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

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GRAPHICAL ABSTRACT

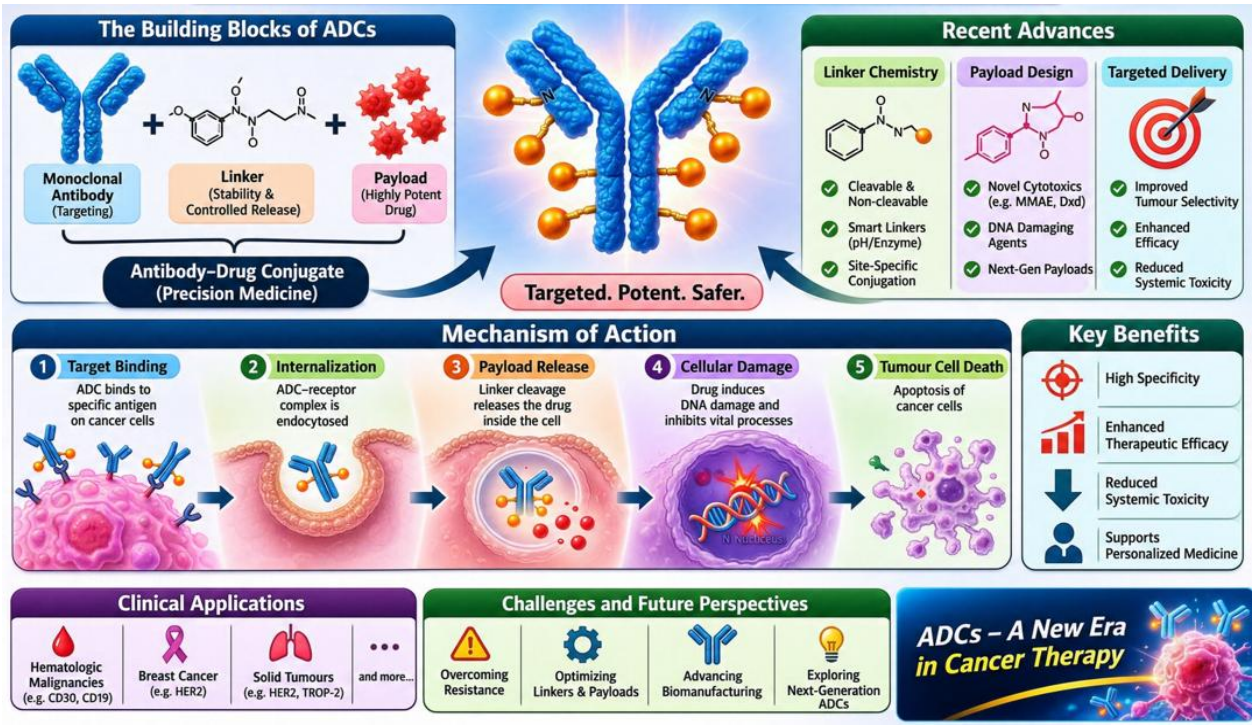


Figure 1. Graphical Abstract of Antibody–Drug Conjugates: Advances in Linker Chemistry, Payload Design and Targeted Drug Delivery. [1]

***Abstract*—Antibody–drug conjugates (ADCs) are innovative targeted therapeutics that combine the specificity of monoclonal antibodies with the cytotoxic activity of potent drug molecules. Their effectiveness depends on the selection of suitable antigens, antibodies, linkers, payloads and conjugation strategies. Recent advances in linker chemistry, including protease-cleavable, acid-sensitive, reduction-responsive and non-**

cleavable linkers, have improved drug stability and controlled intracellular release. Site-specific conjugation and optimized drug-to-antibody ratios have further enhanced ADC development. Novel payloads, particularly topoisomerase-I inhibitors and immunomodulatory agents, have expanded their therapeutic potential. This review highlights ADC architecture, linker chemistry, payload design, targeted drug delivery, clinical applications, resistance mechanisms and associated safety challenges. A narrative literature review was conducted using biomedical databases and regulatory resources. Current developments emphasize improved tumour selectivity, reduced systemic toxicity and enhanced therapeutic efficacy. Future research should focus on advanced conjugation technologies, novel payloads, biomarker-guided treatment and personalized cancer therapy.

