
**ANTIBODY–DRUG CONJUGATES: AN EMERGING TARGETED
APPROACH FOR CANCER THERAPY**

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ABSTRACT

Cancer treatment has progressed from nonspecific cytotoxic chemotherapy toward molecularly guided approaches that seek to improve tumor selectivity while preserving therapeutic potency. Antibody–drug conjugates (ADCs) represent an important evolution of this strategy by combining a tumor-recognizing monoclonal antibody with a highly potent cytotoxic payload through a chemically designed linker. The antibody component contributes selective antigen binding and, in many products, promotes internalization; the linker controls stability during systemic circulation and intracellular drug release; and the payload produces the principal antitumor effect. Advances in antibody engineering, linker chemistry, conjugation control and payload selection have contributed to the clinical success of ADCs in both hematological malignancies and solid tumors. Contemporary products such as trastuzumab deruxtecan, sacituzumab govitecan, mirvetuximab soravtansine, enfortumab vedotin and datopotamab deruxtecan illustrate how ADC design can extend activity across different tumor types and antigen-expression levels. Nevertheless, ADC therapy does not eliminate systemic toxicity and is affected by antigen heterogeneity, limited tumor penetration, altered trafficking, payload resistance and other mechanisms of treatment failure. Toxicities may arise from target expression in

normal tissues, premature payload release or exposure to active metabolites. This review summarizes the historical development, structural components, mechanisms of action, target selection, linker and payload technologies, drug-to-antibody ratio, conjugation methods, pharmacokinetics, clinically approved ADCs, clinical applications, safety considerations, resistance mechanisms, combination strategies and next-generation approaches. Emphasis is placed on critical comparison of ADC technologies and on the emerging role of biomarker-guided and site-specific designs in precision oncology.

KEYWORDS: Antibody–drug conjugates; Targeted cancer therapy; Monoclonal antibodies; Cytotoxic payloads; Linker technology; Precision oncology.

INTRODUCTION

Cancer remains a major global health challenge because it includes a biologically diverse group of diseases with substantial morbidity, mortality and socioeconomic consequences. Global cancer estimates for 2022 reported approximately 20 million new cases and 9.7 million cancer deaths, underscoring the continuing need for more effective and less toxic treatment strategies.[1] Although advances in surgery, radiotherapy, chemotherapy, targeted treatment and immunotherapy have improved outcomes for many patients, therapeutic benefit is often limited by tumor heterogeneity, acquired resistance and cumulative adverse effects. The clinical objective has therefore shifted from simple maximization of cytotoxic exposure toward selective delivery of effective therapy to malignant cells while limiting damage to normal tissues.[1-3]

Conventional chemotherapy remains essential for many malignancies but acts largely through mechanisms that are also relevant to healthy proliferating cells. Myelosuppression, mucosal injury, nausea, alopecia, neuropathy and other toxicities may narrow the therapeutic window and can force dose reductions or interruptions.[2,3] In addition, cancer cells can develop resistance through changes in drug transport, target biology, DNA repair and survival signaling. These limitations helped stimulate the development of targeted therapies that exploit molecular differences between tumors and normal tissues. Monoclonal antibodies provided an important platform because they can recognize cell-surface antigens with high affinity and can alter signaling or recruit immune effector mechanisms. ADCs extend this concept by using the antibody as a delivery vehicle for a cytotoxic drug that may otherwise be too toxic to administer systemically at an effective dose.[3-5]

The conceptual basis of targeted toxin delivery predates modern ADC engineering. Early immunoconjugates used relatively low-potency drugs, heterogeneous antibody preparations or unstable linkers and consequently showed limited clinical performance. Subsequent advances in monoclonal-antibody technology, humanization, highly potent payloads, linker design, conjugation chemistry and analytical characterization progressively improved activity and tolerability.[8,9] The approval of gemtuzumab ozogamicin in 2000 established clinical feasibility, while brentuximab vedotin and trastuzumab emtansine demonstrated that more sophisticated ADC designs could achieve durable clinical benefit.[3,8] The field subsequently expanded rapidly, with newer products incorporating topoisomerase I inhibitors, protease-cleavable linkers and mechanisms that can generate bystander cytotoxicity.[4-7]

An ADC is commonly described as a three-part construct consisting of a monoclonal antibody, a linker and a cytotoxic payload. The antibody identifies the target antigen; the linker determines how the conjugate behaves in blood and how the drug is released after cellular uptake; and the payload causes the intended intracellular damage.[4,5,10,11] The overall pharmacology is therefore an emergent property of the complete conjugate rather than of any single component. Factors such as antigen density, antibody internalization, trafficking to lysosomes, linker stability, payload membrane permeability, drug-to-antibody ratio (DAR), conjugation site and tumor architecture can all influence efficacy and toxicity.[5,10-14]

Current clinical experience demonstrates that the term “targeted” should not be interpreted as synonymous with “tumor-specific.” Several ADC targets are also present, at lower levels, in normal tissues, and ADC-associated toxicities can arise from on-target effects, nonspecific uptake, free-payload exposure or off-target metabolism.[6,7,11] The therapeutic index may also be influenced by how readily the released payload crosses membranes and affects neighboring antigen-negative cells. Thus, the successful development of an ADC requires simultaneous optimization of target biology, molecular design, pharmacology, manufacturing and patient selection rather than simple attachment of a cytotoxic compound to an antibody. [4,6,13]

The present review examines ADCs as an emerging targeted approach to cancer therapy, with emphasis on the scientific principles that distinguish early-generation products from newer constructs. The review covers the history and development of ADC technology; structural and mechanistic features; target-antigen selection; linker, payload and DAR considerations; conjugation methods; pharmacokinetics and pharmacodynamics;

currently established clinical products; therapeutic applications across major cancers; advantages, limitations and adverse effects; mechanisms of resistance; combination strategies; and next-generation platforms. Particular attention is given to the critical questions that continue to determine clinical success, including whether greater molecular homogeneity improves outcome, how antigen expression should be incorporated into patient selection, and how linker and payload innovations can widen the therapeutic index. [4-7,10]

MATERIALS AND METHODS

This manuscript was prepared as a narrative scientific review rather than as a systematic review or meta-analysis. Literature relevant to ADC biology, pharmaceutical development and oncology was identified using PubMed, Google Scholar, Scopus, Web of Science and ScienceDirect. Additional information on current regulatory status and clinically approved indications was obtained from authoritative regulatory sources, principally the U.S. Food and Drug Administration (FDA). Searches emphasized literature published from the early development of ADCs through September 2026, while landmark older studies were retained when they established foundational concepts that remain clinically relevant.[4,5,8-10]

Search concepts included “antibody–drug conjugates,” “ADCs in cancer therapy,” “targeted drug delivery,” “monoclonal antibodies,” “ADC payloads,” “ADC linkers,” “drug-to-antibody ratio,” “site-specific conjugation,” “cancer-targeted therapy,” “ADC resistance,” “bystander effect,” “trastuzumab deruxtecan,” “sacituzumab govitecan,” “mirvetuximab soravtansine,” “enfortumab vedotin,” “datopotamab deruxtecan,” and “telisotuzumab vedotin.” Peer-reviewed research articles, major review articles, randomized clinical trials, clinically informative phase I/II studies, regulatory documents and authoritative scientific sources were prioritized. Duplicate publications, irrelevant reports, unsupported claims and sources that lacked sufficient scientific or regulatory credibility were excluded from the evidence synthesis.[4-7,10]

The retrieved evidence was organized thematically into the following domains: historical development; ADC structure and mechanism; antigen, antibody, linker, payload and DAR selection; conjugation strategies; pharmacokinetic and pharmacodynamic behavior; regulatory and clinical applications; safety and resistance; combinations; and next-generation designs. Evidence was interpreted critically, with a distinction between well-established clinical findings and emerging preclinical or early clinical concepts. Where

regulatory indications changed over time, the current U.S. status was described in the context of the available FDA information through September 2026.[4,6,7]

RESULTS AND DISCUSSION

1. HISTORY AND DEVELOPMENT OF ANTIBODY–DRUG CONJUGATES

The development of ADCs reflects the convergence of immunology, medicinal chemistry and biopharmaceutical engineering. Early “magic bullet” concepts proposed that antibodies could provide selective localization of therapeutic agents, but practical realization depended on identifying antibodies with sufficient tumor selectivity and on discovering cytotoxic molecules potent enough to remain active after conjugation.[8,9] First-generation immunoconjugates were often heterogeneous, carried relatively weak drugs and used unstable attachment strategies, resulting in limited efficacy and clinically meaningful toxicity.

