

Antibody–Drug Conjugates: Recent Advances in Linker Chemistry, Payload Design and Targeted Drug Delivery

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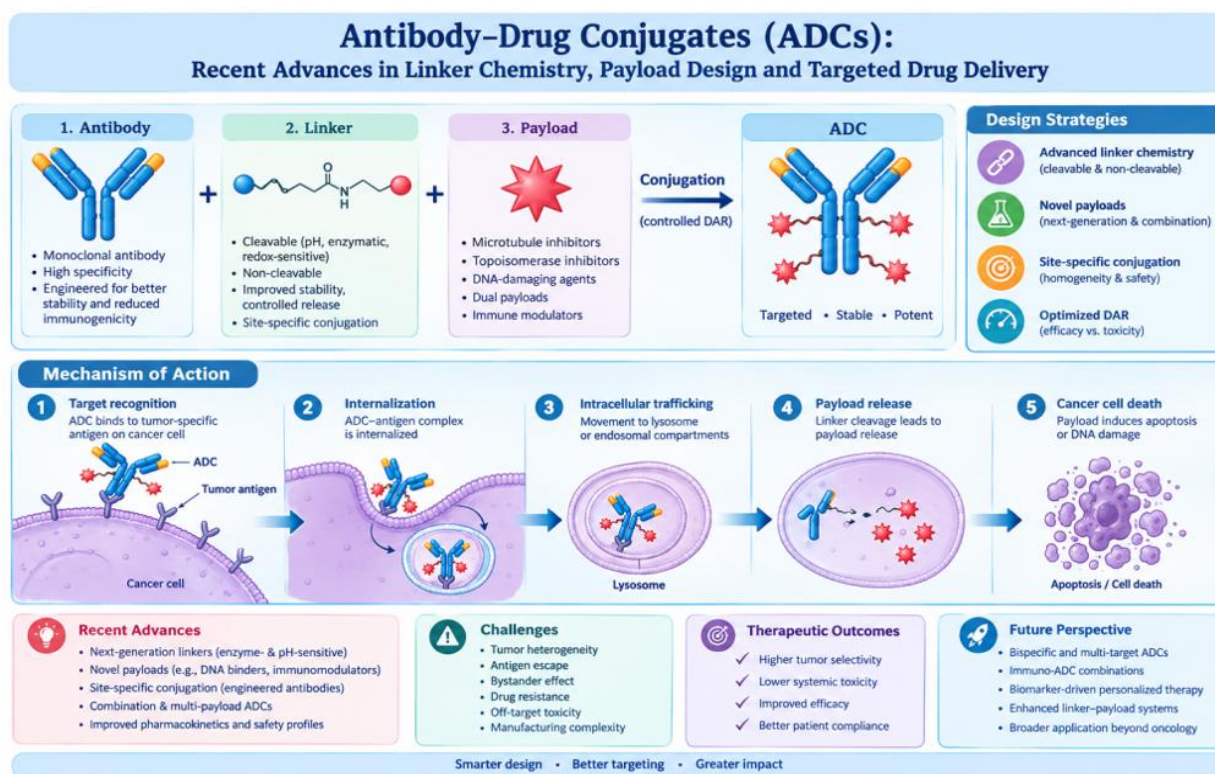


Figure 1. Graphical Abstract [1,2]

Abstract—Antibody–drug conjugates (ADCs) have emerged as promising targeted therapeutics that combine the molecular selectivity of monoclonal antibodies with the potent activity of cytotoxic or biologically active payloads. Their therapeutic

performance depends strongly on the selection of antibody, linker, payload, conjugation strategy, and drug-to-antibody ratio. Recent developments in linker chemistry have introduced cleavable and non-cleavable systems capable of improving plasma stability and

regulating intracellular drug release. Advances in site-specific conjugation have also enabled more homogeneous ADCs with improved pharmacokinetic and safety profiles. Meanwhile, payload innovation has expanded beyond conventional microtubule inhibitors to include topoisomerase inhibitors, DNA-damaging agents, dual payloads, and immune-modulating molecules. This review highlights recent progress in ADC architecture, linker engineering, payload optimization, targeted internalization, intracellular trafficking, and controlled drug release. It also discusses key limitations, including tumor heterogeneity, antigen escape, resistance, bystander effects, off-target toxicity, and manufacturing challenges, together with emerging strategies for next-generation ADC development.

Index Terms—Antibody–drug conjugates (ADCs); targeted drug delivery; linker chemistry; payload engineering; site-specific conjugation; drug-to-antibody ratio; intracellular drug release; precision oncology.