***Index Terms*—Antibody–Drug Conjugates; Linker Chemistry; Cytotoxic Payload; Drug-To-Antibody Ratio; Site-Specific Conjugation; Targeted Drug Delivery; Bystander Effect; Oncology.**

I. INTRODUCTION

Cancer treatment has increasingly shifted towards therapies that exploit molecular differences between malignant and normal tissues. Conventional cytotoxic chemotherapy can produce clinically meaningful tumour responses, but its distribution is not inherently restricted to malignant cells. Monoclonal antibodies introduced a means of recognizing selected cell-surface antigens; however, antibodies alone may not provide sufficient cytotoxic activity in every tumour setting. ADCs were developed to combine antibody-mediated recognition with the potency of small-molecule drugs, thereby creating a modular delivery system in which a biologically active antibody carries a highly potent payload to antigen-expressing cells [2].

A conventional ADC contains three principal components: a monoclonal antibody, a chemical linker and a cytotoxic payload. The antibody determines antigen recognition, circulation behaviour and, in many cases, internalization. The linker controls the stability of the conjugate in blood and the conditions under which the payload is released. The payload determines the intracellular mechanism of action and contributes substantially to potency, bystander activity and toxicity. These elements cannot be optimized independently because a change in one component can alter the pharmacokinetics, aggregation tendency, tissue distribution or biological activity of the complete conjugate [5].

The clinical development of brentuximab vedotin and trastuzumab emtansine established the therapeutic feasibility of ADCs, while subsequent approvals and clinical successes have broadened their use in haematological and solid malignancies. More recent platforms containing topoisomerase-I inhibitor payloads have demonstrated that payload class, drug loading and linker design can influence activity in tumours with heterogeneous antigen expression. Nevertheless, ADCs remain associated with on-target/off-tumour effects, payload-related toxicities, acquired resistance and complex manufacturing requirements [3].

This review focuses on recent advances in linker chemistry, payload design and targeted delivery. It also considers antibody selection, conjugation technologies, clinical translation, resistance, safety and future development priorities. The central premise is that the therapeutic index of an ADC is an integrated property of the complete molecular construct rather than a consequence of antigen specificity alone [10].

II. MATERIALS AND METHODS

2.1 Review design

The present work was prepared as a narrative review with a structured literature-identification approach. The objective was to synthesize evidence concerning ADC architecture, linker chemistry, payload design, conjugation technologies, targeted delivery, clinical translation and resistance. The review was not designed as a meta-analysis, and no pooled effect estimates or formal risk-of-bias scores were calculated. The methodology is therefore intended to provide a transparent account of source identification and selection rather than to claim a fully systematic review [25].

2.2 Information sources and search strategy

A literature search framework was developed for PubMed/MEDLINE, Scopus, Web of Science and Google Scholar. Regulatory information was considered from the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and official prescribing information. Search concepts included “antibody–drug conjugate”, “ADC”, “linker chemistry”, “cleavable linker”, “non-

cleavable linker", "protease-sensitive linker", "site-specific conjugation", "drug-to-antibody ratio", "auristatin", "maytansinoid", "topoisomerase-I inhibitor", "bystander effect", "ADC resistance" and "ADC toxicity". Boolean combinations of these terms were intended to identify foundational studies and developments reported through 7 November 2026 [11].

2.3 Eligibility criteria and data extraction

Priority was assigned to peer-reviewed original research, clinically relevant translational studies, authoritative reviews, regulatory documents and product information that directly addressed ADC structure, chemistry, pharmacology, safety or clinical application. Sources were considered relevant when they provided information on linker structure or release mechanism, payload class or mechanism, conjugation method, DAR, target biology, clinical use, resistance or toxicity. Duplicate records, non-therapeutic conjugate systems and publications lacking sufficient relevance to the review objectives were excluded. Reference lists of key reviews were also used to identify relevant primary studies [12].

2.4 Synthesis of evidence

Information was organized into thematic categories covering antibody and antigen selection, linker design, payload properties, conjugation, intracellular delivery, clinical examples, safety and future directions. Findings were compared qualitatively, with attention to the relationship between molecular design and biological performance. Because clinical indications and regulatory status can change, the final manuscript should be checked against current FDA and EMA records immediately before submission. The search dates, database access dates and exact search strings should be updated by the authors if a formal PRISMA-compliant systematic review is intended [24].