These limitations demonstrated that a successful ADC is not simply an antibody with a drug attached but a highly engineered therapeutic system in which payload potency, linker behavior and conjugation control are inseparable from target selection.[3,8-10]

The first major clinical milestone was gemtuzumab ozogamicin, an anti-CD33 ADC bearing a calicheamicin derivative. Although its initial accelerated approval established the feasibility of ADC treatment in acute myeloid leukemia, the original development experience also revealed the consequences of dose, schedule and safety imbalance, including hepatic veno-occlusive disease and early mortality. The product was withdrawn and later reintroduced with a revised dosing strategy and patient population.[8,15] This history is important because it illustrates that clinical optimization of an ADC can require changes in exposure and regimen as well as changes in molecular structure.

[15,16,43][37,38,43,44]

Second-generation ADCs introduced more potent and better characterized payloads, humanized or fully human antibodies, improved linkers and improved manufacturing control. Brentuximab vedotin combined a CD30-targeting antibody with MMAE through a protease-cleavable linker and showed activity in relapsed CD30-positive lymphomas.[16] Trastuzumab emtansine subsequently demonstrated that an HER2 -targeted ADC could outperform standard therapy in selected HER2-positive breast cancer, validating the strategy in solid tumors.[17] These products established clinically practical relationships among antigen expression, internalization, linker design and intracellular payload release.[3,4,16,17] Third-generation and contemporary

ADCs have expanded the design space further. Topoisomerase I inhibitor payloads, especially deruxtecan and SN-38 derivatives, have increased interest in membrane-permeable payloads and bystander activity. Conjugation chemistry has also shifted toward improved control of DAR and drug-loading distribution, while antibody engineering and site-specific strategies seek more uniform molecules.[4-7,11,12] Trastuzumab deruxtecan has been particularly influential because it combines a high drug load with a cleavable tetrapeptide linker and a membrane-permeable topoisomerase I inhibitor, contributing to activity in HER2-positive and HER2-low disease.[18,19]

The field has now entered a stage in which molecular optimization is closely linked to clinical positioning. ADCs are moving into earlier treatment lines, combination regimens and biomarker-defined populations, while new targets are being explored in both hematological and solid tumors.[4,6,7] Regulatory expansion in 2025 and 2026, including additional indications for datopotamab deruxtecan, telisotuzumab vedotin, sacituzumab govitecan and trastuzumab deruxtecan, illustrates that the clinical trajectory of an ADC can evolve through iterative label expansion rather than a single approval event.[20-23]

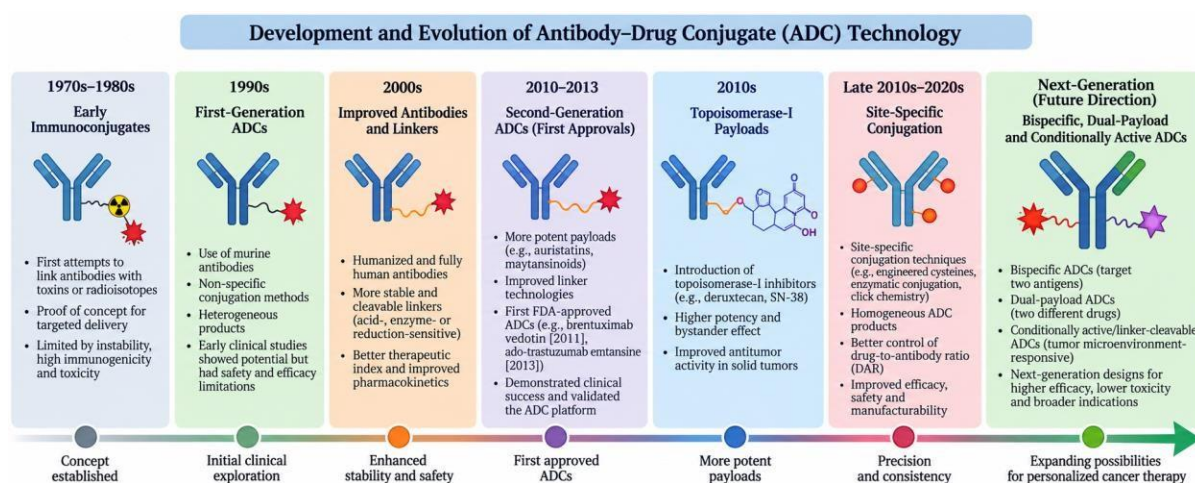


Figure 1. Development and Evolution of Antibody–Drug Conjugate Technology.

2. BASIC STRUCTURE OF ANTIBODY–DRUG CONJUGATES

An ADC contains three principal components: the monoclonal antibody, the linker and the cytotoxic payload. Each component influences the biological behavior of the whole molecule. The antibody determines target recognition, size and much of the systemic pharmacokinetic profile; the linker governs chemical stability and drug release; and the payload determines the mechanism and potency of intracellular killing.[4,5,10,11] The

practical objective is to balance sufficient stability in circulation with efficient release at the intended site and to maintain a molecular architecture that can be manufactured reproducibly.[3,11,13]

A. MONOCLONAL ANTIBODY

The antibody is the targeting element of an ADC and typically recognizes a cell-surface antigen enriched in malignant tissue. Ideal targets should show high or preferential expression on tumor cells, limited expression on essential normal tissues, accessibility to circulating antibody, stable or sufficiently persistent tumor expression and a useful ability to internalize after binding.[4,10,13] Antibody affinity alone is not sufficient: excessively strong binding can sometimes worsen tumor penetration through a “binding-site barrier,” whereas very low affinity may reduce tumor retention. Antibody isotype, Fc interactions, glycosylation, stability and the location of conjugation sites can also influence overall behavior.[6,10,13]

B. LINKER

The linker connects the antibody to the payload and is often the decisive component controlling plasma stability and intracellular release. A therapeutically useful linker should remain sufficiently intact during circulation to minimize premature payload release, while permitting efficient drug liberation after internalization. Cleavable linkers respond to intracellular or tumor-associated conditions such as acidic pH, proteases or reducing environments. Non-cleavable linkers rely on lysosomal degradation of the antibody to generate an active drug-containing catabolite.[10,11]

Cleavable linkers include acid-sensitive hydrazones, reduction-sensitive disulfides and protease-sensitive peptide linkers such as valine-citrulline or related sequences. Enzyme-cleavable peptide linkers are widely used because lysosomal proteases provide a biologically relevant trigger and can be engineered for improved stability in plasma.[11] Non-cleavable linkers, exemplified by the MCC-based linker in trastuzumab emtansine, can provide high plasma stability but depend on complete intracellular processing. Linker choice therefore affects not only release kinetics but also the chemical nature and membrane permeability of the active catabolite.[10,11,18]