I. INTRODUCTION

Antibody–drug conjugates are modular biopharmaceuticals designed to transport a highly potent therapeutic payload to cells expressing a selected surface antigen. The basic construct contains an antibody that provides molecular recognition, a chemical linker that governs conjugate stability and drug release, and a payload that supplies the principal pharmacological effect. This architecture creates a pharmacological bridge between biologics and small molecules: the antibody determines where the construct preferentially accumulates, while the linker and payload determine how much active drug is ultimately released and where it acts. The clinical experience of early ADCs established that success depends not on any single component but on optimization of the complete molecular system. [1] The field has expanded rapidly because improvements in linker stability, conjugation chemistry, antibody engineering and payload selection have transformed the therapeutic index of newer ADCs. Modern constructs can maintain prolonged systemic stability while permitting efficient intracellular release, and some use membrane-permeable payloads to create a bystander effect capable of killing neighboring antigen-low or antigen-negative cells. Clinical experience with trastuzumab deruxtecan and Sacituzumab govitecan has demonstrated that carefully selected payload-linker combinations can

produce meaningful activity even when antigen expression is lower or more heterogeneous than was traditionally considered necessary. [6]

As of 2026, ADC development is no longer limited to conventional internalizing constructs. Next-generation programs include bispecific and biparatopic antibodies, conditionally activated ADCs, dual-payload and multi-payload systems, immune-stimulating conjugates, protein-degrader ADCs and approaches designed to release payload extracellularly in the tumor microenvironment. These strategies aim to address biological limitations such as antigen heterogeneity, poor internalization, tumor penetration, acquired resistance and dose-limiting toxicity. Recent reviews also emphasize that ADC development is becoming increasingly data-driven, with computational methods and quantitative pharmacology being integrated into target selection, molecular optimization and translational modeling. [13]

II. STRUCTURAL ARCHITECTURE AND MECHANISM OF ACTION

The antibody component is usually a monoclonal IgG selected for high-affinity binding to a tumor-associated antigen that is sufficiently accessible and preferably enriched in malignant tissue. Beyond antigen recognition, antibody properties influence systemic half-life, Fc-mediated interactions, tumor penetration, internalization and intracellular trafficking. An ideal antigen is abundant on tumor cells, limited on essential normal tissues, capable of productive internalization and relatively stable during treatment. However, clinical experience has shown that absolute tumor specificity is not always necessary; payload permeability and bystander killing can compensate partly for heterogeneous antigen expression. [3]

After systemic administration, an ADC circulates as an intact macromolecule and encounters both target-positive and target-negative tissues. Binding to a cell-surface antigen can promote receptor-mediated endocytosis, followed by trafficking to endosomal and lysosomal compartments. Depending on the linker design, the payload may be released through acidic hydrolysis, protease cleavage, reduction, or intracellular processing of a non-cleavable linker. The liberated payload then interacts with its molecular

target, commonly producing microtubule disruption, topoisomerase inhibition or DNA damage. [5]

ADC pharmacology is therefore a sequence of coupled events rather than a simple antibody-binding reaction. Systemic stability determines the fraction of dose that reaches the tumor in conjugated form; antigen binding and internalization determine cellular uptake; linker

chemistry determines the rate and site of payload liberation; and payload physicochemical properties determine intracellular retention, diffusion and bystander activity. Variations in any step can change efficacy and toxicity, explaining why apparently small structural modifications may produce major clinical differences. [7,10]