III. STRUCTURAL COMPONENTS AND MECHANISM OF ACTION OF ADCS

The antibody component is generally a monoclonal immunoglobulin selected to bind a cell-surface antigen that is sufficiently expressed on tumour cells and accessible to circulating antibody. An ideal target shows limited expression in essential normal tissues, is present at adequate density on malignant cells and supports productive internalization. Antigen shedding, heterogeneous expression, slow internalization and expression in healthy organs can reduce efficacy or increase toxicity. The antibody also influences Fc-receptor interactions, half-life, tissue distribution and immunological properties [4].

The linker connects the antibody to the payload and must remain sufficiently stable in plasma while allowing the drug to become pharmacologically active at the intended site. Linker design includes the antibody-attachment handle, spacer, trigger and, where required, a self-immolative unit. The payload is a highly potent drug selected for a mechanism that can kill tumour cells at the intracellular concentration achievable after antibody-mediated delivery. Figure 1 summarizes the three-part architecture of a conventional ADC [13].

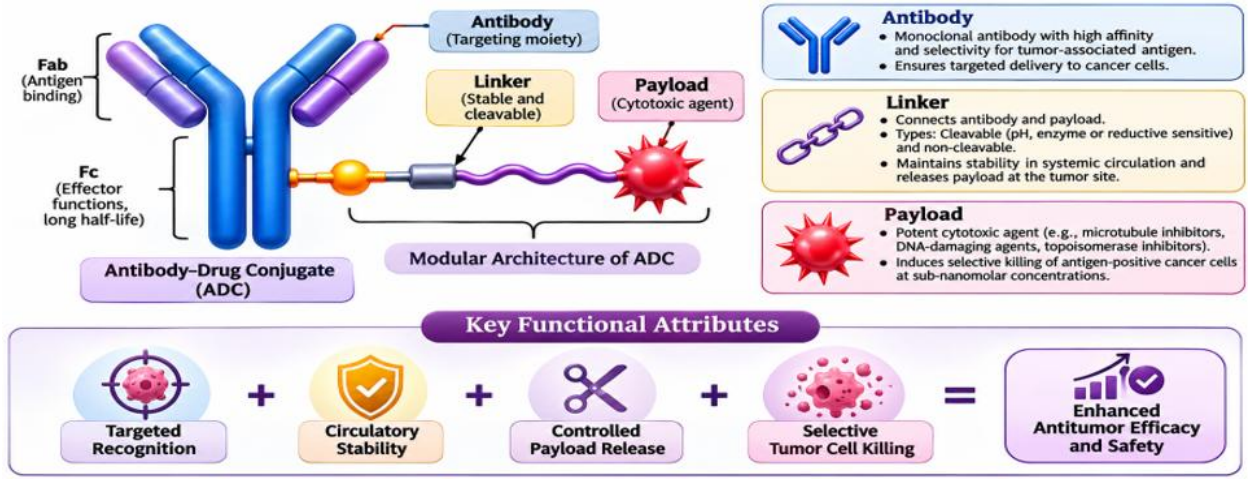


Figure 2. Schematic representation of the modular architecture of an antibody–drug conjugate.[14]

Following systemic administration, the ADC circulates and binds to its target antigen on a tumour cell. Binding may initiate receptor-mediated endocytosis, followed by trafficking through endosomal compartments towards lysosomes. Depending on linker design, the payload may be released by proteolytic cleavage, acid-mediated cleavage, reduction or degradation of the antibody–linker structure. The released active compound then interacts with its intracellular target, causing cell-cycle arrest, DNA damage, replication stress or other cytotoxic effects. This generalized pathway is not identical for every ADC because some constructs can undergo extracellular or cell-surface payload release [15].

