)**.

4.2 Programmable and sequence-integrated aptamer systems

A major research direction of aptamer-based chemotherapy delivery focuses on sequence-integrated or programmable designs, where payloads are embedded into aptamer sequences or nucleic acid frameworks, rather than being linked as external payloads. In these systems, payload loading status is determined during oligonucleotide synthesis, enabling the type, quantity and location of loaded drugs to be precisely defined at the sequence level. This characteristic differentiates sequence-integrated designs from traditional post-synthetic conjugation strategies.

Typical examples include APTA-12, a gemcitabine-integrated G-quadruplex aptamer designed for pancreatic cancer therapy, and G12msi, a glypican-3-targeting DNA aptamer incorporated with gemcitabine for hepatocellular carcinoma research models.[66,67] These systems present a format where the aptamer sequence acts as both the targeting scaffold and the carrier for chemotherapeutic nucleotide analogues. Relevant studies have extended this design strategy to drugs beyond gemcitabine. For instance, EGFR-targeted aptamers incorporating 5-fluorouracil residues have been reported for pancreatic ductal adenocarcinoma models, proving that sequence-integrated design is not limited to one nucleoside analogue class.[68]

Drugtamers represent an advanced extension of this format, in which aptamer sequences are assembled entirely with therapeutic nucleoside analogues, including clofarabine, ara-guanosine, gemcitabine, and floxuridine.[25] In these constructs, natural nucleosides are completely substituted with drug-derived monomers throughout the whole sequence, generating fully drug-assembled nucleic acid structures that maintain intact target-binding capacity. Such constructs represent a more extensive form of sequence integration than aptamers carrying selected drug-containing positions, and confirm that aptamer-based delivery can be optimized to largely blur the boundary between targeting scaffolds and payload-carrying frameworks.

Sequence-integrated designs possess multiple practical advantages over conventional ApDCs. First, payload placement is precisely controlled during synthesis, rather than relying on unstable post-synthetic coupling efficiency. Second, these designs are highly compatible with nucleoside analogue chemotherapeutics, whose structural similarity to natural nucleic acid monomers allows efficient embedding into oligonucleotide backbones. Third, this strategy achieves higher loading accuracy and potentially greater payload density within a compact targeting structure. These superior properties make programmable aptamer systems a distinct branch in targeted chemotherapy design

(**Figure 3**).[26]

At the same time, sequence-integrated systems remain subject to several of the same pharmacological constraints observed in conventional aptamer platforms. Because payload liberation is often linked to scaffold degradation or intracellular processing, drug release and aptamer stability cannot be treated as fully separate variables.[69] In such systems, the relevant question is not only whether the aptamer reaches target-positive cells, but also whether scaffold processing yields pharmacologically useful active species within the appropriate biological context. In addition, aptamers remain susceptible to rapid renal clearance and serum degradation unless additional stabilization or half-life-extension strategies are implemented.[70]

Overall, aptamer-based chemotherapy delivery systems can be classified into two broad categories: conventional conjugates, in which the aptamer and payload remain structurally distinct components, and programmable sequence-integrated systems, in which payload incorporation is built into the nucleic acid framework itself. Across both categories, existing literature indicates that aptamers have been utilized with classical chemotherapeutics, active metabolites, highly potent payloads, and therapeutic nucleotide analogues. These reports collectively demonstrate that aptamer-guided chemotherapy has been explored via multiple structural formats, while also highlighting recurring design variables including scaffold stability, payload incorporation strategy, intracellular processing, and circulation behavior. Although these systems are promising in preclinical models, aptamer-based systems still require further optimization of serum stability, renal clearance, and half-life extension to improve clinical translatability.[71] With the in-depth application of artificial intelligence (AI) technology in aptamer screening, continuous breakthroughs in sequence-integrated design and stabilization chemistry strategies are steadily narrowing this gap.[72]

The critical value of aptamer-based systems lies in the fact that they are not merely smaller alternatives to antibodies. Their sequence-defined nature provides a level of molecular programmability that is difficult to achieve in protein-based platforms, especially in terms of payload positioning, chemical modification, and sequence-integrated drug incorporation. However, this advantage also creates a unique design constraint: in many aptamer systems, targeting, structural stability, and payload release are closely coupled within the same nucleic acid scaffold. As a result, improving one property may influence another. For example, modifications that enhance nuclease resistance or circulation time may alter folding, binding, or intracellular processing. Therefore, the future development of ApDCs should not only address serum stability and renal clearance, but also establish more predictable relationships among aptamer folding, target recognition, scaffold degradation, and active drug liberation. This distinguishes aptamer-based chemotherapy delivery from conventional ligand-drug conjugation and supports its role as a programmable platform rather than only a compact targeting format.

5. SMALL MOLECULE, PEPTIDE, AND HYBRID CHEMOTHERAPY DELIVERY SYSTEMS

Compared with antibody- and aptamer-based systems, small molecule, peptide, and hybrid delivery platforms generally represent more compact or modular approaches for targeted chemotherapy. These formats are of research interest because they may offer advantages in chemical accessibility, structural flexibility, payload integration, and tissue penetration, while also presenting distinct limitations in systemic persistence, selectivity, and pharmacokinetic control. The following sections

describe these three formats sequentially, with an emphasis on their representative examples, characteristic design logic, and major constraints in chemotherapy delivery (**Figure 4)**.

5.1 Small molecule ligands as targeting heads

Small molecule ligands provide a distinct route to targeted chemotherapy because they combine compact size, synthetic accessibility, and relatively straightforward conjugation chemistry. In contrast to larger biologic ligands, they can often be prepared and modified through more direct chemical routes, which facilitates linker and payload diversification. One of the best-known examples is vintafolide (EC145), a folate-desacetylvinblastine monohydrazide conjugate developed for folate receptor-positive tumors, particularly ovarian cancer.[73] Although its later clinical development was limited, vintafolide remains a representative example because it integrates a tumor-associated receptor, a cytotoxic payload, and a companion imaging strategy within a relatively compact molecular design.[74] A second folate-targeted example is EC1456, a folate-tubulysin conjugate that was investigated as a next-generation folate receptor-targeted small-molecule drug conjugate and exhibited preclinical activity in folate receptor-positive tumor models, followed by early clinical evaluation.[75] Together, these folate-directed systems illustrate how small molecule targeting has been used to couple relatively simple recognition chemistry with increasingly potent payload classes.

Another important direction is prostate-specific membrane antigen (PSMA)-targeted chemotherapy, which has been explored because prostate-specific membrane antigen is well established as a disease-associated target in prostate cancer. A previously reported example was developed by Kozikowski's group, who utilized glutaric acid to link a urea-based PSMA ligand with extremely high affinity to DOX. However, the amide linkage of the linker is too stable *in vivo* to release DOX efficiently within cells. Therefore, the desired therapeutic effect is not achieved despite the high ligand affinity.[76] In addition, novel PSMA-directed small-molecule drug conjugates carrying auristatin-derived payloads, such as MMAE via pH-responsive linkers, have also been developed, enabling the specific delivery of chemotherapeutic agents to prostate cancer tumors while minimizing systemic toxicity.[77] Recent studies have also reported OncoPSMA-based auristatin conjugates and related designs intended to adopt the same targeting logic applied in PSMA radioligand therapy and extend it to cytotoxic drug delivery.[78] These systems demonstrate that small molecule-guided chemotherapy is not restricted to folate receptor targeting but has been extended to additional clinically relevant receptor systems through diverse linker-payload combinations. Meanwhile, existing literature reveals a recurring limitation of this format: although small-molecule systems are chemically modular and relatively compact, they frequently exhibit shorter circulation times and narrower exposure windows than larger targeting platforms.[79] In this regard, small molecule-guided delivery represents a format that favors modular chemistry and tissue access, while remaining strongly constrained by systemic pharmacokinetics and the degree of tumor-restricted target expression *in vivo* (**Figure 4)**.