C. CYTOTOXIC PAYLOAD

ADC payloads must be exceptionally potent because only a fraction of administered antibody reaches the tumor and only a fraction of the internalized drug is ultimately

released in the cytosol or nucleus. Most clinically successful payloads act at very low intracellular concentrations and include microtubule inhibitors, DNA-damaging agents and topoisomerase inhibitors.[4,5,10] Payload physicochemical properties are also important: molecular size, lipophilicity, charge, membrane permeability and the presence of a suitable conjugation handle can influence both efficacy and toxicity.[10,11]

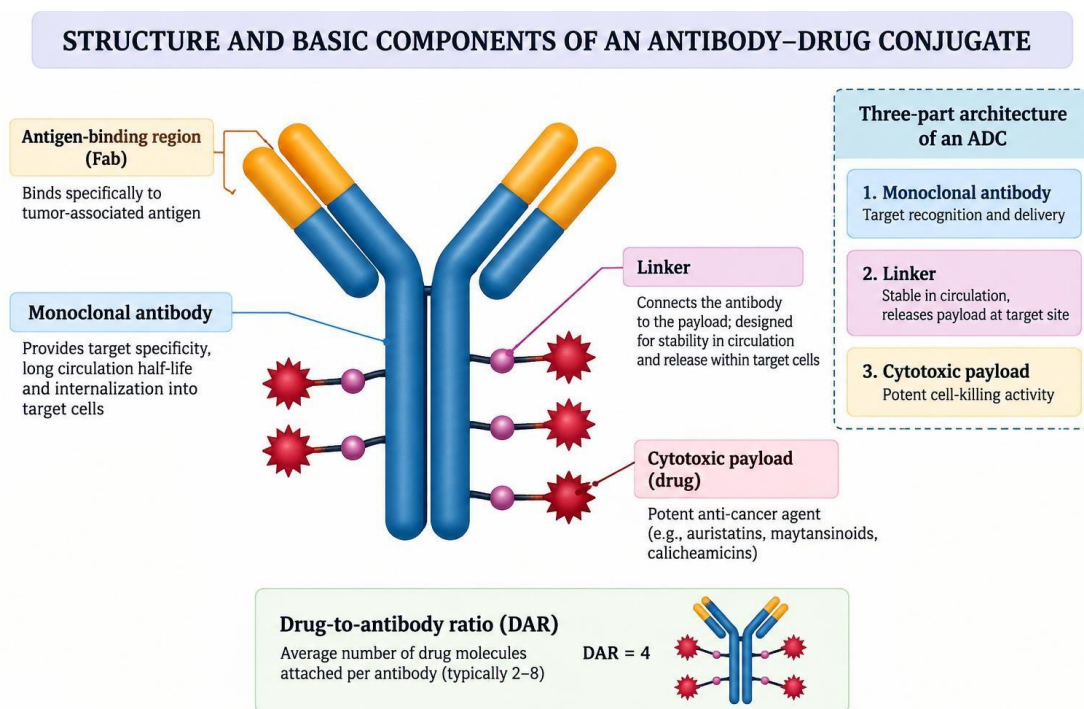


Figure 2. Structure And Basic Components of An Antibody–Drug Conjugate

Table 1. Major components of antibody–drug conjugates and their functions.

Component	Primary role	Key design considerations	Examples
Monoclonal antibody	Target recognition and delivery	Antigen specificity, affinity, internalization, behavior, stability Fc	Trastuzumab; brentuximab; inotuzumab; sacituzumab
Linker	Connects antibody and payload; controls release	Plasma stability, cleavage mechanism, hydrophilicity, catabolite properties	Val-Cit; GGFG; CL2A; MCC
Cytotoxic payload	Intracellular antitumor activity	Potency, mechanism, membrane permeability, stability, conjugation chemistry	MMAE; DM1; DM4; DXd; SN-38; calicheamicin
Conjugation site	Controls attachment pattern and heterogeneity	DAR distribution, structural integrity, manufacturing reproducibility	Lysine; native cysteine; engineered cysteine; enzymatic sites

The three-component architecture explains why ADC development is an optimization problem rather than a single molecular-choice problem. Increasing payload permeability may strengthen bystander killing but also raise off-target exposure; and using a very labile linker may improve intracellular release while increasing systemic toxicity if the conjugate is unstable before reaching the tumor.[5,10,11,13]

3. MECHANISM OF ACTION OF ANTIBODY–DRUG CONJUGATES

The canonical ADC mechanism begins with recognition of a cell-surface tumor-associated antigen by the antibody. After binding, the ADC is internalized through receptor-mediated endocytosis and trafficked through early and late endosomal compartments toward lysosomes. The antibody is then degraded and/or the linker is cleaved, depending on the molecular design, releasing an active payload or drug-containing catabolite.

The liberated cytotoxic agent subsequently interacts with its intracellular target and induces irreversible damage or cell-cycle disruption.[4,5,10,18]

For microtubule-directed payloads such as MMAE, inhibition of tubulin dynamics interferes with mitotic spindle function and promotes mitotic arrest followed by apoptotic or other forms of cell death. DNA-damaging payloads such as calicheamicin or pyrrolobenzodiazepines create severe genomic injury that can activate cell-death pathways. Topoisomerase I inhibitors such as SN-38 and DXd stabilize the topoisomerase I-DNA cleavage complex, producing DNA damage during replication and transcription.[4,5,10]

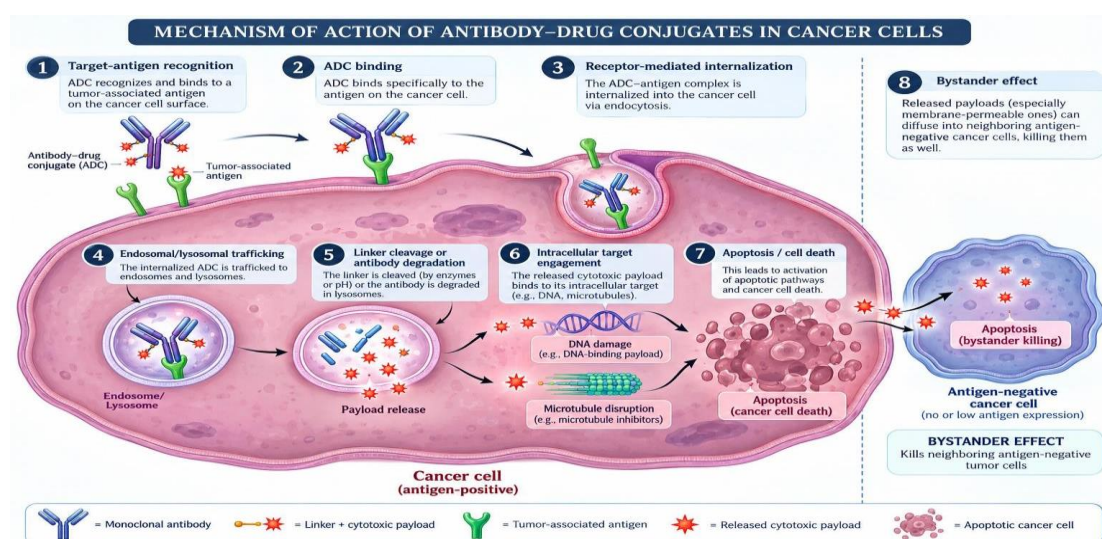


Figure 3. Mechanism of Action of Antibody–Drug Conjugates in Cancer Cells.