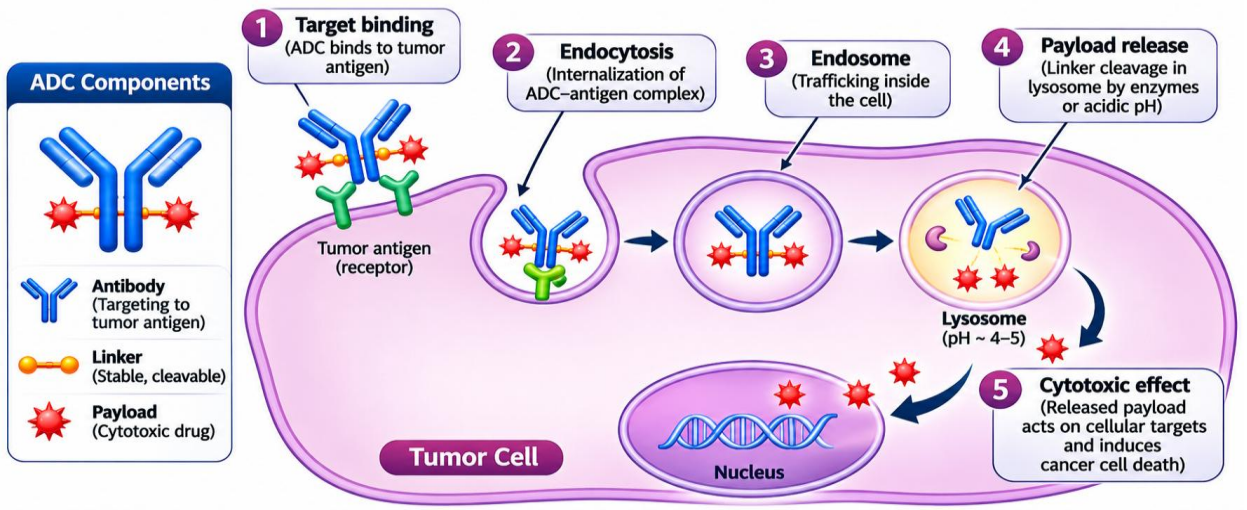


Figure 3. Generalized intracellular trafficking and payload-release pathway of a conventional ADC.[16]

The drug-to-antibody ratio represents the average number of payload molecules attached to each antibody molecule. Increasing DAR can increase the amount of drug delivered per antibody, but excessive loading may increase hydrophobicity, aggregation, clearance and toxicity. The optimal DAR depends on payload properties, linker architecture, antibody format and the biological target. Average DAR alone is insufficient to describe a heterogeneous product; the distribution of individual drug-loaded species and the location of conjugation sites are also important [21].

VI. RECENT ADVANCES IN LINKER CHEMISTRY

4.1 Cleavable linkers

Cleavable linkers are designed to respond to biological or chemical conditions that are more prominent within tumour cells or intracellular compartments than in plasma. Protease-cleavable linkers commonly use peptide sequences recognized by lysosomal enzymes such as cathepsins. The valine–citrulline sequence is widely used in clinically validated ADCs and is often combined with a PABC self-immolative spacer. Following enzymatic cleavage, the spacer undergoes a rearrangement that releases the unmodified payload. The performance of this system depends on enzyme accessibility, peptide stability, steric effects and the chemical structure of the payload [17].

Acid-sensitive linkers exploit the lower pH of endosomes and lysosomes relative to blood. Hydrazone-containing systems have been used in early ADC designs, including calicheamicin-containing conjugates. However, acid-labile chemistry can be associated with premature cleavage under some conditions, and the stability–release balance must be optimized for each construct. Disulfide linkers use differences in reducing conditions and intracellular thiol concentrations to facilitate payload release. Their behaviour is influenced by steric shielding, linker substitution and the accessibility of the disulfide bond [18].

4.2 non-cleavable linkers

Non-cleavable linkers are designed to remain attached to the payload until the antibody is internalized and

degraded in lysosomes. The active species released is commonly a drug-containing amino-acid or linker–drug catabolite rather than the free payload. This strategy can provide high plasma stability and has been clinically validated by trastuzumab emtansine, which uses a non-cleavable thioether linker. The biological activity of the catabolite, its ability to cross membranes and the efficiency of lysosomal processing are important determinants of efficacy [6,18].