5.2 Peptide-guided chemotherapy delivery

Peptide-guided systems occupy an intermediate position between small-molecule ligands and larger biologic scaffolds (**Figure 4)**. Their main features include relatively small size, modular sequence design, and the ability to target tumor-associated receptors, tumor vasculature, or microenvironmental features. Among the most widely studied examples are arginine-glycine-aspartic acid (RGD)-based systems directed against integrin αvβ3. In an early representative study,

a DOX-RGD-4C peptide conjugate with antitumor activity in an orthotopic murine hepatoma model was described. The use of peptide-guided chemotherapy to bias drug delivery to a defined tumor-associated binding axis was illustrated.[80] Subsequent work has extended this principle beyond direct peptide-drug conjugates to RGD-modified carrier systems, including micelles, polymers, liposomes, and nanoparticle assemblies loaded with DOX or other chemotherapeutics.[81] As indicated by the above-mentioned reports, peptides function either as stand-alone targeting heads or as recognition modules grafted onto larger drug-bearing structures.

Besides integrin-targeting peptides, more compact and clinically oriented peptide-drug conjugates have also been developed. One representative example is PEN-221, a somatostatin receptor 2-targeting peptide-drug conjugate that links an octreotide-derived peptide to the maytansinoid payload DM1 and has been investigated in neuroendocrine tumors and small-cell lung cancer.[82] Furthermore, BT1718, a bicyclic peptide toxin conjugate directed against membrane type 1 matrix metalloproteinase/matrix metalloproteinase-14 (MT1-MMP/MMP-14) and linked to DM1, has entered early clinical evaluation.[83] These systems are of critical significance, which can be explained below. They demonstrate that peptide-guided chemotherapy is not limited to classic homing motifs such as RGD, but also includes receptor-directed and protease-associated targeting strategies that align more closely with the clinical development pathway of modern drug conjugates. At the same time, peptide-based formats remain constrained by factors such as proteolytic instability, relatively short half-life, and the need to balance receptor affinity with sufficient tissue penetration and systemic exposure. Thus, peptide-guided chemotherapy provides a chemically tractable and biologically directed targeting option, yet its performance remains closely tied to stabilization and formulation strategies.

5.3 Hybrid delivery systems

Hybrid delivery systems refer to architectures in which a targeting ligand, such as an aptamer, peptide, or small molecule, is combined with a larger carrier platform to increase payload capacity, improve release control, or enhance pharmacokinetic performance (**Figure 4)**. In the context of chemotherapy, this usually means that target recognition and drug loading are assigned to distinct structural modules: the ligand provides selective binding, while the carrier serves as the primary drug reservoir and, in some cases, also contributes to molecular protection, prolonged retention, or stimulus-responsive drug release. Typical carriers include liposomes, micelles, nanoparticles, polymeric assemblies, and DNA nanostructures.

Representative examples include aptamer-targeted DNA nanostructures loaded with DOX, such as PTK7-targeted DNA tetrahedron systems, which have been reported to enhance cytotoxicity in PTK7-positive cells while reducing activity in target-negative cells.[84] Another prevalent approach is AS1411-based hybrid delivery, in which the nucleolin-binding aptamer AS1411 has been utilized to functionalize nanoparticles, liposomes, micelles, and nanospheres for DOX delivery.[85] These systems demonstrate that aptamer-mediated recognition can be integrated with higher-capacity drug-bearing platforms rather than being restricted to single ligand-one drug constructs. A similar principle applies to RGD-modified liposomes and nanoparticles, in which peptide-based recognition is coupled with a larger carrier to improve tumor uptake while providing an expanded payload reservoir.[81]

In this sense, hybrid systems are best understood not as a distinct biological class, but as an architectural strategy for combining recognition moieties with drug-loading platforms. Their

primary practical value is the ability to partially compensate for a major weakness of minimal ligand-only systems, namely, limited payload capacity and short systemic persistence, by pairing an effective targeting head with a larger delivery platform. At the same time, hybrid designs introduce additional variables, including carrier-associated clearance, biodistribution heterogeneity, altered release behavior, and more stringent requirements for manufacturing control. Accordingly, hybrid systems broaden the design space for targeted chemotherapy but also increase the number of structural and pharmacological parameters that must be regulated during development.

Taken together, small molecule, peptide, and hybrid systems can be regarded as streamlined, more modular alternatives to larger biologic delivery platforms. Their main advantage lies in improved compactness, loading flexibility, and tissue accessibility, though these benefits are often accompanied by inherent constraints in circulation time, exposure stability, and translational simplicity. In this regard, these systems expand the repertoire of available delivery architectures while further clarifying the fundamental trade-offs inherent to targeted chemotherapy.

A critical comparison of these systems suggests that compact delivery formats should not be viewed simply as less developed versions of antibody-based platforms. Instead, small molecules and peptides address a different delivery problem: they are more suitable for situations in which tissue access, synthetic modularity, or local diffusion is more important than prolonged systemic persistence. Their therapeutic limitation is therefore often not initial tumor access, but insufficient retention, rapid clearance, or limited payload capacity. Hybrid systems emerge as a practical response to this limitation by combining compact recognition elements with larger drug reservoirs or controlled-release carriers. However, this strategy also partially sacrifices the simplicity and penetration advantages of minimal ligand-based systems. Thus, the major design challenge for small molecule, peptide, and hybrid platforms is to improve exposure and payload capacity without eliminating the transport advantages that originally justify their use.

6. DISCUSSION AND PERSPECTIVE

A major challenge in targeted chemotherapy is that effective delivery relies on far more than target recognition alone. Even when a targeting moiety binds robustly to tumor cells, therapeutic efficacy can still be limited by inadequate tumor accumulation, poor tissue penetration, insufficient circulation time, incomplete coverage of heterogeneous lesions, or nonproductive payload release. These bottlenecks vary in severity across different disease settings, indicating that future development should prioritize identifying the dominant delivery barrier within a specific tumor context rather than maximizing binding affinity in isolation.[86] Effective targeted chemotherapy therefore requires coordinated optimization across multiple interdependent parameters, rather than isolated improvements in binding performance.

From this perspective, different targeting heads may be more suitable for different therapeutic scenarios. Antibody-based systems remain highly attractive in tumors with high target expression and less restrictive spatial distribution, particularly when durable systemic exposure is more important than deep tissue penetration. This may be the case in lesions where tumor cells are readily accessible from the vasculature or where sufficient drug delivery can already be achieved without requiring extensive diffusion into a dense stromal matrix.[79,87] In such settings, antibodies benefit from their long circulation time, high selectivity, and well-established translational framework. Their performance may be further improved through payloads with bystander capability, optimized

extracellular or pericellular release strategies, or stricter biomarker-guided patient selection, enabling this format to be applied in tumors with sufficiently high and homogeneous target expression. Put differently, antibody-based systems do not need to overcome every penetration barrier to be effective; in some disease settings, sustained exposure and highly selective delivery already constitute decisive advantages.

By contrast, in tumors where penetration represents a more immediate bottleneck, such as lesions with dense stroma, uneven perfusion, or dispersed target distribution, small molecules and peptides may offer distinct advantages due to their compact size and chemical flexibility. Their main limitation is often not tissue access, but retention: they may penetrate tissues more readily than antibodies but persist for a shorter duration and, in some cases, exhibit lower tumor selectivity.[88] Future optimization for this class of delivery systems should therefore focus on improving tumor exposure and retention without compromising the inherent transport advantages of small-format agents. Feasible strategies include reversible albumin binding, multivalency modification, self-assembly, and carrier-assisted design. In this context, hybrid systems do not need to be regarded as an entirely independent category; instead, they can be viewed as an approach to extend small-molecule or peptide targeting by coupling targeting moiety recognition with a larger payload reservoir or a more controlled release module.