4. SELECTION OF TARGET ANTIGENS

Target selection is one of the most important determinants of ADC success. An ideal target has high density on malignant cells, minimal expression on critical normal tissues, extracellular accessibility, internalization after antibody engagement and relatively stable expression during treatment.[4,6,13] Targets that satisfy these criteria can provide greater tumor-to-normal tissue exposure ratios, whereas targets broadly present in normal organs may create on-target/off-tumor toxicity even when the ADC is molecularly specific for the intended antigen.[3,4,6]

HER2 is one of the best established examples because its overexpression identifies a clinically relevant subgroup of breast and gastric cancers and because the antigen undergoes antibody-mediated internalization. Trastuzumab-based ADCs also illustrate how target biology can support multiple generations of molecular design, from trastuzumab emtansine to trastuzumab deruxtecan.[17-19] Importantly, trastuzumab deruxtecan demonstrated clinically meaningful activity in HER2-low breast cancer, broadening the concept of targetability beyond strong amplification or overexpression.[19]

Tumor heterogeneity remains a central challenge because antigen expression may vary between tumor cells, metastases and treatment time points. A biopsy used for initial selection may therefore not perfectly represent the biology present at progression. Repeated testing, quantitative imaging, circulating biomarkers and functional assessment of antigen accessibility are potential approaches to improve patient selection, although many are still investigational.[6,7]

5. TYPES OF ANTIBODY–DRUG CONJUGATES

ADCs can be classified according to antibody format, linker type, payload class, DAR and conjugation strategy. Based on antibody format, most clinically established products use intact monoclonal antibodies, although antibody fragments and alternative scaffolds are being explored. Based on linker design, ADCs can be divided broadly into cleavable and non-cleavable constructs. Based on payload, the major clinically established groups include microtubule inhibitors, topoisomerase I inhibitors, calicheamicin derivatives and DNA-alkylating payloads.[4,5,10,11]

A useful development-oriented classification is by ADC “generation.” First-generation products were often limited by low potency, immunogenic antibodies, unstable linkers or unfavorable pharmacology. Second-generation products incorporated humanized

antibodies, improved linkers and more potent payloads. Third-generation approaches added greater control of conjugation and payload release, while contemporary next-generation programs increasingly emphasize site-specific attachment, novel mechanisms, dual payloads, bispecific targeting, conditional activation and immunological effects.[3,6,7,11,12]

This generational framework is useful but imperfect because regulatory and clinical success does not always track a simple increase in molecular sophistication. A technologically simpler conjugate may outperform a more complex candidate if it has the right target, adequate exposure and a manageable safety profile. Consequently, “generation” should be interpreted as a historical design framework rather than a formal regulatory category.[3,4,10]

6. LINKER TECHNOLOGY IN ADCS

Linker chemistry is central to ADC performance because the molecule must remain stable in the extracellular environment while permitting timely release after target-mediated uptake. Premature cleavage can expose normal tissues to the payload, whereas incomplete or inefficient cleavage can reduce the intracellular dose delivered to cancer cells.[10,11] Linkers also influence ADC hydrophobicity, aggregation, pharmacokinetics, tissue distribution and the chemical form of the released drug.

[11,13][42]

Cleavable linkers can respond to acidic compartments, reducing conditions or lysosomal enzymes. Acid-labile hydrazones were historically important but can be less stable in plasma than newer peptide-based systems. Disulfide linkers can exploit differences between extracellular and intracellular redox environments, whereas protease-cleavable peptide linkers can provide a more biomolecule-compatible release mechanism. The Val-Cit linker used in several vedotin ADCs became a widely adopted example of protease-triggered release.[11,16]

Non-cleavable linkers are chemically stable and release payload through antibody degradation rather than a specific labile bond. Their advantage is often greater circulating stability, while a limitation is that the resulting drug catabolite may remain charged or polar and therefore may have less bystander activity.[10,11] This can be beneficial where localized activity is desired but may reduce effectiveness against tumors with heterogeneous antigen expression.[11,13]

Table 2. Comparison of cleavable and non-cleavable linkers.

Feature	Cleavable linkers	Non-cleavable linkers
Release trigger	Acidic pH, reducing conditions or lysosomal enzymes	Lysosomal degradation of antibody-linker-payload complex
Representative chemistry	Hydrazone, disulfide, peptide	Thioether such as MCC/SMCC
Plasma stability	Depends strongly on linker chemistry; optimized systems can be highly stable	Generally high
Bystander activity	More feasible when released payload is membrane permeable	Usually more limited because catabolites may be less permeable
Key advantage	Controlled intracellular release and potential bystander killing	High systemic stability and predictable catabolite generation
Key limitation	Premature release can increase toxicity if poorly optimized	Potentially reduced diffusion into neighboring antigen-negative cells

7. CYTOTOXIC PAYLOADS USED IN ADCS

ADC payloads are selected under the constraint that only a small fraction of the administered molecule reaches an intracellular target in the tumor. Consequently, successful payloads are substantially more potent than many conventional chemotherapeutic drugs.[4,5,10] Payload selection must balance potency with the ability to maintain activity after conjugation, chemical stability, controlled release, acceptable solubility, suitable linker chemistry and a toxicity profile that can be managed clinically.[11,13,49]

A. MICROTUBULE INHIBITORS

Auristatins and maytansinoids are major microtubule-directed payload classes. MMAE disrupts tubulin polymerization and is widely used in vedotin ADCs including brentuximab vedotin, polatuzumab vedotin, enfortumab vedotin, tisotumab vedotin and telisotuzumab vedotin. MMAF is less membrane permeable than MMAE and has been used in belantamab mafodotin. DM1 and DM4 are maytansinoid derivatives that have been incorporated into trastuzumab emtansine and mirvetuximab soravtansine, respectively.[4,5,16,20-23]

B. DNA-DAMAGING AGENTS

Calicheamicin derivatives generate highly potent DNA damage and are used in gemtuzumab ozogamicin and inotuzumab ozogamicin. Pyrrolobenzodiazepine (PBD)

dimers, used in loncastuximab tesirine, can form DNA interstrand crosslinks. These payloads illustrate the ability of ADCs to deliver extremely potent compounds that would have limited feasibility as unconjugated systemic drugs.[4,10,20]

C. TOPOISOMERASE I INHIBITORS

Topoisomerase I inhibitor payloads have become a major contemporary class. SN-38 is the active metabolite of irinotecan and is used in sacituzumab govitecan, while DXd is a derivative used in trastuzumab deruxtecan and datopotamab deruxtecan. These payloads are generally potent and membrane permeable, enabling a bystander effect that can be useful in tumors with heterogeneous antigen expression. Their clinical activity has helped shift ADC development toward payloads that can act beyond the initially antigen-positive cell.[6,18,19,21]

Payload innovation is now expanding beyond classical cytotoxins. Investigational programs include immune-stimulating compounds, DNA-repair modulators, apoptosis-inducing agents and protein degraders. Such approaches may allow ADCs to engage mechanisms less vulnerable to established resistance pathways. However, new payloads also create new pharmacology, metabolic liabilities and analytical requirements, so molecular novelty alone does not guarantee a better therapeutic index.[6,7]

Table 3. Major Cytotoxic Payloads Used in ADCS.