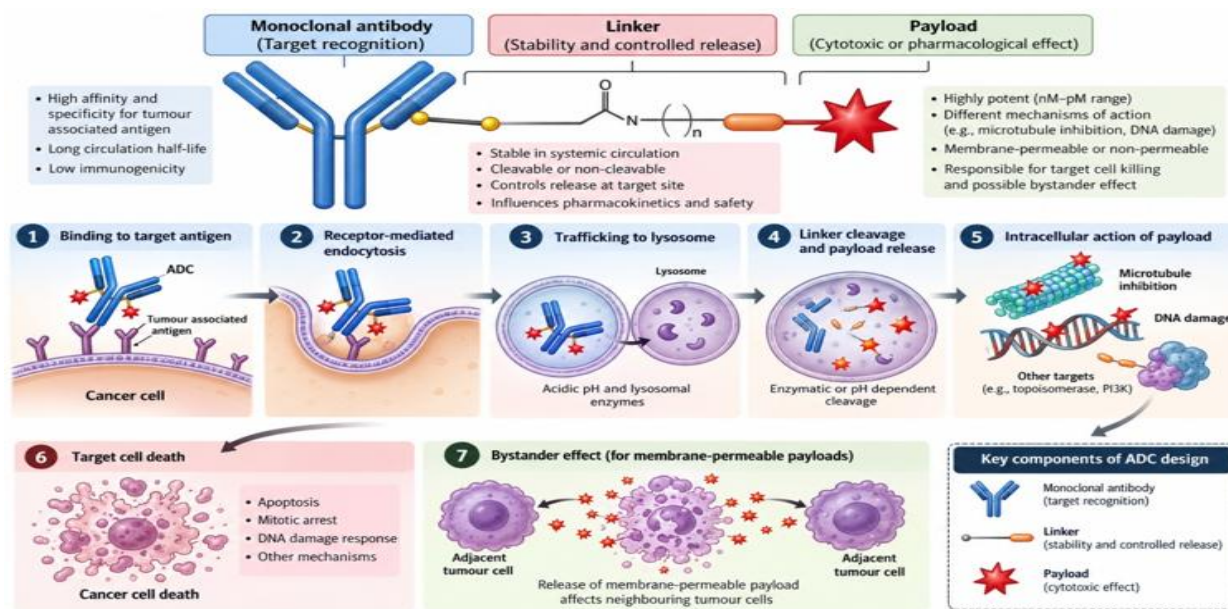


Figure 2. Antibody-Drug Conjugate (ADC) Structure, Intracellular Delivery, and Targeted Cytotoxic Mechanism. [3]

III. LINKER CHEMISTRY: FROM CONVENTIONAL TO NEXT-GENERATION DESIGNS

The linker is often the smallest structural component of an ADC but has an outsized influence on clinical behavior. A useful linker must remain sufficiently stable in plasma to prevent premature payload liberation while allowing efficient release after the conjugate reaches the intended biological compartment. Linkers therefore function as molecular timing and localization devices. Their architecture can alter hydrophobicity, aggregation, DAR tolerance, intracellular processing, payload permeability and ultimately the balance between efficacy and toxicity. [4,8]

Cleavable linkers are designed to respond to biological conditions that differ between circulation and the tumor-cell interior. Acid-labile linkers exploit the lower pH of endosomal or lysosomal compartments;

disulfide linkers exploit reducing conditions; and peptide linkers are substrates for lysosomal proteases such as cathepsins. Peptide linkers, especially valine-citrulline-derived designs combined with self-immolative spacers, have become central to the success of several ADCs because they can combine plasma stability with efficient intracellular payload release. [12]

Non-cleavable linkers use a different pharmacological strategy. Instead of requiring a discrete cleavage event, the antibody is degraded intracellularly and the payload remains attached to a residual amino-acid-containing fragment. Trastuzumab emtansine is the canonical clinical example. Non-cleavable linkers can reduce premature systemic release and may limit bystander diffusion, but they also place greater dependence on efficient antigen internalization and intracellular catabolism. [16]

Recent linker innovation has moved toward conditional and multi-trigger systems that seek to

increase the difference between tumor and normal tissues. Dual-cleavable designs can require two sequential biological events, while tumor-microenvironment-responsive linkers can respond to extracellular enzymes, pH, redox state or other disease-associated conditions. Click-to-release and traceless release strategies are also being explored to minimize residual chemical fragments on the liberated payload. Such approaches attempt to decouple stability from release efficiency more precisely than conventional single-trigger linkers. [14]

Spacer engineering has become equally important. Hydrophobic payloads can increase aggregation, accelerate clearance and narrow the therapeutic window, particularly when DAR is high. Hydrophilic spacers, charged groups and carefully positioned polyethylene glycol-like elements can moderate these liabilities without preventing intracellular activity. The medicinal-chemistry perspective has therefore shifted from treating the linker as a passive tether to treating it as an active determinant of ADC physicochemical and pharmacological behavior. [14]