Aptamer-based systems occupy a particularly interesting position because they combine a favorable molecular size with sequence-level programmability. This characteristic grants them potential value in settings where both tissue access and structural tunability are critical. These systems are especially advantageous when the design goal is not only to improve penetration, but also to coordinate targeting with programmable payload placement or release logic. Reported strategies demonstrate several avenues through which this platform can be optimized. Long-acting modification approaches encompass conjugation with small-molecule coupling agents. These approaches can help extend circulation half-life. Notably, sequence-integrated designs embedding chemotherapeutic agents directly into the aptamer scaffold can enhance payload loading.[89–92] More broadly, aptamer systems can be developed to achieve more controllable degradation behavior, improved intracellular processing, and greater compatibility with multivalent or logic-gated recognition. Their greatest promise therefore lies not simply in their smaller size relative to antibodies, but in their capacity to enable integrated design of recognition, loading, and release.

These considerations suggest that the future of targeted chemotherapy should center on problem-oriented platform selection rather than the pursuit of a universally superior targeting format. Some cancers benefit most from prolonged exposure and highly selective recognition, for which antibodies remain a rational choice. Other cancers pose greater challenges in tissue access, modularity, or adaptable release control, rendering smaller ligands, peptides, or aptamer-based systems more appealing. The key design question is therefore not which targeting head is intrinsically optimal, but which format best matches the dominant biological and transport constraints of a given therapeutic setting. In this sense, more effective targeted chemotherapy will likely arise from selecting delivery architectures based on scenario-specific bottlenecks and refining each platform via modification strategies that directly resolve these limitations. Moreover, tumor heterogeneity should be regarded as a dynamic rather than static process. Treatment-induced alterations in target expression, receptor trafficking, or cellular phenotype can progressively reshape target availability during therapy, indicating that future delivery systems should be designed with greater adaptability to temporal heterogeneity and evolving tumor biology.[93] Furthermore, the

design of next-generation systems must also account for dynamic biological resistance mechanisms, such as target downregulation and impaired endosomal escape, which frequently limit long-term therapeutic efficacy. Emerging AI-assisted computational approaches can further facilitate the rational design of targeted chemotherapy platforms. By improving the prediction of ligand-target binding modes, identifying optimal conjugation or modification sites, and modeling aptamer structures and sequence-dependent drug-incorporation positions, AI can reduce empirical screening and accelerate the development of more efficient and programmable delivery systems.[94–96] To address these increasingly complex multivariable designs, the field will inevitably rely more heavily on quantitative systems pharmacology and AI-driven modeling to accurately predict the optimal balance among circulation stability, tissue penetration, and intratumoral drug release.

FUNDING AND ACKNOWLEDGMENTS

This study was supported by the Young Scientists Fund of the National Natural Science Foundation of China (82304378), Hong Kong General Research Fund (HKBU 12100125, HKBU 12100921, HKBU 12102524, HKBU 12102223, CUHK 14108322, CUHK 14109721), Guangdong-Hong Kong Technology Cooperation Funding Scheme (GHP/149/21GD, 2023A0505010015), Theme-based Research Scheme (T12-201-20R), Hong Kong Pneumoconiosis Compensation Fund Board Research Fund, HKBU start-up Grant (RC-STARTUP/23-24/58), Hong Kong Innovation and Technology Fund-Partnership Research Programme (PRP/044/24FX). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

S.Y., G.Z., A.L., Ba.Z. and W. K. devised the project. S.Y., H.Z., Z.P., and M.R. wrote the paper. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

Aiping Lyu is an Editorial Board member of The Innovation Drug Discovery and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

REFERENCES

1. Corrie, P.G. (2008). Cytotoxic chemotherapy: clinical aspects. *Medicine (Baltimore)* **36**:24–28. DOI:10.1016/j.mpmed.2007.10.012

2. Patel, K.J., Trédan, O., and Tannock, I.F. (2013). Distribution of the anticancer drugs doxorubicin, mitoxantrone and topotecan in tumors and normal tissues. *Cancer Chemother. Pharmacol.* **72**:127–138. DOI:10.1007/s00280-013-2176-z

3. Trédan, O., Galmarini, C.M., Patel, K., et al. (2007). Drug Resistance and the Solid Tumor Microenvironment. *JNCI J. Natl. Cancer Inst.* **99**:1441–1454.

DOI:10.1093/jnci/djm135

4. Chauhan, V.P., Stylianopoulos, T., Boucher, Y., et al. (2011). Delivery of Molecular and Nanoscale Medicine to Tumors: Transport Barriers and Strategies. *Annu. Rev. Chem. Biomol. Eng.* **2**:281–298. DOI:10.1146/annurev-chembioeng-061010-114300

5. Wu, J. (2021). The enhanced permeability and retention (Epr) effect: The significance of the concept and methods to enhance its application. *J. Pers. Med.* **11**. DOI:10.3390/jpm11080771

6. Jain, R.K., and Stylianopoulos, T. (2010). Delivering nanomedicine to solid tumors. *Nat. Rev. Clin. Oncol.* **7**:653–664. DOI:10.1038/nrclinonc.2010.139

7. Fu, Y.-C., Liang, S.-B., Luo, M., et al. (2025). Intratumoral heterogeneity and drug resistance in cancer. *Cancer Cell Int.* **25**:103. DOI:10.1186/s12935-025-03734-w

8. Jia, Q., Wu, W., Wang, Y., et al. (2018). Local mutational diversity drives intratumoral immune heterogeneity in non-small cell lung cancer. *Nat. Commun.* **9**:5361. DOI:10.1038/s41467-018-07767-w

9. Thurber, G.M., Schmidt, M.M., and Wittrup, K.D. (2008). Antibody tumor penetration: Transport opposed by systemic and antigen-mediated clearance. *Adv. Drug Deliv. Rev.* **60**:1421–1434. DOI:10.1016/j.addr.2008.04.012

10. Bargh, J.D., Isidro-Llobet, A., Parker, J.S., et al. (2019). Cleavable linkers in antibody–drug conjugates. *Chem. Soc. Rev.* **48**:4361–4374. DOI:10.1039/C8CS00676H

11. Pirollo, K.F., and Chang, E.H. (2008). Does a targeting ligand influence nanoparticle tumor localization or uptake? *Trends Biotechnol.* **26**:552–558. DOI:10.1016/j.tibtech.2008.06.007

12. Ma, Y., Yu, S., Ni, S., et al. (2021). Targeting Strategies for Enhancing Paclitaxel Specificity in Chemotherapy. *Front. Cell Dev. Biol.* **9**. DOI:10.3389/fcell.2021.626910

13. Esapa, B., Jiang, J., Cheung, A., et al. (2023). Target Antigen Attributes and Their Contributions to Clinically Approved Antibody-Drug Conjugates (ADCs) in Haematopoietic and Solid Cancers. *Cancers* **15**:1845. DOI:10.3390/cancers15061845

14. Liang, Z., Liu, L., Li, W., et al. (2023). Efficacy and safety of zolbetuximab for first-line treatment of advanced Claudin 18. 2-positive gastric or gastro-esophageal junction adenocarcinoma: a systematic review and meta-analysis of randomized controlled trials. *Front. Oncol.* **13**. DOI:10.3389/fonc.2023.1258347

15. Shah, M.A., Shitara, K., Ajani, J.A., et al. (2023). Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat. Med.* **29**:2133–2141. DOI:10.1038/s41591-023-02465-7

16. Shitara, K., Lordick, F., Bang, Y.-J., et al. (2023). Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *The Lancet* **401**:1655–1668. DOI:10.1016/S0140-6736(23)00620-7

17. Sadekar, S., Figueroa, I., and Tabrizi, M. (2015). Antibody Drug Conjugates: Application of Quantitative Pharmacology in Modality Design and Target Selection. *AAPS J.* **17**:828–836. DOI:10.1208/s12248-015-9766-0

18. Sharma, S., Li, Z., Bussing, D., et al. (2020). Evaluation of Quantitative Relationship Between Target Expression and Antibody-Drug Conjugate Exposure Inside Cancer Cells.