Payload class	Representative payloads	Primary mechanism	Clinical examples	Key considerations
Microtubule inhibitors	MMAE, MMAF, DM1, DM4	Disrupt microtubule dynamics; mitotic arrest	Brentuximab vedotin; T-DM1; mirvetuximab; enfortumab	Potent; neuropathy and hematologic toxicity can occur
DNA-damaging agents	Calicheamicin, PBD dimer	DNA cleavage or crosslinking	Gemtuzumab; inotuzumab; loncastuximab	Very high potency; systemic toxicity must be tightly controlled
Topoisomerase I inhibitors	SN-38, DXd	Topoisomerase inhibition and replication-associated DNA damage	Sacituzumab; T-DXd; Dato-DXd	Strong clinical activity; bystander effect; diarrhea and hematologic effects may occur
Emerging payloads	Immune stimulants, degraders, novel DNA-active compounds	Mechanism dependent	Mostly investigational	Potential to overcome resistance; greater translational uncertainty

8. DRUG-TO-ANTIBODY RATIO

The drug-to-antibody ratio (DAR) is the average number of payload molecules attached to one antibody molecule and is a major determinant of ADC pharmacology.[5,10] In principle, increasing DAR can increase the amount of payload delivered per internalized antibody. However, highly loaded molecules are often more hydrophobic, may aggregate more readily and can exhibit faster clearance or increased nonspecific tissue uptake. Therefore, maximizing DAR is not the same as maximizing therapeutic benefit.[6,10,13] Clinically established ADCs commonly have DAR values within a broad range, often approximately 2–8, although newer conjugates may use different loading distributions and some historical products have lower values.[4,5] Trastuzumab emtansine has a DAR of approximately 3.5, while trastuzumab deruxtecan carries a higher nominal payload load.[18,19] The fact that both can be clinically effective emphasizes that optimal DAR is product-specific and interacts with linker chemistry, payload properties and conjugation site.[12,50]

DAR is measured as an average because many stochastic ADCs contain a distribution of species. Two products with the same mean DAR may therefore have different distributions of low- and high-load species and consequently different pharmacological behavior.[5,13] Modern analytical technologies such as hydrophobic interaction chromatography, mass spectrometry and intact or subunit analysis support tighter control of DAR and related critical quality attributes. In site-specific conjugation, a narrower DAR distribution can improve batch consistency and may facilitate more predictable relationships between dose, exposure and response.[12,14]

9. METHODS OF ADC CONJUGATION

Traditional ADC conjugation frequently uses reactive lysine residues or cysteine thiols. Lysine conjugation is chemically accessible but can produce substantial heterogeneity because antibodies contain many lysines with different reactivities. Native cysteine conjugation after partial reduction of interchain disulfides is more controlled but still generates mixtures of attachment sites and DAR states.[12-14]

Site-specific approaches were developed to reduce this molecular heterogeneity. Engineered cysteine technology introduced defined thiol residues at selected antibody positions and demonstrated that more homogeneous conjugates can retain efficacy while improving tolerability and pharmacokinetics.[12] Other approaches include enzymatic conjugation, glycan remodeling, unnatural amino acids and bioorthogonal “click”

chemistry. These technologies aim to control both the location and number of payloads attached to the antibody.[13,14]

Table 4. Random Versus Site-Specific ADC Conjugation.

Feature	Random/stochastic conjugation	Site-specific conjugation
Typical sites	Multiple lysine residues or native cysteines	Engineered cysteine, enzymatic tag, glycan or defined chemical handle
Product heterogeneity	Higher	Lower
DAR control	Broad distribution	Tighter distribution
Manufacturing maturity	Extensive clinical precedent	Increasing but more technology dependent
Main advantage	Simple, scalable and clinically validated	Greater homogeneity and tunability
Main limitation	Species heterogeneity and variable pharmacology	Higher development and manufacturing complexity

10. PHARMACOKINETICS AND PHARMACODYNAMICS OF ADCS

ADC pharmacokinetics cannot be understood solely from the behavior of the antibody or payload. The circulating conjugate, total antibody, released payload and active metabolites may all display different exposure profiles.[5,10] Most ADCs are administered intravenously and show prolonged systemic residence because of their antibody component, but clearance can be altered by antigen-mediated uptake, Fc receptor interactions, proteolytic degradation and the physicochemical properties introduced by conjugation.[3,6,13]

Target-mediated drug disposition is particularly relevant when the target antigen is expressed on normal tissues or on circulating cells. Binding can accelerate clearance when target-mediated uptake is substantial. Increasing DAR or hydrophobicity may also increase nonspecific uptake and hepatic clearance. These effects create a complex relationship between molecular structure, dose and systemic exposure, and they explain why dose selection often differs considerably among products.[5,10,13]

Tumor penetration is another major limitation. The large size of intact antibodies restricts passive diffusion through dense tumor tissue, and rapid binding near blood vessels can reduce penetration into distant tumor regions. In some settings, heterogeneous vascularization and high interstitial pressure further constrain distribution.[6,13] Bystander-active payloads may partially compensate by allowing drug diffusion among neighboring cells, but they cannot fully solve physical barriers to ADC delivery.[3,6]

Pharmacodynamic behavior depends on antigen abundance, internalization, lysosomal processing, linker cleavage and intracellular target engagement. Clinical response may therefore correlate imperfectly with simple immunohistochemical antigen intensity. The optimal biomarker may combine antigen quantity with measures of internalization, tumor accessibility or functional target biology.[6,7]

11. CLINICALLY APPROVED ANTIBODY–DRUG CONJUGATES

The clinical landscape has expanded substantially from the single ADC approved in 2000. By late 2025, 14 distinct ADCs had received FDA approval, and in 2026 pivekimab sunirine became an additional FDA-approved ADC for blastic plasmacytoid dendritic cell neoplasm. Current FDA-approved products cover hematological malignancies and multiple solid tumors, with newer approvals emphasizing TROP-2, HER2, c-Met and CD123 biology. The table below summarizes major FDA-approved ADCs and their principal molecular features; exact label details should always be checked against current prescribing information before clinical use.[20,24,51]

ADC Name	Target	Linker	Payload	Cancer Indication	Key Features
Gemtuzumab ozogamicin	CD33	Hydrazone acid-labile	Calicheamicin derivative	CD33+ AML	Initial 2000; re-approved 2017 with revised regimen
Brentuximab vedotin	CD30	Val-Cit-PABC / protease-cleavable	MMAE	CD30+ lymphomas	2011; multiple later expansions
Trastuzumab emtansine	HER2	MCC / non-cleavable	DM1	HER2+ breast cancer	2013
Inotuzumab ozogamicin	CD22	Hydrazone acid-labile	Calicheamicin derivative	Relapsed/refractory B-cell precursor ALL	2017
ADC Name	Target	Linker	Payload	Cancer Indication	Key Features
Polatuzumab vedotin	CD79b	Val-Cit-PABC / protease-cleavable	MMAE	Diffuse large B-cell lymphoma	2019
Enfortumab vedotin	Nectin-4	Val-Cit-PABC / protease-cleavable	MMAE	Urothelial carcinoma	2019
Trastuzumab deruxtecan	HER2	Tetrapeptide (GGFG) cleavable	DXd (TOP1 inhibitor)	HER2+ and HER2-low cancers; HER2-mutant NSCLC	2019
Sacituzumab govitecan	TROP-2	CL2A cleavable	SN-38 (TOP1 inhibitor)	Breast cancer and selected epithelial cancers	2020
Belantamab mafodotin	BCMA	Maleimidocaproyl / non-	MMAF	Relapsed/refractory multiple myeloma	2020; withdrawn 2022;

		cleavable			re-approved in combination regimen 2025
Loncastuximab tesirine	bCD19	Val-Ala-PABC cleavable	/PBD dimer	Relapsed/refractory large B-cell lymphoma	2021
Tisotumab vedotin	Tissue factor	Val-Cit-PABC cleavable	/MMAE	Recurrent/metastatic cervical cancer	2021; full approval 2024
Mirvetuximab soravtansine	FR α	Sulfo-SPDB disulfide-cleavable	/DM4	FR α + platinum-resistant ovarian/fallopian tube/primary peritoneal cancer	2022 accelerated; regular approval 2024
Datopotamab deruxtecan	TROP-2	Tetrapeptide cleavable	/DXd (TOP1 inhibitor)	HR+/HER2- metastatic breast cancer; selected EGFR-mutant NSCLC	2025
Telisotuzumab vedotin	bc-Met	Val-Cit-PABC cleavable	/MMAE	c-Met-overexpressing non-squamous NSCLC	2025 accelerated approval
Pivekimab sunirine	CD123	Proprietary	FGN849 alkylating-agent payload	Blastic plasmacytoid dendritic cell neoplasm	Initial U.S. approval 2026; first FDA-Approved ADC in this indication