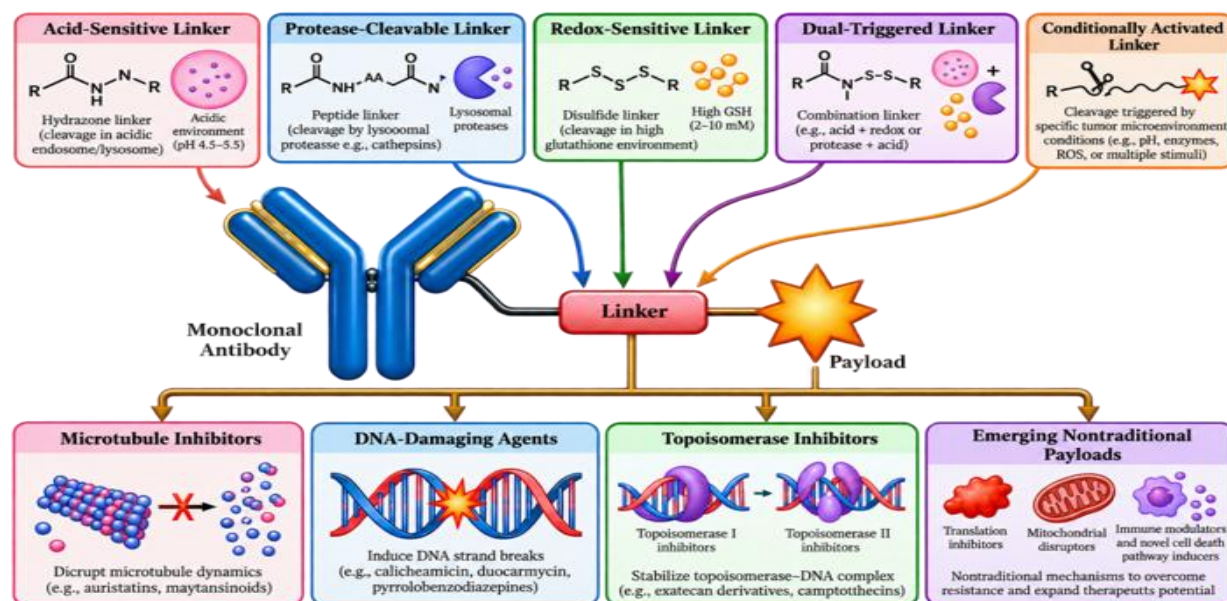


Figure 3. ADC Linker Cleavage Strategies and Payload Design Approaches. [8,11]

IV. SITE-SPECIFIC CONJUGATION AND CONTROL OF DRUG-TO-ANTIBODY RATIO

Traditional ADC manufacturing frequently relies on stochastic modification of lysine or cysteine residues, generating a distribution of species with different conjugation sites and DAR values. Such heterogeneity

can alter charge, hydrophobicity, aggregation, pharmacokinetics, tissue distribution and potency. Site-specific conjugation was developed to address this problem by restricting drug attachment to defined amino-acid positions, engineered residues or selected carbohydrate structures. [21]

Table 1. Major ADC components and their design considerations [34]

Component	Primary role	Key design variables	Major development challenge
Antibody	Target recognition and systemic delivery	Affinity, internalization, Fc properties, tumor penetration	Antigen heterogeneity; on-target/off-tumor binding
Linker	Controls stability and payload release	Cleavability, trigger, spacer, hydrophilicity, self-immolation	Premature release vs incomplete intracellular release

Payload	Produces pharmacological effect	Potency, permeability, mechanism, metabolic stability	Resistance, toxicity, loss of activity after conjugation
Conjugation site/DAR	Controls molecular homogeneity and exposure	Site, chemistry, DAR distribution	Aggregation, altered PK, manufacturing reproducibility

Engineered cysteine approaches, exemplified by THIOMAB technology, introduce accessible thiol groups at predetermined positions. Enzymatic methods can target glutamine residues through microbial transglutaminase, while glycan remodeling can install reactive handles in the Fc glycan region. Other approaches use aldehyde tags, unnatural amino acids, sortase-mediated reactions, disulfide re-bridging or bioorthogonal chemistry. These methods can produce narrower DAR distributions and improved batch-to-batch consistency. [22]

The importance of site-specificity is not merely manufacturing convenience. Conjugation location can influence antigen binding, Fc interactions, stability and the orientation of the linker-payload relative to the antibody surface. Consequently, the optimal site depends on the complete molecular design rather than on conjugation yield alone. Recent work increasingly evaluates linker chemistry and conjugation site as a coupled design problem, reflecting the recognition that identical payloads can behave differently when attached at different positions. [26]

Precise DAR control is similarly important. Increasing DAR can increase payload delivery per antibody molecule, but excessive loading may increase hydrophobicity, aggregation and nonspecific uptake. The optimal DAR is therefore a system-level variable that depends on payload potency, linker polarity, antibody properties and target biology. New conjugation platforms capable of reproducibly producing defined DAR values are particularly valuable for high-payload constructs and multi-payload ADCs. [9,27]

V. PAYLOAD DESIGN: FROM CONVENTIONAL CYTOTOXINS TO NEW MECHANISMS

The payload must be sufficiently potent to produce meaningful cell killing after only a limited number of ADC molecules enter each tumor cell. Historically, this requirement favored highly potent microtubule inhibitors such as auristatins and maytansinoids, as well as DNA-damaging agents such as calicheamicin and pyrrolobenzodiazepines. More recently,

topoisomerase I inhibitors have become an important payload family because their potency, intracellular behavior and membrane permeability can support activity across tumors with heterogeneous antigen expression. [11]

Auristatin-based ADCs remain important because MMAE and related compounds inhibit microtubule dynamics at very low intracellular concentrations. Their clinical success demonstrates the value of highly potent payloads combined with protease-cleavable linkers. Maytansinoid payloads such as DM1 and DM4 have similarly validated tubulin inhibition, while their use with non-cleavable or disulfide-based architectures illustrates how the same broad payload class can be adapted to different release mechanisms. [17]