Drug Metab. Dispos. **48**:368–377. DOI:10.1124/dmd.119.089276

19. Perez, J., Garrigós, L., Gion, M., et al. (2021). Trastuzumab deruxtecan in HER2-positive metastatic breast cancer and beyond. *Expert Opin. Biol. Ther.* **21**:811–824. DOI:10.1080/14712598.2021.1890710

20. He, J., Duan, Q., Ran, C., et al. (2023). Recent progress of aptamer–drug conjugates in cancer therapy. *Acta Pharm. Sin. B* **13**:1358–1370. DOI:10.1016/j.apsb.2023.01.017

21. Rudnick, S.I., Lou, J., Shaller, C.C., et al. (2011). Influence of Affinity and Antigen Internalization on the Uptake and Penetration of Anti-HER2 Antibodies in Solid Tumors. *Cancer Res.* **71**:2250–2259. DOI:10.1158/0008-5472.CAN-10-2277

22. Perrault, S.D., Walkey, C., Jennings, T., et al. (2009). Mediating Tumor Targeting Efficiency of Nanoparticles Through Design. *Nano Lett.* **9**:1909–1915. DOI:10.1021/nl900031y

23. Narayan, P., Osgood, C.L., Singh, H., et al. (2021). FDA Approval Summary: Fam-trastuzumab deruxtecan-nxki for the treatment of unresectable or metastatic HER2-positive breast cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **27**:4478–4485. DOI:10.1158/1078-0432.CCR-20-4557

24. Goldenberg, D.M., Cardillo, T.M., Govindan, S.V., et al. (2015). Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget* **6**:22496–22512. DOI:10.18632/oncotarget.4318

25. Zhu, L., Yang, J., Ma, Y., et al. (2022). Aptamers Entirely Built from Therapeutic Nucleoside Analogues for Targeted Cancer Therapy. *J. Am. Chem. Soc.* **144**:1493–1497. DOI:10.1021/jacs.1c09574

26. Li, Y., Zhao, J., Xue, Z., et al. (2022). Aptamer nucleotide analog drug conjugates in the targeting therapy of cancers. *Front. Cell Dev. Biol.* **10**. DOI:10.3389/fcell.2022.1053984

27. Jang, J.Y., Kim, D., Lee, N.K., et al. (2025). Antibody–Drug Conjugates Powered by Deruxtecan: Innovations and Challenges in Oncology. *Int. J. Mol. Sci.* **26**:6523. DOI:10.3390/ijms26136523

28. Jafari, K.N., Chai, C., Kim, S., et al. (2026). Receptor-Mediated Drug Delivery: Redefining Targeted Drug Conjugates in Oncology. *Pharmaceutics* **18**:386. DOI:10.3390/pharmaceutics18030386

29. Kopp, A., and Thurber, G.M. (2019). Severing Ties: Quantifying the Payload Release from Antibody Drug Conjugates. *Cell Chem. Biol.* **26**:1631–1633. DOI:10.1016/j.chembiol.2019.12.001

30. Aviñó, A., Clua, A., Bleda, M.J., et al. (2021). Evaluation of Floxuridine Oligonucleotide Conjugates Carrying Potential Enhancers of Cellular Uptake. *Int. J. Mol. Sci.* **22**:5678. DOI:10.3390/ijms22115678

31. Modi, S., Jacot, W., Yamashita, T., et al. (2022). Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study. *J. Clin. Oncol.* **40**:LBA3–LBA3. DOI:10.1200/JCO.2022.40.17_suppl.LBA3

32. Meric-Bernstam, F., Makker, V., Oaknin, A., et al. (2024). Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J. Clin. Oncol.* **42**:47–58. DOI:10.1200/JCO.23.02005

33. Bardia, A., Hurvitz, S.A., Tolaney, S.M., et al. (2021). Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N. Engl. J. Med.* **384**:1529–1541. DOI:10.1056/NEJMoa2028485

34. Shimizu, T., Sands, J., Yoh, K., et al. (2023). First-in-Human, Phase I Dose-Escalation and Dose-Expansion Study of Trophoblast Cell-Surface Antigen 2–Directed Antibody-Drug Conjugate Datopotamab Deruxtecan in Non–Small-Cell Lung Cancer: TROPION-PanTumor01. *J. Clin. Oncol.* **41**:4678–4687. DOI:10.1200/JCO.23.00059

35. Moore, K.N., Oza, A.M., Colombo, N., et al. (2021). Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. *Ann. Oncol.* **32**:757–765. DOI:10.1016/j.annonc.2021.02.017

36. Camidge, D.R., Bar, J., Horinouchi, H., et al. (2024). Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein–Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non–Small Cell Lung Cancer in the Phase II LUMINOSITY Trial. *J. Clin. Oncol.* **42**:3000–3011. DOI:10.1200/JCO.24.00720

37. Lewis Phillips, G.D., Li, G., Dugger, D.L., et al. (2008). Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody–Cytotoxic Drug Conjugate. *Cancer Res.* **68**:9280–9290. DOI:10.1158/0008-5472.CAN-08-1776

38. Nakada, T., Masuda, T., Naito, H., et al. (2016). Novel antibody drug conjugates containing exatecan derivative-based cytotoxic payloads. *Bioorg. Med. Chem. Lett.* **26**:1542–1545. DOI:10.1016/j.bmcl.2016.02.020

39. Cardillo, T.M., Govindan, S.V., Sharkey, R.M., et al. (2011). Humanized Anti-Trop-2

IgG-SN-38 Conjugate for Effective Treatment of Diverse Epithelial Cancers: Preclinical Studies in Human Cancer Xenograft Models and Monkeys. *Clin. Cancer Res.* **17**:3157–3169. DOI:10.1158/1078-0432.CCR-10-2939

40. Okajima, D., Yasuda, S., Maejima, T., et al. (2021). Datopotamab Deruxtecan, a Novel TROP2-directed Antibody–drug Conjugate, Demonstrates Potent Antitumor Activity by Efficient Drug Delivery to Tumor Cells. *Mol. Cancer Ther.* **20**:2329–2340. DOI:10.1158/1535-7163.MCT-21-0206

41. Ogitani Y., Hagihara K., Oitate M., et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. DOI:10.1111/cas.12966

42. Tsao, L.-C., Wang, J.S., Ma, X., et al. (2025). Effective extracellular payload release and immunomodulatory interactions govern the therapeutic effect of trastuzumab deruxtecan (T-DXd). *Nat. Commun.* **16**:3167. DOI:10.1038/s41467-025-58266-8

43. Fu, Z., Li, S., Han, S., et al. (2022). Antibody drug conjugate: the “biological missile” for targeted cancer therapy. *Signal Transduct. Target. Ther.* **7**:93. DOI:10.1038/s41392-022-00947-7

44. Zacharias, N., N. Podust, V., K. Kajihara, K., et al. (2022). A homogeneous high-DAR antibody–drug conjugate platform combining THIOMAB antibodies and XTEN polypeptides. *Chem. Sci.* **13**:3147–3160. DOI:10.1039/D1SC05243H