12. CLINICAL APPLICATIONS OF ADCS IN DIFFERENT CANCERS

BREAST CANCER

Breast cancer is one of the most important clinical settings for ADC development. HER2-directed ADCs transformed treatment sequencing in HER2-positive disease. Trastuzumab emtansine improved outcomes after prior trastuzumab-based therapy, while trastuzumab deruxtecan later demonstrated superior progression-free and overall survival compared with trastuzumab emtansine in previously treated HER2-positive metastatic breast cancer.[17,18] The clinical difference was accompanied by a distinct toxicity profile, including clinically important interstitial lung disease/pneumonitis with trastuzumab deruxtecan, illustrating again that greater efficacy does not imply lower toxicity.[18]

The concept of HER2 targeting was further expanded by DESTINY-Breast04, which demonstrated benefit with trastuzumab deruxtecan in HER2-low metastatic breast cancer.[19] This finding was important not only therapeutically but conceptually because it suggested that a highly potent, bystander-capable payload can generate clinically meaningful activity even when antigen density is below the conventional threshold for

HER2 -targeted therapy. The result has encouraged renewed exploration of other “low-expression” ADC targets and more quantitative approaches to biomarker definition.[6,19]

TROP-2-directed ADCs have added another major dimension to breast cancer treatment. Sacituzumab govitecan established a role in metastatic triple-negative breast cancer, and datopotamab deruxtecan expanded TROP-2 targeting into HR-positive/HER2-negative disease.[21,22] In 2026, FDA approvals further broadened the use of sacituzumab govitecan in first-line TNBC and datopotamab deruxtecan in unresectable or metastatic TNBC, showing how ADC development is moving progressively earlier and across molecular subgroups.[21,22]

A. HEMATOLOGICAL MALIGNANCIES

Hematological malignancies were the earliest successful clinical environment for ADCs because malignant cells are often highly accessible in blood, marrow or lymphoid compartments and may express lineage-associated antigens with relatively favorable selectivity.[3,8] Brentuximab vedotin targets CD30 in Hodgkin lymphoma and other CD30-positive lymphomas, while gemtuzumab ozogamicin and inotuzumab ozogamicin target myeloid and B-cell antigens, respectively.[15,16]

Multiple myeloma has provided an additional lesson in ADC design. Belantamab mafodotin targets BCMA and uses the MMAF payload. Its earlier regulatory history was complicated by ocular toxicity and subsequent withdrawal in the United States, but its 2025 re-approval with bortezomib and dexamethasone reflected new clinical evidence and a revised treatment strategy.[24] This case emphasizes that improvements in regimen design, patient selection and monitoring can sometimes revive a molecular platform that previously had an unfavorable regulatory trajectory.[24]

B. LUNG CANCER

Lung cancer has become an increasingly important field for ADC development because tumors can express HER2, TROP-2, c-Met and other clinically relevant targets. Trastuzumab deruxtecan has demonstrated activity in HER2-mutant non-small-cell lung cancer, while datopotamab deruxtecan has entered treatment of previously treated EGFR-mutant disease and, in 2026, received an FDA approval in a TNBC setting as well.[18,22,26] Telisotuzumab vedotin provides a distinct biomarker-selected approach for non-squamous NSCLC with high c-Met protein overexpression.[20,25]

In lung cancer, ADC safety considerations are particularly important because pulmonary adverse events may overlap with underlying lung disease and prior treatment effects. The interstitial lung disease signal associated with trastuzumab deruxtecan and pulmonary monitoring requirements in some newer ADC programs demonstrate the need for proactive surveillance, early diagnosis and treatment interruption when indicated.[18,28] The clinical value of a lung-cancer ADC therefore depends on both antitumor activity and the ability to manage organ-specific toxicity in a population with limited physiological reserve.[18,28]

C. UROTHELIAL CANCER[29,30]

Enfortumab vedotin is a major example of an ADC progressing from refractory urothelial cancer to combination-based frontline therapy. In the EV-301 phase III trial, enfortumab vedotin improved overall survival and progression-free survival compared with standard chemotherapy in previously treated advanced urothelial carcinoma.[29] More recently, the EV-302 trial established enfortumab vedotin plus pembrolizumab as a highly effective first-line regimen for untreated advanced urothelial cancer, demonstrating the growing importance of ADC-immunotherapy combinations.[30]

D. GASTRIC CANCER[31]

HER2-targeted therapy is also clinically relevant in gastric and gastroesophageal cancers. Trastuzumab deruxtecan improved outcomes compared with chemotherapy in previously treated HER2-positive gastric or gastroesophageal junction adenocarcinoma, supporting continued use of ADCs in cancers where target expression is a clinically actionable subtype.[31] The experience also shows that ADC efficacy may depend on the intensity and pattern of antigen expression, prior therapy and the biological characteristics of the tumor rather than target positivity alone.[18,31]

E. OVARIAN CANCER[25,32,33]

Mirvetuximab soravtansine targets folate receptor alpha and provides a targeted treatment option for FR α -positive, platinum-resistant ovarian, fallopian tube and primary peritoneal cancers.[25] The MIRASOL trial supported regular FDA approval after an earlier accelerated pathway, illustrating the importance of confirmatory randomized evidence in converting promising activity into a more established treatment position.[25,32] The ocular toxicity profile of mirvetuximab also demonstrates why target and payload selection must be accompanied by organ-specific monitoring

strategies.[25,32,33]

13. ADVANTAGES OF ANTIBODY–DRUG CONJUGATES

The most important theoretical advantage of ADCs is selective delivery of highly potent cytotoxic agents to cells that express a chosen antigen. By concentrating drug activity within the target tissue, the system can potentially achieve a higher therapeutic index than the same payload administered freely. Clinical success with multiple products supports the broader proposition that targeted payload delivery can generate meaningful antitumor activity while retaining manageable systemic exposure.[3-7]

ADCs can also exploit potency that would be impractical for conventional chemotherapy. Payloads such as calicheamicin, PBD dimers and potent microtubule or topoisomerase inhibitors are generally unsuitable as nonspecific drugs at the exposures required for selective tumor killing. Antibody-mediated delivery provides a pharmacological route for using these compounds in a controlled manner.[10] The ability to combine targeting with payload mechanisms from different therapeutic classes expands the design space available to oncologists and medicinal chemists.[11,13]