Topoisomerase I inhibitor payloads represent one of the most consequential recent developments. Trastuzumab deruxtecan uses a highly potent derivative of exatecan with a cleavable tetrapeptide-based linker and a relatively high DAR, while sacituzumab govitecan delivers SN-38 through a hydrolysable linker. These architectures can produce membrane-permeable active metabolites and clinically meaningful bystander effects. T-DXd has demonstrated activity in HER2-low disease, showing that ADC pharmacology can expand the therapeutic relevance of a target beyond traditional high-expression categories. [18]

Payload innovation is now extending beyond direct cytotoxins. Immune-stimulatory agents, apoptosis modulators, transcriptional inhibitors, protein degraders and other mechanistically distinct molecules are being explored as conjugated cargos. Protein-degrader ADCs are particularly interesting because a single intracellular delivery event could trigger catalytic degradation of a target protein rather than requiring stoichiometric occupancy. These approaches remain largely investigational, but they illustrate how ADCs can evolve from drug-delivery vehicles into programmable intracellular pharmacology platforms. [11]

Payload medicinal chemistry increasingly emphasizes not only target potency but also permeability, stability,

metabolic fate and the chemical requirements of conjugation. A payload that is extremely potent as a free drug may perform poorly as an ADC if attachment destroys activity, if the linker-payload is too hydrophobic, or if intracellular processing generates an inactive metabolite. Rational ADC development therefore requires medicinal chemistry to optimize the payload in its conjugated context rather than evaluating the unconjugated drug alone. [19]

VI. TARGETED DRUG DELIVERY AND THE BYSTANDER EFFECT

Targeted delivery is based on the principle that antibody binding concentrates the ADC at antigen-expressing cells before intracellular processing releases the payload. However, the relationship between antigen expression and response is not linear. Tumors are spatially and genetically heterogeneous, and antigen density can vary between lesions and within a single lesion. Consequently, ADCs with nonpermeable payloads may be highly dependent on antigen-positive cells, whereas ADCs releasing membrane-permeable metabolites may extend cytotoxicity to neighboring cells. [6,20]

The bystander effect can be advantageous when antigen expression is heterogeneous because released payload diffuses from an antigen-positive cell into nearby antigen-low or antigen-negative cells. This mechanism is influenced by payload lipophilicity, linker cleavability, release kinetics and the extracellular environment. The phenomenon is clinically relevant for several modern ADCs, but it must be balanced against the possibility that excessive payload diffusion increases damage to normal tissues. [20]

Tissue penetration also remains a major limitation. Large antibody-based constructs can exhibit perivascular accumulation and limited penetration into dense solid tumors. The so-called binding-site barrier can cause rapid uptake near blood vessels while reducing deeper distribution. Strategies under investigation include moderate-affinity antibodies, biparatopic binding, smaller antibody-derived formats, optimized dosing schedules and payloads capable of bystander diffusion. [29]

Non-internalizing ADCs represent a further conceptual expansion of targeted delivery. Rather than relying exclusively on endocytosis, these constructs

are designed to release payload extracellularly in response to tumor-associated conditions. Such strategies may be useful when antigen internalization is inefficient or when the target is predominantly stromal. Their development remains early, but they demonstrate that antibody targeting and intracellular uptake do not necessarily have to be inseparable design requirements. [30]

VII. REPRESENTATIVE CLINICAL PROGRESS

The clinical evolution of ADCs demonstrates the consequences of improved molecular design. Brentuximab vedotin established the clinical feasibility of an antibody carrying MMAE through an enzyme-cleavable linker, while trastuzumab emtansine demonstrated the power of combining a validated antibody with a highly potent maytansinoid through a stable non-cleavable linker. These agents established two complementary design principles: efficient intracellular payload delivery can arise from different linker mechanisms, and clinically useful ADCs can exploit both the antibody's biological activity and the payload's cytotoxicity. [31,32]

Trastuzumab deruxtecan subsequently illustrated how a higher DAR, cleavable peptide linker and topoisomerase I payload can generate a particularly broad therapeutic phenotype. In DESTINY-Breast03, T-DXd produced markedly longer progression-free survival than T-DM1 in HER2-positive metastatic breast cancer, and longer-term follow-up confirmed sustained benefit. In DESTINY-Breast04, activity extended into HER2-low breast cancer, helping establish the concept that ADC pharmacology can make a target therapeutically relevant across a continuum of expression. [18,19]

Sacituzumab govitecan provides a second major example of a topoisomerase I payload platform. In the phase III ASCENT study, sacituzumab govitecan significantly improved progression-free and overall survival compared with physician's-choice chemotherapy in previously treated metastatic triple-negative breast cancer. Its hydrolysable linker and SN-38 payload support both intracellular activity and extracellular or bystander exposure, helping explain its activity in tumors that are not uniformly antigen-high. [28]