45. Ochtrop, P., Jagtap, A.P., Felber, J.G., et al. (2026). Expanding the payload scope in antibody-drug conjugates by delivery of hydroxy-containing drugs through self-immolative phosphoramidates. *Nat. Commun.* **17**:759. DOI:10.1038/s41467-026-68605-y

46. Hamblett, K.J., Senter, P.D., Chace, D.F., et al. (2004). Effects of Drug Loading on the Antitumor Activity of a Monoclonal Antibody Drug Conjugate. *Clin. Cancer Res.* **10**:7063–7070. DOI:10.1158/1078-0432.CCR-04-0789

47. Agarwal, P., and Bertozzi, C.R. (2015). Site-Specific Antibody–Drug Conjugates: The Nexus of Bioorthogonal Chemistry, Protein Engineering, and Drug Development. *Bioconjug. Chem.* **26**:176–192. DOI:10.1021/bc5004982

48. Lei, Y., Zheng, M., Chen, P., et al. (2025). Linker Design for the Antibody Drug Conjugates: A Comprehensive Review. *ChemMedChem* **20**:e202500262. DOI:10.1002/cmdc.202500262

49. Meric-Bernstam, F., Beeram, M., Hamilton, E., et al. (2022). Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. *Lancet Oncol.* **23**:1558–1570. DOI:10.1016/S1470-2045(22)00621-0

50. Pegram, M.D., Hamilton, E.P., Tan, A.R., et al. (2021). First-in-Human, Phase 1 Dose-Escalation Study of Biparatopic Anti-HER2 Antibody–Drug Conjugate MEDI4276 in Patients with HER2-positive Advanced Breast or Gastric Cancer. *Mol. Cancer Ther.* **20**:1442–1453. DOI:10.1158/1535-7163.MCT-20-0014

51. Ma, Y., Huang, Y., Zhao, Y., et al. (2024). BL-B01D1, a first-in-class EGFR–HER3 bispecific antibody–drug conjugate, in patients with locally advanced or metastatic solid tumours: a first-in-human, open-label, multicentre, phase 1 study. *Lancet Oncol.* **25**:901–911. DOI:10.1016/S1470-2045(24)00159-1

52. Yamazaki, C.M., Yamaguchi, A., Anami, Y., et al. (2021). Antibody-drug conjugates

with dual payloads for combating breast tumor heterogeneity and drug resistance. *Nat. Commun.* **12**:3528. DOI:10.1038/s41467-021-23793-7

53. Zhao, Y., Ren, P., Guan, M., et al. (2025). Abstract 1585: KH815, a novel dual-payload TROP2-directed antibody-drug conjugate, shows potent antitumor efficacy in pre-clinical tumor model. *Cancer Res.* **85**:1585. DOI:10.1158/1538-7445.AM2025-1585

54. Yu, S., Li, D., Zhang, N., et al. (2022). Drug discovery of sclerostin inhibitors. *Acta Pharm. Sin. B* **12**:2150–2170. DOI:10.1016/j.apsb.2022.01.012

55. Yu, Y., Wang, L., Ni, S., et al. (2022). Targeting loop3 of sclerostin preserves its cardiovascular protective action and promotes bone formation. *Nat. Commun.* **13**:4241. DOI:10.1038/s41467-022-31997-8

56. Zhang, Y., Zhang, H., Chan, D.W.H., et al. (2022). Strategies for developing long-lasting therapeutic nucleic acid aptamer targeting circulating protein: The present and the future. *Front. Cell Dev. Biol.* **10**. DOI:10.3389/fcell.2022.1048148

57. Zhu, G., Niu, G., and Chen, X. (2015). Aptamer–Drug Conjugates. *Bioconjug. Chem.* **26**:2186–2197. DOI:10.1021/acs.bioconjchem.5b00291

58. Huang, Y.-F., Shangguan, D., Liu, H., et al. (2009). Molecular Assembly of an Aptamer–Drug Conjugate for Targeted Drug Delivery to Tumor Cells. *ChemBioChem* **10**:862–868. DOI:10.1002/cbic.200800805

59. Liu, Z., Duan, J.-H., Song, Y.-M., et al. (2012). Novel HER2 Aptamer Selectively Delivers Cytotoxic Drug to HER2-positive Breast Cancer Cells in Vitro. *J. Transl. Med.* **10**:148. DOI:10.1186/1479-5876-10-148

60. Trinh T.L., Zhu G., Xiao X., et al. (2015). A Synthetic Aptamer-Drug Adduct for

Targeted Liver Cancer Therapy. *PLOS ONE* **10**:e0136673. DOI:10.1371/journal.pone.0136673

61. Wu, X., Li, F., Li, Y., et al. (2020). A PD-L1 Aptamer Selected by Loss-Gain Cell-SELEX Conjugated with Paclitaxel for Treating Triple-Negative Breast Cancer. *Med. Sci. Monit.* **26**:0–0. DOI:10.12659/MSM.925583

62. Ma, Y., Xie, D., Chen, Z., et al. (2024). Advancing targeted combination chemotherapy in triple negative breast cancer: nucleolin aptamer-mediated controlled drug release. *J. Transl. Med.* **22**:604. DOI:10.1186/s12967-024-05429-8

63. Qi, J., Zeng, Z., Chen, Z., et al. (2022). Aptamer–Gemcitabine Conjugates with Enzymatically Cleavable Linker for Targeted Delivery and Intracellular Drug Release in Cancer Cells. *Pharmaceuticals* **15**:558. DOI:10.3390/ph15050558

64. Xiao, Y., Pan, T., Da, W., et al. (2024). Aptamer-drug conjugates-loaded bacteria for pancreatic cancer synergistic therapy. *Signal Transduct. Target. Ther.* **9**:272. DOI:10.1038/s41392-024-01973-3

65. Yoon, S., Huang, K.-W., Reebye, V., et al. (2017). Aptamer-Drug Conjugates of Active Metabolites of Nucleoside Analogs and Cytotoxic Agents Inhibit Pancreatic Tumor Cell Growth. *Mol. Ther. Nucleic Acids* **6**:80–88. DOI:10.1016/j.omtn.2016.11.008

66. Park, J.Y., Cho, Y.L., Chae, J.R., et al. (2018). Gemcitabine-Incorporated G-Quadruplex Aptamer for Targeted Drug Delivery into Pancreas Cancer. *Mol. Ther. Nucleic Acids* **12**:543–553. DOI:10.1016/j.omtn.2018.06.003

67. Park, J.Y., Chae, J.R., Cho, Y.L., et al. (2020). Targeted Therapy of Hepatocellular Carcinoma Using Gemcitabine-Incorporated GPC3 Aptamer. *Pharmaceutics* **12**:985.