4.3 Self-immolative spacers and hydrophilic linkers

Self-immolative spacers enable the release of a chemically unmodified payload after an initial trigger event. PABC is a widely used example in which enzymatic cleavage initiates a subsequent elimination reaction. Newer designs seek to improve release kinetics, minimize residual linker fragments and accommodate payloads with different functional groups. Hydrophilic elements such as polyethylene glycol, charged groups, carbohydrates or zwitterionic motifs can be introduced to counteract payload-associated hydrophobicity. These modifications may reduce aggregation and improve solubility, although their effect on tumour penetration, clearance and release must be assessed experimentally [26].

4.4 Linker selection and critical quality attributes

Linker selection should be based on the complete ADC rather than on cleavage chemistry alone. Relevant attributes include plasma stability, intracellular release rate, chemical compatibility, hydrophilicity, conjugation yield, residual free drug, aggregation, stability during storage and scalability. A linker that releases payload efficiently in vitro may still perform poorly in vivo if it is unstable in circulation or produces an inactive catabolite. Linker optimization therefore requires orthogonal analytical methods and suitable biological models [7].

Table 1. Major linker classes used in ADC development and their design considerations.[8]

Linker class	Typical trigger / release principle	Potential advantages	Key limitations
Protease-cleavable peptide	Lysosomal protease cleavage; often followed by self-immolation	Intracellularly directed release; broad clinical validation	Enzyme variability; premature cleavage risk depends on sequence and context
Acid-labile	Hydrolysis under acidic conditions	Can exploit endosomal/lysosomal acidity	Potential instability in circulation or formulation
Disulfide / reduction-sensitive	Reduction or thiol-mediated cleavage	Can respond to intracellular reducing environment	Release may depend on steric accessibility and redox conditions
Non-cleavable thioether	Antibody degradation generates active drug-linker catabolite	Often high systemic stability	Requires efficient internalization and lysosomal processing
Hydrophilic / advanced spacer systems	Solubilizing motifs modify physicochemical behaviour; may be paired with cleavable triggers	Can reduce hydrophobicity and improve developability	Added complexity; effect on PK and tumour penetration must be established

V. PAYLOAD DESIGN AND EMERGING CYTOTOXIC AGENTS

Payload selection is central to ADC development because the antibody generally delivers a limited number of drug molecules to each target cell. Consequently, payloads often require very high intrinsic potency, suitable chemical functionality for conjugation and sufficient stability during circulation. An ideal payload should retain activity after release, possess a manageable safety profile and be compatible with the selected linker and conjugation chemistry. The payload should also be considered in relation to tumour growth rate, target distribution and resistance mechanisms [19].

5.1 Microtubule inhibitors

Auristatins, including monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), are synthetic derivatives of dolastatin-related compounds that disrupt microtubule dynamics. Interference with tubulin function causes mitotic arrest and can initiate apoptosis. MMAE is relatively membrane permeable and may contribute to bystander killing after release, whereas the charged MMAF derivative generally exhibits lower membrane permeability. Maytansinoids such as DM1 and DM4 also disrupt microtubule function and have been incorporated into

clinically established ADCs. The distinct physicochemical properties of these payloads influence linker selection, intracellular activity and toxicity [27].

5.2 DNA-damaging payloads

Calicheamicin derivatives bind to DNA and induce strand cleavage through a highly potent oxidative mechanism. Pyrrolobenzodiazepine dimers form DNA interstrand crosslinks, interfering with DNA replication and transcription. Other DNA-damaging payloads, including duocarmycins, have been explored to increase potency or provide alternative mechanisms. These agents can be effective at very low intracellular concentrations, but their extreme potency requires careful control of systemic exposure and release [20].

5.3 Topoisomerase-I inhibitors

Topoisomerase-I inhibitor payloads have become a major class in contemporary ADC development. SN-38, the active metabolite of irinotecan, and deruxtecan (DXd), a camptothecin-derived payload, interfere with topoisomerase-I-mediated DNA relaxation and generate replication-associated DNA damage. Their clinical relevance has been demonstrated by ADC platforms such as sacituzumab govitecan and trastuzumab deruxtecan. The membrane permeability of released payloads can support bystander activity, which may be advantageous in antigen-heterogeneous tumours but may also increase exposure of neighbouring normal cells [9,28].