Mirvetuximab soravtansine and tisotumab vedotin illustrate how ADCs can be directed against different

tumor antigens and paired with payload-linker combinations appropriate to the target biology. Mirvetuximab targets folate receptor alpha and delivers DM4 through a cleavable linker, while tisotumab targets tissue factor and delivers MMAE. Their clinical development also demonstrates that ADC optimization must include management of distinctive organ toxicities, biomarker selection and careful patient monitoring. [33]

The clinical landscape continues to expand. Datopotamab deruxtecan, a TROP2-directed ADC

carrying a topoisomerase I inhibitor, received FDA approval in 2025 and additional indications in 2026. Pivekimab sunirine became an FDA-approved CD123-directed antibody–drug conjugate for blastic plasmacytoid dendritic cell neoplasm in May 2026, while sacituzumab govitecan gained first-line TNBC indications in June 2026. These developments reinforce the broader trend toward using ADCs across earlier treatment lines and a wider range of antigen–tumor combinations. [34]

Table 2. Selected clinically important ADCs illustrating different linker and payload strategies [33]

ADC	Target	Payload	Linker concept	Representative setting	Design lesson
Brentuximab vedotin	CD30	MMAE	Protease-cleavable peptide	CD30-positive lymphomas	Validated cleavable linker + auristatin
Trastuzumab emtansine	HER2	DM1	Non-cleavable thioether	HER2-positive breast cancer	Stable linker with intracellular catabolism
Trastuzumab deruxtecan	HER2	DXd	Tetrapeptide-cleavable	HER2-positive/HER2-low cancers	High DAR + potent permeable payload + bystander effect
Sacituzumab govitecan	TROP2	SN-38	Hydrolysable linker	Triple-negative breast cancer	Topoisomerase I payload and bystander activity
Mirvetuximab soravtansine	FR α	DM4	Cleavable disulfide-derived linker	FR α -positive ovarian cancer	Biomarker-selected targeted delivery
Tisotumab vedotin	Tissue factor	MMAE	Protease-cleavable peptide	Recurrent/metastatic cervical cancer	Target diversification + potent payload
Datopotamab deruxtecan	TROP2	Topoisomerase I inhibitor	Cleavable peptide architecture	Breast cancer	Expansion of TROP2-targeted ADCs
Pivekimab sunirine	CD123	Alkylating agent	Targeted conjugate platform	BPDCN	Application of ADCs to rare hematologic disease

VIII. TOXICITY, RESISTANCE AND THERAPEUTIC-INDEX OPTIMIZATION

ADC toxicity can arise from target-dependent mechanisms, target-independent uptake, premature payload release, systemic distribution of released drug and class-specific effects of the payload. The antibody may contribute to on-target toxicity when the antigen is present on normal cells, whereas the linker-payload may produce toxicity when released before reaching the intended compartment. Common clinical toxicities therefore differ substantially among ADCs and can include myelosuppression, peripheral neuropathy, ocular toxicity, hepatotoxicity, interstitial lung disease,

diarrhea and other payload- or target-specific adverse effects. [5,10]

The therapeutic index can be improved by increasing the ratio of tumor exposure to normal-tissue exposure rather than simply increasing payload potency. Site-specific conjugation, controlled DAR, hydrophilic linkers, stable plasma chemistry, optimized antibody affinity and selective release mechanisms can all contribute. Quantitative pharmacology is particularly important because ADCs generate multiple analytes, including total antibody, conjugated antibody, deconjugated species and free payload, each with distinct relationships to efficacy and toxicity. [27]

Resistance may develop at multiple stages of the ADC mechanism. Tumor cells can lose or reduce antigen expression, alter internalization, modify intracellular trafficking, increase lysosomal or drug-efflux activity, alter payload targets, or activate alternative survival pathways. These mechanisms imply that simply increasing dose may not restore sensitivity. Rational strategies include changing the target, using a payload with a different mechanism, exploiting bystander killing, combining ADCs with pathway inhibitors or immunotherapy, and designing multispecific or dual-payload constructs. [38]

Antigen heterogeneity remains especially important in solid tumors. A highly antigen-dependent ADC may select for antigen-low clones, whereas a membrane-permeable payload can suppress adjacent cells but may increase normal-tissue exposure. This trade-off explains why there is no universal “best” ADC architecture. The preferred design depends on antigen distribution, internalization kinetics, tumor microenvironment, payload sensitivity and the clinical safety margin of the target tissue. [20]

IX. EMERGING NEXT-GENERATION ADC PLATFORMS

Bispecific and biparatopic ADCs are being developed to increase target selectivity, improve internalization or recognize two antigenic features simultaneously. Dual targeting may reduce the probability of escape through loss of one antigen and may improve activity in tumors with heterogeneous target expression. The main challenges are increased molecular complexity, manufacturability, immunogenicity assessment and the need to prove that additional targeting translates into a clinically meaningful therapeutic advantage. [23]