DOI:10.3390/pharmaceutics12100985

68. Mahajan, U.M., Li, Q., Alnatsha, A., et al. (2021). Tumor-Specific Delivery of 5-Fluorouracil–Incorporated Epidermal Growth Factor Receptor–Targeted Aptamers as an Efficient Treatment in Pancreatic Ductal Adenocarcinoma Models. *Gastroenterology* **161**:996-1010.e1. DOI:10.1053/j.gastro.2021.05.055

69. Jin, C., Zhang, H., Zou, J., et al. (2018). Floxuridine Homomeric Oligonucleotides "Hitchhike" with Albumin In Situ for Cancer Chemotherapy. *Angew. Chem. Int. Ed.* **57**:8994–8997. DOI:10.1002/anie.201804156

70. Röthlisberger, P., and Hollenstein, M. (2018). Aptamer chemistry. *Adv. Drug Deliv. Rev.* **134**:3–21. DOI:10.1016/j.addr.2018.04.007

71. Pan, Z., Pan, Y., Zhang, H., et al. (2026). Stability modification of therapeutic aptamers: from biostability bottlenecks to nuclease-resistant construct design. *RSC Chem. Biol.* **7**:964–982. DOI:10.1039/D6CB00062B

72. Yang, X., Ding, S., Ren, M., et al. (2026). From selection to design: Reshaping aptamer discovery with artificial intelligence. *Chem. Eng. J.* **538**:176731. DOI:10.1016/j.cej.2026.176731

73. Reddy, J.A., Dorton, R., Westrick, E., et al. (2007). Preclinical Evaluation of EC145, a Folate-Vinca Alkaloid Conjugate. *Cancer Res.* **67**:4434–4442. DOI:10.1158/0008-5472.CAN-07-0033

74. Naumann, R.W., Coleman, R.L., Burger, R.A., et al. (2013). PRECEDENT: A Randomized Phase II Trial Comparing Vintafolide (EC145) and Pegylated Liposomal Doxorubicin (PLD) in Combination Versus PLD Alone in Patients With Platinum-Resistant

Ovarian Cancer. *J. Clin. Oncol.* **31**:4400–4406. DOI:10.1200/JCO.2013.49.7685

75. Reddy, J.A., Dorton, R., Bloomfield, A., et al. (2018). Pre-clinical evaluation of EC1456, a folate-tubulysin anti-cancer therapeutic. *Sci. Rep.* **8**:8943. DOI:10.1038/s41598-018-27320-5

76. Jayaprakash, S., Wang, X., Heston, W.D., et al. (2006). Design and Synthesis of a PSMA Inhibitor–Doxorubicin Conjugate for Targeted Prostate Cancer Therapy. *ChemMedChem* **1**:299–302. DOI:10.1002/cmdc.200500044

77. Olatunji, F.P., Pun, M., Herman, J.W., et al. (2022). Modular Smart Molecules for PSMA-Targeted Chemotherapy. *Mol. Cancer Ther.* **21**:1701–1709. DOI:10.1158/1535-7163.MCT-22-0160

78. Georgiev, T., Puglioli, S., Principi, L., et al. (2025). PSMA-Targeted Small Molecule–Drug Conjugates Based on a Postprolyl Peptidase–Cleavable Linker for the Treatment of Prostate Cancer. *Mol. Cancer Ther.* **24**:1561–1569. DOI:10.1158/1535-7163.MCT-24-0750

79. Cazzamalli, S., Dal Corso, A., Widmayer, F., et al. (2018). Chemically Defined Antibody– and Small Molecule–Drug Conjugates for in Vivo Tumor Targeting Applications: A Comparative Analysis. *J. Am. Chem. Soc.* **140**:1617–1621. DOI:10.1021/jacs.7b13361

80. Kim J.-W., and Lee H.-S. (2004). Tumor targeting by doxorubicin-RGD-4C peptide conjugate in an orthotopic mouse hepatoma model. *Int. J. Mol. Med.* **14**:529–564. DOI:10.3892/ijmm.14.4.529

81. Sun, Y., Kang, C., Liu, F., et al. (2017). RGD Peptide-Based Target Drug Delivery of Doxorubicin Nanomedicine. *Drug Dev. Res.* **78**:283–291. DOI:10.1002/ddr.21399

82. Whalen, K.A., White, B.H., Quinn, J.M., et al. (2019). Targeting the Somatostatin Receptor 2 with the Miniaturized Drug Conjugate, PEN-221: A Potent and Novel Therapeutic for the Treatment of Small Cell Lung Cancer. *Mol. Cancer Ther.* **18**:1926–1936. DOI:10.1158/1535-7163.MCT-19-0022

83. Cook, N., Banerji, U., Evans, J., et al. (2019). 464P - Pharmacokinetic (PK) assessment of BT1718: A phase I/II a study of BT1718, a first in class bicycle toxin conjugate (BTC), in patients (pts) with advanced solid tumours. *Ann. Oncol.* **30**:v174. DOI:10.1093/annonc/mdz244.026

84. Liu, M., Ma, W., Li, Q., et al. (2019). Aptamer-targeted DNA nanostructures with doxorubicin to treat protein tyrosine kinase 7-positive tumours. *Cell Prolif.* **52**:e12511. DOI:10.1111/cpr.12511

85. Tong, X., Ga, L., Ai, J., et al. (2022). Progress in cancer drug delivery based on AS1411 oriented nanomaterials. *J. Nanobiotechnology* **20**:57. DOI:10.1186/s12951-022-01240-z

86. Lei, Y., Xiao, T., Hu, X., et al. (2026). Advanced Drug Delivery Strategies for Overcoming Biological Barriers: Tumor Microenvironment and Blood–Brain Barrier. *Drugs RD* **26**:1–30. DOI:10.1007/s40268-026-00538-9

87. Dennis, M.S., Jin, H., Dugger, D., et al. (2007). Imaging Tumors with an Albumin-Binding Fab, a Novel Tumor-Targeting Agent. *Cancer Res.* **67**:254–261. DOI:10.1158/0008-5472.CAN-06-2531

88. Zhang, J., Hu, F., Aras, O., et al. (2024). Small Molecule-Drug Conjugates: Opportunities for the Development of Targeted Anticancer Drugs. *ChemMedChem*

19:e202300720. DOI:10.1002/cmdc.202300720

89. Zhang, H., Yu, S., Ni, S., et al. (2023). A bimolecular modification strategy for developing long-lasting bone anabolic aptamer. *Mol. Ther. Nucleic Acids* **34**. DOI:10.1016/j.omtn.2023.102073

90. Gubu, A., Ma, Y., Yu, S., et al. (2024). Unique quinoline orientations shape the modified aptamer to sclerostin for enhanced binding affinity and bone anabolic potential. *Mol. Ther. Nucleic Acids* **35**. DOI:10.1016/j.omtn.2024.102146

91. Ni, S., Zhuo, Z., Pan, Y., et al. (2021). Recent Progress in Aptamer Discoveries and Modifications for Therapeutic Applications. *ACS Appl. Mater. Interfaces* **13**:9500–9519. DOI:10.1021/acsami.0c05750

92. Chen, Z., Luo, H., Gubu, A., et al. (2023). Chemically modified aptamers for improving binding affinity to the target proteins via enhanced non-covalent bonding. *Front. Cell Dev. Biol.* **11**. DOI:10.3389/fcell.2023.1091809

93. Zhang, A., Miao, K., Sun, H., et al. (2022). Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. *Int. J. Biol. Sci.* **18**:3019–3033. DOI:10.7150/ijbs.72534

94. Yao, S., Yang, X., Ren, M., et al. (2026). AI-powered therapeutic aptamer drug discovery: Targeting the CT-domain of CTGF for duchenne muscular dystrophy. *Acta Pharm. Sin. B*. DOI:10.1016/j.apsb.2026.02.016

95. Yang, X., Chan, C.H., Yao, S., et al. (2025). DeepAptamer: Advancing high-affinity aptamer discovery with a hybrid deep learning model. *Mol. Ther. Nucleic Acids* **36**. DOI:10.1016/j.omtn.2024.102436

96. Zhang, Y., Deng, Q., Yang, X., et al. (2026). Generative Artificial Intelligence Optimization of Albumin Binders: Coumarin and Fatty Acid Derivatives. *J. Chem. Inf. Model.* **66**:6910–6920. DOI:10.1021/acs.jcim.6c00296