A further advantage is the potential to overcome some forms of classical chemoresistance because ADC activity depends on cellular uptake and the specific mechanism of the payload rather than on the mechanism of the free drug used previously. In some cases, membrane-permeable payloads and bystander effects may also reduce the impact of incomplete antigen expression within a tumor.[6,18,19] However, these advantages are not universal and resistance to internalization, lysosomal processing or the payload mechanism can still emerge.[34,4]

ADCs also fit naturally into precision-medicine frameworks. Target testing, immunohistochemistry, molecular diagnostics and clinical sequencing can identify patients with higher probabilities of benefit. Recent approvals using explicit biomarker thresholds, such as FR α positivity and high c-Met overexpression, demonstrate how companion diagnostics can become integrated into ADC practice.[20,25]

14. LIMITATIONS AND CHALLENGES OF ADCS

Despite their targeted design, ADCs remain systemic drugs and can cause substantial toxicity. The antibody may recognize the intended target in normal tissues, producing on-target/off-tumor effects. Alternatively, free payload released in circulation, nonspecific uptake by the liver or reticuloendothelial system, and tissue distribution of active

metabolites can generate off-target toxicity.[6,7,10,11] The most clinically important consequence is that targeted delivery narrows but does not eliminate normal-tissue exposure.[13,15]

Tumor heterogeneity is another fundamental problem. Antigen expression may vary between cells or may be lost during treatment, producing subpopulations that escape target-dependent uptake. Conversely, strong binding near blood vessels can limit penetration into deeper tumor regions. The bystander effect can partly address antigen-negative neighboring cells when the payload is membrane permeable, but may simultaneously reduce the separation between tumor and healthy tissue.[6,7,18]

Manufacturing complexity also remains a challenge. ADCs combine a biological component with a synthetic payload and linker, creating critical quality attributes that include antibody identity, conjugation-site distribution, DAR distribution, free payload, aggregates, charge variants and product-related impurities. Each component may introduce its own control strategy, and analytical methods must be sufficiently sensitive to detect changes that could alter efficacy or safety.[5,13,14]

Cost is a related systems-level limitation. Many ADCs require specialized antibodies, potent payload synthesis, controlled conjugation, aseptic processing and detailed analytical characterization. These demands can increase the cost of goods and complicate access in settings where cancer therapy is already resource constrained. Broader uptake therefore depends not only on clinical efficacy but also on manufacturing efficiency, payer systems, infrastructure and the availability of diagnostic testing.[4,7]

15. MECHANISMS OF RESISTANCE TO ADCS

ADC resistance can arise at multiple stages along the drug-delivery pathway. Reduced or heterogeneous antigen expression decreases the probability of binding, while antigen shedding, receptor internalization defects and altered endocytic trafficking can limit intracellular delivery. After lysosomal entry, changes in protease activity, lysosome function or intracellular trafficking may reduce payload release. Even when the payload is released normally, drug efflux or intrinsic resistance to the cytotoxic mechanism can prevent cell death.[34,35]

Target-mediated resistance may emerge under therapeutic pressure when tumor clones with reduced antigen expression are preferentially selected. This mechanism is especially relevant to tumors in which the target is not an essential driver of malignant survival. In such settings, antigen-negative or antigen-low cells may persist and become dominant

after treatment.[34,35] The clinical consequence is that a previously positive biopsy may no longer accurately represent target abundance at the time of progression.[34]

Payload-related resistance can include increased expression of drug efflux pumps, changes in tubulin dynamics, altered DNA-repair pathways or activation of survival signaling that counteracts payload-induced damage. Because different ADCs using different payload classes engage different intracellular mechanisms, switching to an ADC with a non-cross-resistant payload may be a rational strategy in selected situations, although clinical sequencing must be supported by evidence rather than assumed.[6,34]

Strategies under investigation include dual-targeting or bispecific ADCs, payload switching, combination with immune checkpoint inhibitors, use of membrane-permeable payloads to exploit the bystander effect, novel targets that remain stable during therapy, and delivery designs that avoid conventional lysosomal dependence.[6,7,35] Resistance research is therefore shifting from a single-mechanism view to a systems model encompassing antigen biology, intracellular trafficking, payload pharmacology and tumor evolution.[6,11,13]

16. ADVERSE EFFECTS AND SAFETY CONSIDERATIONS

ADC toxicities are highly product-specific but several recurring patterns are clinically relevant. Hematologic adverse effects such as anemia, thrombocytopenia and neutropenia occur with multiple ADCs, reflecting payload effects, marrow exposure and disease-related vulnerability. Peripheral neuropathy is particularly associated with MMAE-containing ADCs, while gastrointestinal adverse effects are common with several topoisomerase I inhibitor-based products.[4,5,10,20]

Hepatotoxicity can occur with ADCs containing calicheamicin or other payload classes, and gemtuzumab ozogamicin and inotuzumab ozogamicin have important liver-related safety considerations.[15,16] Ocular toxicity is a defining monitoring concern for mirvetuximab soravtansine and belantamab mafodotin, illustrating that the tissue distribution of either the antibody target or payload can produce an organ-specific safety signature.[24,25]

Interstitial lung disease and pneumonitis are important adverse events with trastuzumab deruxtecan and require clinical vigilance, especially because early symptoms may be nonspecific and irreversible progression can occur.[18,28] The risk-benefit profile of an ADC therefore includes not just frequency of adverse effects but also reversibility, monitoring burden, time to onset and the availability of effective mitigation

strategies.[18,28]

A key reason toxicity persists despite targeted design is that target expression is rarely perfectly tumor-specific. In addition, ADCs may release payload extracellularly, and active metabolites can distribute beyond the initial target cell. The practical goal is thus not to eliminate exposure to normal tissues entirely but to optimize the differential exposure and pharmacodynamic consequences between malignant and normal compartments.[6,7,10]

17. COMBINATION THERAPY INVOLVING ADCS

ADC combinations are being developed because the mechanism of targeted payload delivery can complement other forms of cancer treatment. Combining an ADC with chemotherapy may increase cytotoxic pressure but can also produce overlapping myelosuppression or neuropathy. Rational combinations therefore require attention to mechanism, schedule, pharmacokinetics and non-overlapping toxicity rather than additive efficacy alone.[4,6] Combination with immune checkpoint inhibitors is especially attractive because ADC-induced tumor-cell death may release tumor antigens, alter the tumor microenvironment or create immunogenic signals. The clinical success of enfortumab vedotin plus pembrolizumab in advanced urothelial cancer has strengthened this strategy, and additional ADC-immunotherapy combinations are being evaluated across solid tumors.[30]

The 2026 FDA approval of sacituzumab govitecan in combination with pembrolizumab for first-line TNBC in PD-L1-positive tumors provides another example of how ADCs are moving from salvage monotherapy toward biologically selected combination regimens.[21]

The challenge is to distinguish mechanistically productive combinations from combinations that merely increase toxicity or delay the use of a more effective established regimen.[54] Targeted therapy combinations are also under study. ADCs may be combined with kinase inhibitors, antiangiogenic agents or other receptor-directed treatments when there is a strong biological rationale. The main concerns include cumulative toxicity, pharmacokinetic interactions and the possibility that one treatment may alter target expression or intracellular trafficking of the other.[6,7]

18. NEXT-GENERATION ANTIBODY-DRUG CONJUGATES

Next-generation ADC development increasingly focuses on controlling properties that

were previously treated as fixed. Site-specific conjugation can narrow DAR distribution; novel linkers can improve plasma stability and release efficiency; and hydrophilic spacer elements can reduce nonspecific uptake of highly loaded molecules.[6,7,11-14] These changes are intended to widen the therapeutic index rather than simply increase potency.[6,12,40,41] Bispecific ADCs represent one emerging strategy for addressing tumor heterogeneity. By recognizing two antigens, a bispecific construct may increase tumor selectivity or retain uptake when one antigen is lost. Dual-payload ADCs seek to deliver two cytotoxic mechanisms within one molecule, potentially reducing the chance that resistance to a single mechanism will dominate.[6,7] These approaches remain largely investigational and require careful control of molecular complexity.[6,7]