Multi-payload ADCs attempt to reproduce the pharmacological logic of combination therapy within

one targeted molecule. A single antibody can carry two different payloads with complementary mechanisms, potentially reducing the chance of resistance while synchronizing tumor exposure. Homogeneous multi-payload systems are technically demanding because they require controlled attachment of chemically distinct cargos at defined sites, but advances in site-specific conjugation and orthogonal chemistry are making these constructs increasingly feasible. [15]

Conditionally activated ADCs seek to hide or reduce target binding until the conjugate reaches the tumor microenvironment. Protease-activated masking domains and other “probody” concepts can potentially reduce binding to normal tissues while preserving activity in tumors with suitable enzymatic conditions. These strategies are particularly attractive for antigens that are biologically relevant but also expressed at clinically limiting levels in normal tissues. [6,24]

Payload diversity is likely to be one of the defining directions of the next generation. Immune agonists, protein degraders, transcriptional modulators and other nontraditional cargos could broaden the mechanism of action beyond direct cytotoxicity. The key requirement will be to retain the pharmacological advantages of targeted delivery while ensuring that the payload remains active after conjugation and intracellular processing. [25]

The concept of linker-free or near-linker-free targeted delivery is also emerging. These approaches seek to simplify molecular architecture by attaching therapeutic groups directly or through minimal chemical handles, potentially reducing manufacturing complexity and minimizing linker-derived metabolites. Whether such approaches can match the stability, release control and modularity of optimized linker systems remains an open question. [14]

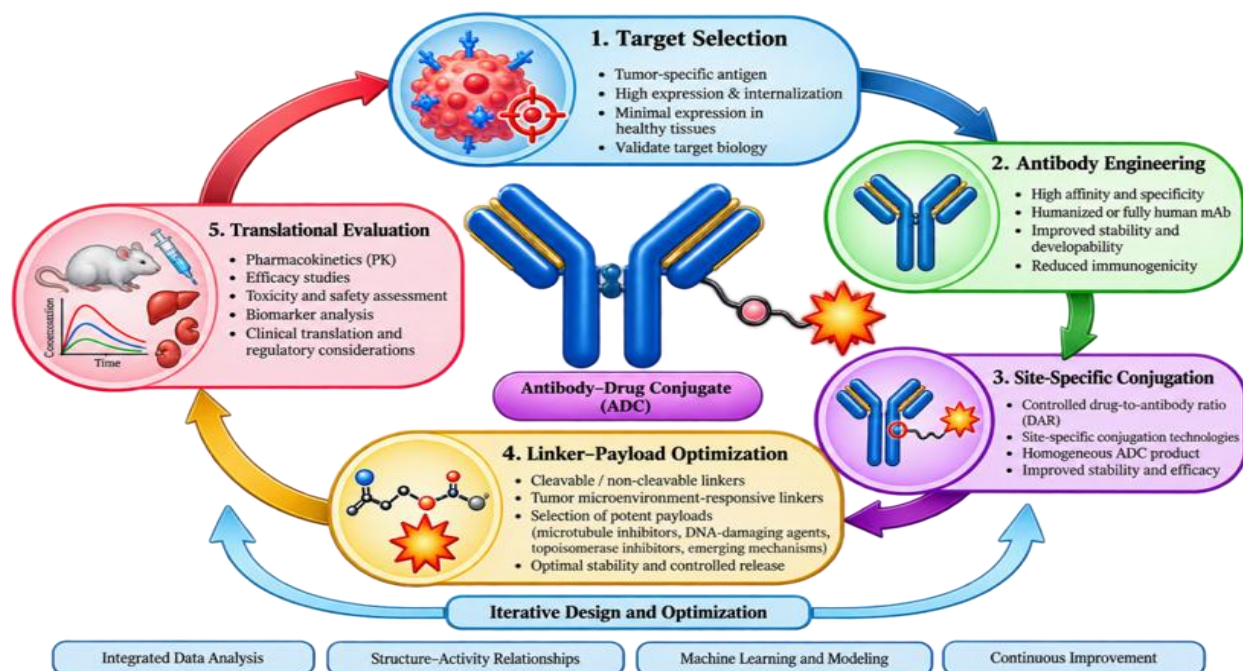


Figure 3. Integrated Next-Generation ADC Development and Optimization Workflow. [14]

Table 3. Recent innovation directions and their intended advantages [30]

Innovation	Rationale	Potential advantage	Remaining limitation
Site-specific conjugation	Reduce positional and DAR heterogeneity	More consistent PK, stability and activity	Process complexity; site selection remains critical
High-DAR ADCs	Increase payload delivered per antibody	Greater intracellular drug delivery	Hydrophobicity and aggregation
Hydrophilic spacers	Offset payload hydrophobicity	Better solubility and developability	May alter release or membrane permeability
Dual/conditional linkers	Require specific biological triggers	Improved spatial control of release	Complex synthesis and uncertain tumor specificity
Multi-payload ADCs	Combine mechanisms in one construct	Potential resistance suppression	Orthogonal chemistry and manufacturing burden
Immune/protein-degrader payloads	Expand beyond classical cytotoxicity	New mechanisms and possible synergy	Early-stage clinical validation
Bispecific/biparatopic ADCs	Address heterogeneity or improve uptake	Broader target coverage	Larger molecular complexity
Non-internalizing ADCs	Release payload in tumor microenvironment	May overcome poor internalization	Risk of systemic or stromal exposure