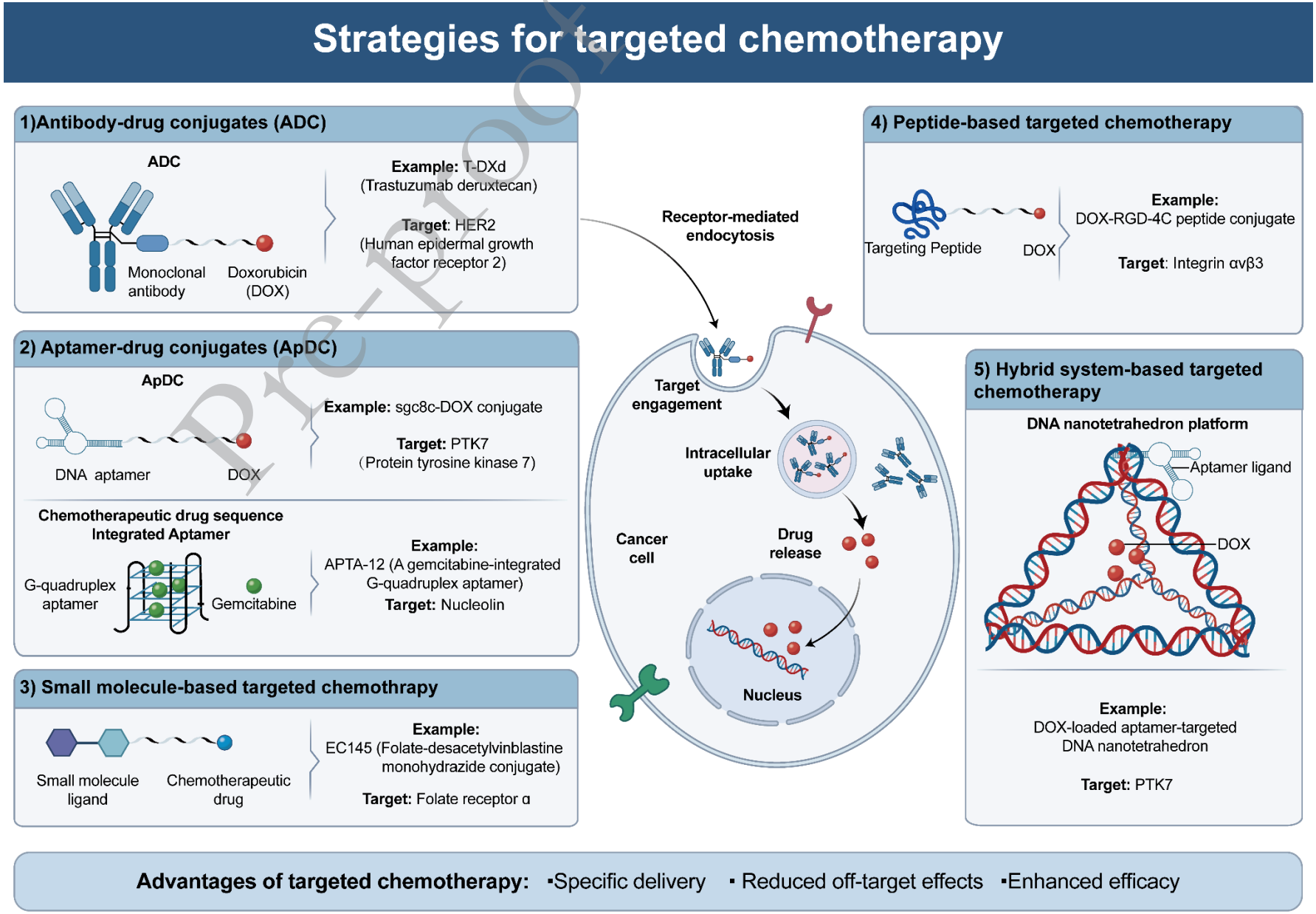

Figure 1. Differences in targeted delivery systems for chemotherapy

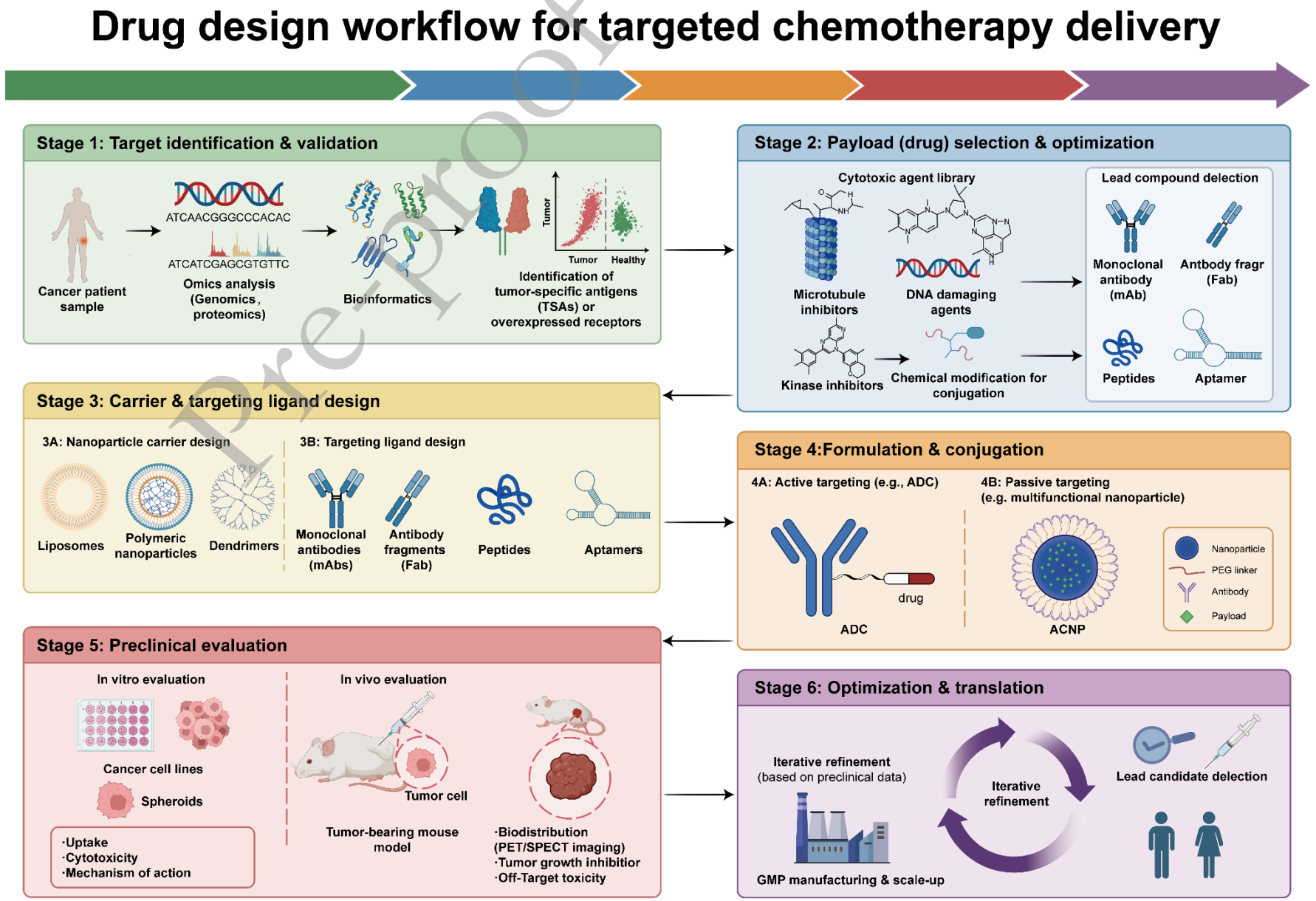

Figure 2. A diagram shows the drug design workflow for targeted chemotherapy delivery