Conditionally active or “probody”-type ADCs are designed to remain relatively inactive until tumor-associated conditions unmask or activate the binding domain. Such designs may reduce on-target/off-tumor exposure when the antigen is also present in healthy tissues.[6,7] Similar principles are being applied to tumor-microenvironment-responsive linkers, where protease activity or other local cues act as an additional layer of selectivity.[6,40]

Antibody engineering may also increase penetration or alter receptor trafficking. Smaller antibody formats, engineered Fc regions, pH-dependent binding and affinity tuning are being investigated to optimize tissue distribution and clearance.[6,7] The challenge is maintaining sufficient serum stability and manufacturability while introducing the desired pharmacological behavior.[6]

ADC payload innovation is moving beyond classical microtubule, DNA-damaging and topoisomerase mechanisms. Immune-stimulating ADCs, protein-degrader conjugates and other “smart” payloads aim to convert the ADC into a programmable intracellular delivery platform.[7,36] These approaches could open applications beyond conventional cytotoxicity, but they also make biomarker selection, mechanism-of-action validation and clinical monitoring more complex.[6,7]

Table 5. Emerging next-generation ADC Technologies.

Technology	Rationale	Potential benefit	Main development challenge
Site-specific conjugation	Reduce molecular heterogeneity	More consistent DAR, PK and manufacturing control	Process complexity and site-selection effects

Bispecific ADCs	Target two antigens	Improved selectivity or resistance management	Large molecular size and complex CMC
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Technology	Rationale	Potential benefit	Main development challenge
Dual-payload ADCs	Deliver two mechanisms	Potentially broader killing and reduced single-payload resistance	Payload compatibility, stability and analytics
Probody/conditionally active ADCs	Activate preferentially in tumors	Lower normal-tissue target exposure	Reliable activation control
TME-responsive linkers	Exploit tumor-associated chemistry	More localized release	Tumor heterogeneity and trigger variability
Immune-stimulating ADCs	Combine payload delivery with immune activation	Potential systemic and immune-mediated synergy	Balancing efficacy with immune toxicity
Protein-degrader ADCs	Deliver targeted degraders intracellularly	Access to non-classical targets	Degrader chemistry, intracellular release and pharmacology

19. FUTURE PERSPECTIVES

The future of ADC therapy is likely to depend increasingly on patient selection and molecular precision rather than on payload potency alone. Better characterization of antigen density, spatial distribution, internalization and target turnover could allow clinicians to distinguish patients most likely to benefit. Quantitative imaging, digital pathology, circulating biomarkers and multimodal molecular profiling may eventually provide a more complete picture than a single immunohistochemical score.[6,7]

Artificial intelligence and computational modeling may support ADC development by integrating antibody sequence, target biology, linker properties, payload chemistry, conjugation site and clinical exposure data. Machine-learning approaches could help predict manufacturability, aggregation, DAR-related behavior and toxicity, while simulation and model-based drug development may improve dose selection and combination design.[6,7] However, computational prediction should remain connected to experimental and clinical validation because ADC behavior depends on emergent biological processes that are difficult to capture fully in silico.[6,7,20]

Manufacturing innovation is another priority. Greater adoption of site-specific conjugation, continuous processing, improved analytical methods and platform-based manufacturing may reduce the burden of producing highly potent biologics. Robust

control of free payload, aggregates and conjugation heterogeneity will remain important because small changes in these attributes can materially affect safety and efficacy.[5,13,14]

Future clinical development will probably involve more combinations, earlier lines of treatment and disease stages in which tumor burden is lower. This may increase cure rates in selected settings but also raises the importance of balancing long-term tolerability against incremental efficacy. The 2026 regulatory expansion of several ADCs demonstrates that the field is moving toward earlier and more biomarker-defined use, but the same period also highlights the importance of confirmatory trials and careful post-marketing evaluation.[21-23,24,26]

From a pharmacy perspective, ADCs are especially important because they integrate principles of medicinal chemistry, bioconjugation, pharmacokinetics, formulation, analytical characterization, pharmacovigilance and clinical therapeutics into a single dosage form. Pharmacists and pharmaceutical scientists therefore have roles across development and use, including stability assessment, manufacturing control, dose management, handling of potent compounds, adverse-event monitoring and education of patients and healthcare teams.[4,6][45]

Ultimately, the most successful next-generation ADCs will probably be those that solve a clearly defined clinical problem rather than those that simply add molecular complexity. A useful design should improve tumor selectivity, maintain sufficient systemic stability, achieve reliable intracellular delivery and provide a safety profile that can be monitored in routine practice.[6,7] Continued integration of target biology, chemistry, quantitative pharmacology and clinical evidence should therefore determine the next phase of ADC innovation.[4,6]

CONCLUSION

Antibody–drug conjugates (ADCs) have evolved from an experimental form of immunoconjugate therapy into a cornerstone of targeted oncology. Often described as "guided missiles," ADCs achieve targeted cytotoxicity by uniting three distinct elements: a monoclonal antibody designed to recognize specific tumor cell surface antigens, a highly potent cytotoxic payload capable of inducing cell death, and a specialized chemical linker that ensures the complex remains stable in systemic circulation until reaching its destination. Upon binding to the target antigen, the ADC complex is internalized into the tumor cell via endocytosis, where lysosomal enzymes degrade the

linker or antibody to release the payload directly within the intracellular environment. This refined delivery mechanism has led to significant clinical breakthroughs and expanded therapeutic options across diverse malignancies, including breast, urothelial, ovarian, gastric, cervical, lung, and hematological cancers.

Despite these clinical achievements, the full therapeutic potential of ADCs is challenged by biological, pharmacological, and technical barriers. Tumor heterogeneity often results in variable antigen expression across cell populations, allowing antigen-negative tumor cells to evade detection and drive disease relapse. Furthermore, dense solid tumor microenvironments impede complete drug penetration, while systemic toxicities—such as off-target cell death, interstitial lung disease, ocular toxicities, and neutropenia—frequently constrain the maximum tolerated dose. These safety concerns stem from premature payload release in circulation or off-target uptake by non-malignant tissues expressing low levels of the target antigen. Adding to these biological hurdles is the intrinsic complexity of ADC manufacturing, which requires precise chemistry to control the drug-to-antibody ratio (DAR) and maintain structural uniformity across production batches.

Unlocking the next generation of ADCs requires advances in molecular design, biomarker integration, and targeted pharmacology. Researchers are increasingly turning to site-specific conjugation methods to produce homogenous drug profiles with predictable pharmacokinetic profiles, replacing traditional heterogeneous attachment techniques. Parallel developments in linker technology are yielding cleavage mechanisms that remain completely stable in plasma yet rapidly breakdown within the tumor microenvironment, minimizing systemic exposure. Furthermore, expanding beyond conventional tubulin and DNA-damaging agents to explore novel payloads—such as immunostimulatory molecules or protein degraders—offers promising paths to overcome acquired resistance. Ultimately, the long-term impact of ADCs will hinge on integrating these refined bioengineering approaches with biomarker-driven patient selection, shifting the paradigm from simply maximizing cytotoxic potency toward delivering safer, highly individualized cancer therapies.

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