X. MANUFACTURING, ANALYTICAL AND REGULATORY CONSIDERATIONS

ADC manufacturing must control both the biologic component and the chemical conjugation process. Key quality attributes include antibody identity and integrity, conjugation site, DAR distribution, aggregate content, free payload, residual reagents, linker stability and potency. Random conjugation

processes can create complex product distributions, whereas site-specific methods can simplify characterization but introduce additional process steps or engineered starting materials. [21]

Analytical characterization is correspondingly multidimensional. Chromatographic and spectrometric methods are used to assess intact molecular species, DAR distribution, free payload and degradation products, while biochemical and cell-

based assays assess antigen binding and functional potency. Because ADCs can change composition during storage and circulation, stability programs should consider deconjugation and payload release rather than relying only on conventional protein aggregation measurements. [7,39]

Regulatory evaluation also requires an integrated understanding of the antibody, linker-payload and conjugate. The FDA's clinical-pharmacology guidance for ADCs highlights the need to consider the unique pharmacokinetic behavior of ADC analytes and the small-molecule component alongside biologic properties. Manufacturing oversight likewise emphasizes control of conjugation reactions, raw materials, purification and removal of unconjugated payload. [36]

From a development perspective, the most useful strategy is to define critical quality attributes early and link them to clinical performance. For example, DAR should not be treated as an isolated specification; it should be connected to exposure, clearance, aggregation, efficacy and toxicity. Similarly, linker stability should be evaluated with assays capable of detecting both intact ADC and released payload under physiologically relevant conditions. This quality-by-design perspective is increasingly important as ADC structures become more heterogeneous and sophisticated. [37]

XI. FUTURE PERSPECTIVES

The next phase of ADC development will likely be defined by rational integration rather than by optimization of individual components in isolation. Target biology, antibody affinity, conjugation site, DAR, linker release, payload permeability and tumor microenvironment should be selected as interdependent variables. Computational modeling and data-driven approaches may assist this process by integrating historical clinical outcomes with molecular descriptors, pharmacokinetic parameters and experimental measurements. [35]

Biomarker development will also become increasingly important. Conventional immunohistochemical antigen positivity may not fully capture the biological determinants of response, especially for ADCs capable of bystander killing. Future biomarkers may combine antigen density, internalization rate, intracellular trafficking, payload sensitivity, DNA-repair status,

drug-efflux activity and spatial tumor characteristics. Such multidimensional biomarkers could improve patient selection and rational sequencing of multiple ADCs. [38]

Resistance management will require deliberate treatment sequencing. Because different ADCs may share targets but differ in payload, linker and conjugation architecture, switching to another ADC is not automatically equivalent to changing therapy. Cross-resistance may arise from antigen loss or efflux, whereas payload-specific resistance may be bypassed by a different mechanism. Prospective studies incorporating molecular profiling at progression will therefore be important for defining rational ADC-to-ADC sequencing strategies. [35]

Beyond oncology, the platform has potential for targeted delivery of biologically active molecules to diseased tissues in other therapeutic areas. The principal barrier is the same one that governs oncology: identifying an accessible, sufficiently selective target and engineering a conjugate whose release occurs at the intended site. If linker chemistry, payload diversity and site-specific manufacturing continue to improve, ADCs may evolve from a cancer-focused class into a broader precision-delivery technology. [36]

XII. CONCLUSION

Antibody–drug conjugates have become one of the most mature examples of precision drug delivery, but their continued evolution depends on solving a series of coupled chemical and biological problems. Advances in linker chemistry have improved the balance between systemic stability and controlled release, while site-specific conjugation has reduced molecular heterogeneity and enabled more predictable DAR control. Payload development has expanded from classic tubulin and DNA poisons toward topoisomerase inhibitors and emerging immunological and protein-degrader mechanisms. Clinical successes with T-DXd, sacituzumab govitecan and other ADCs demonstrate that these design improvements can translate into meaningful activity across increasingly diverse tumor phenotypes. [6]

The next generation will likely combine precise conjugation, conditional release, multi-payload or multispecific targeting and improved translational

biomarkers. The central design objective should remain the same: maximize biologically active drug exposure in the tumor while minimizing exposure in normal tissues. Achieving this objective requires treating the antibody, linker, payload and manufacturing process as one integrated therapeutic system rather than as independent modules. [14]

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