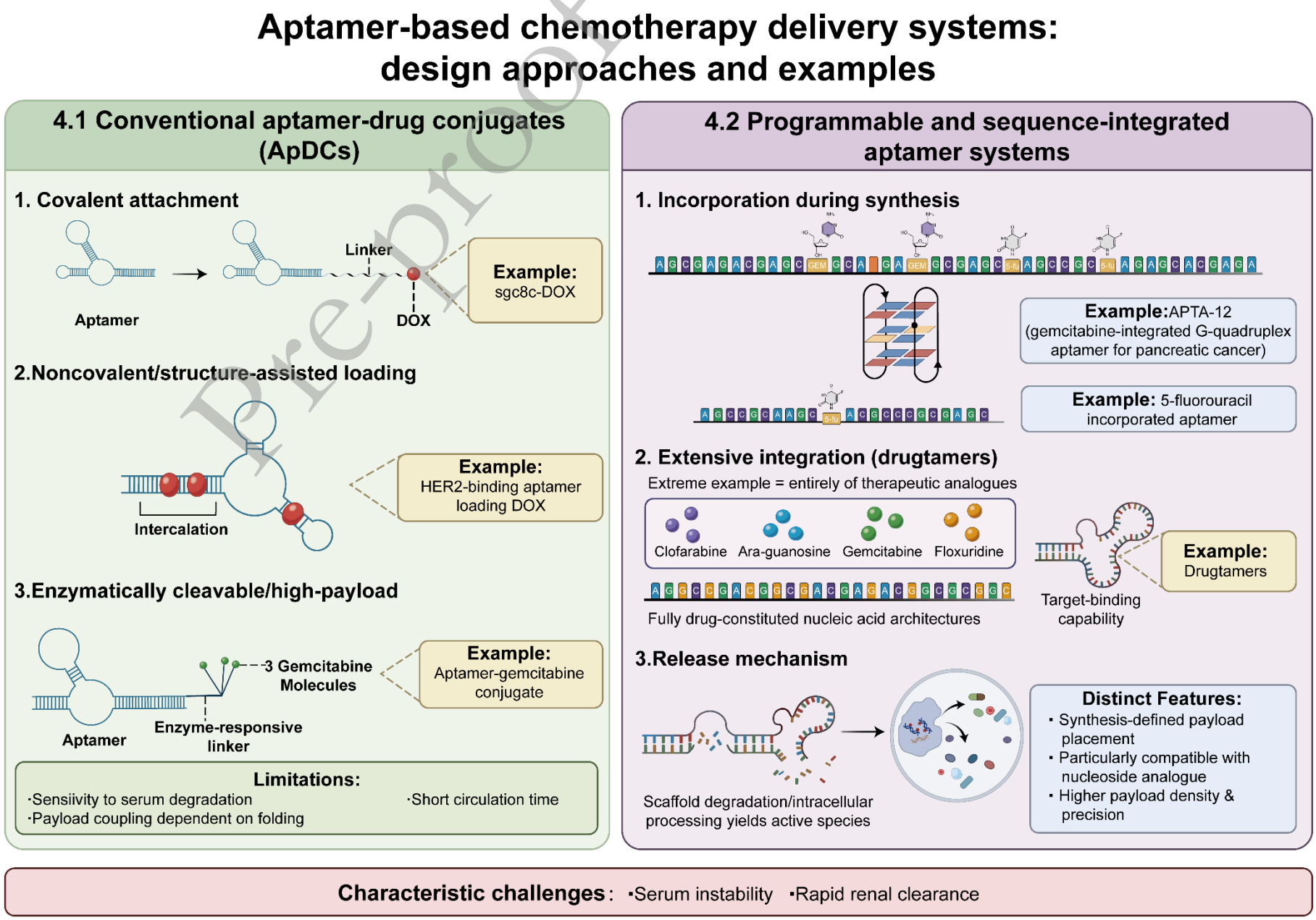

Figure 3. Designs and examples for aptamer-based chemotherapy delivery systems

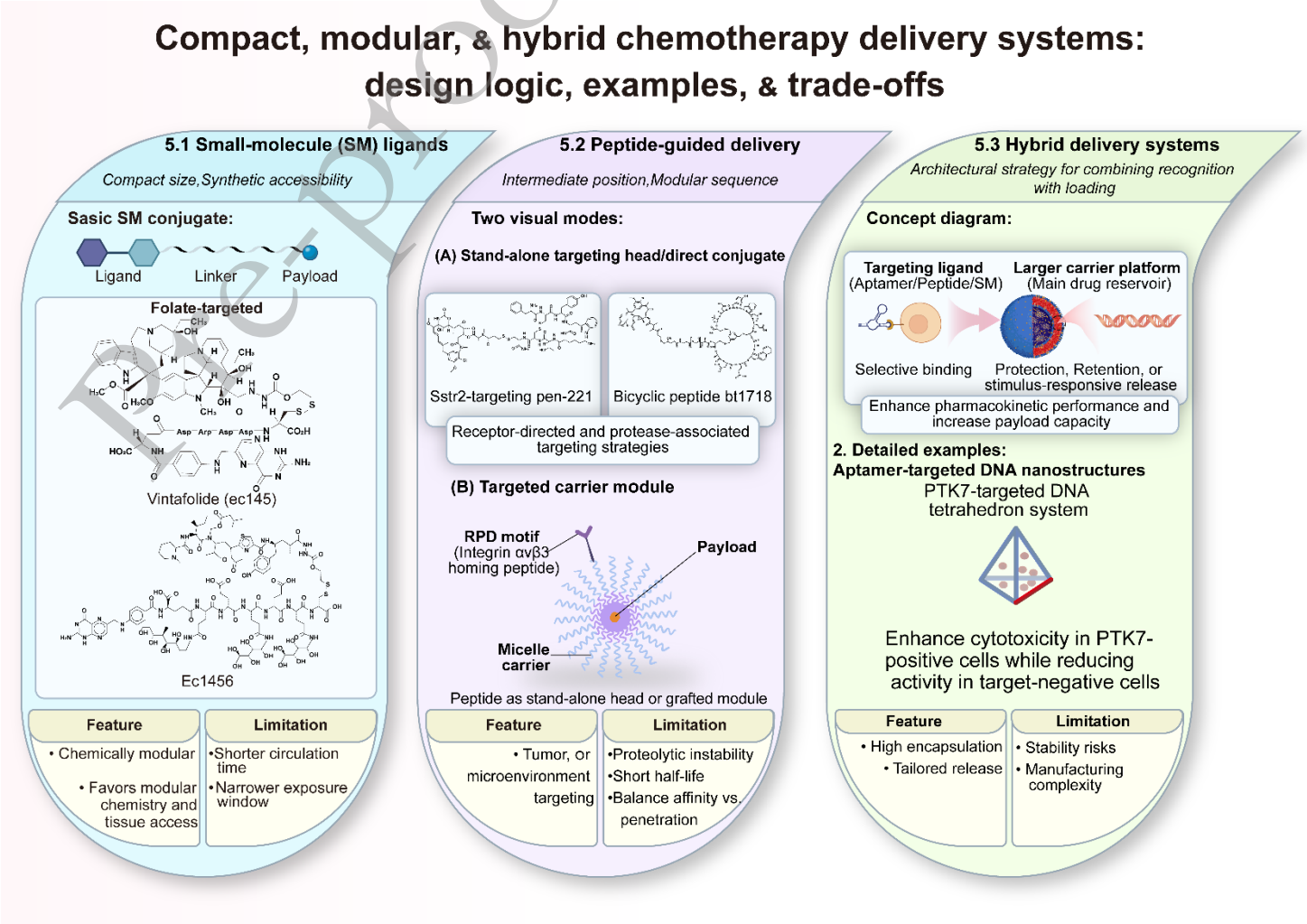

Figure 4. Designs and examples for small molecule, peptide, and hybrid chemotherapy delivery systems