5.4 Emerging payload concepts

The payload landscape is expanding beyond conventional cytotoxic mechanisms. Investigational approaches include immune-stimulatory payloads, toll-like receptor agonists, STING agonists, radiotherapeutic components, protein-degrading agents and other biologically active molecules. These approaches aim to use antibody targeting to concentrate immune activation or alternative pharmacology within the tumour microenvironment. Their development requires careful assessment of payload stability, immune effects, dose-limiting toxicity and the possibility of systemic inflammatory responses [29].

Table 2. Representative payload classes and principal pharmacological actions.[30]

Payload class	Representative payloads	Primary mechanism	Design / delivery consideration
Auristatins	MMAE, MMAF	Disruption of microtubule dynamics	MMAE can support bystander activity; MMAF is less membrane permeable
Maytansinoids	DM1, DM4	Inhibition of microtubule assembly	Linker and catabolite properties influence activity
DNA-cleaving agents	Calicheamicin	DNA strand cleavage	Very high potency; systemic release must be minimized
DNA crosslinkers	PBD dimers, duocarmycins	DNA crosslinking / alkylation	Potency requires tight control of exposure and release
Topoisomerase-I inhibitors	SN-38, DXd	Topoisomerase-I inhibition and replication-associated DNA damage	Often associated with bystander potential; manage payload-related toxicities
Immune-modulating payloads	STING or TLR agonists (investigational)	Activation of innate immune signalling	Requires spatially controlled immune stimulation and safety evaluation

VI. ANTIBODY SELECTION AND CONJUGATION TECHNOLOGIES

Antigen selection is a major determinant of ADC performance. A suitable antigen should be expressed at a sufficient density on tumour cells, accessible to the antibody and ideally restricted in normal tissues. The antigen should remain present during disease progression and should support internalization when intracellular payload release is required. However, high antigen expression does not guarantee clinical response because tumour penetration, receptor turnover, lysosomal trafficking, payload sensitivity and intratumoural heterogeneity also influence outcome [5,22].

Traditional conjugation approaches commonly modify accessible lysine residues or interchain disulfide bonds. These methods are comparatively established but may generate heterogeneous mixtures with different attachment sites and DAR values. Site-specific methods seek to attach payloads at defined positions using engineered cysteine residues, enzymatic reactions, glycan remodelling, unnatural amino acids or selective chemical handles. Better-defined conjugates can improve product consistency and facilitate structure–activity comparisons, although each method introduces specific manufacturing and analytical requirements [30].

The selection of conjugation technology should consider reaction efficiency, antibody integrity, control of DAR, linker compatibility, scale-up, raw-material quality and analytical characterization. Critical analytical attributes include identity, purity, free payload, aggregate content, DAR distribution, conjugation-site occupancy, potency and stability. A successful ADC must be both biologically active and manufacturable to a reproducible quality standard [23].

VII. TARGETED DRUG DELIVERY, TUMOUR PENETRATION AND BYSTANDER ACTIVITY

The principal delivery advantage of ADCs is the ability to use antibody–antigen recognition to concentrate a potent drug at selected cells. Nevertheless, the antibody must travel from the circulation through tumour vasculature and interstitial tissue before reaching its antigen. High-affinity binding near blood vessels can create a binding-site barrier, in which ADC molecules are retained by cells close to the vasculature and penetrate less effectively into deeper tumour regions. Antigen density, antibody affinity, tumour perfusion, interstitial pressure and molecular size can therefore influence distribution [31].

The bystander effect occurs when a released payload exits an antigen-positive cell and enters nearby antigen-low or antigen-negative cells. This may help address heterogeneous antigen expression, a common feature of solid tumours. Bystander activity is influenced by linker cleavage, payload membrane permeability, intracellular release and local tissue conditions. It is not uniformly beneficial: diffusion beyond the intended target compartment may increase damage to neighbouring normal cells. Thus, payload permeability and linker release should be selected according to the expected spatial distribution of antigen within the tumour [32].

Targeted delivery also depends on the intracellular route followed by the ADC. Efficient receptor-mediated internalization and lysosomal processing are often important for conventional ADCs, although extracellular cleavage and alternative delivery mechanisms are being explored. The optimal construct may differ between haematological malignancies and solid tumours because target accessibility, tissue architecture, antigen turnover and the tumour microenvironment are distinct [31].

VIII. CLINICAL APPLICATIONS AND REPRESENTATIVE ADC PLATFORMS

Clinically established ADCs demonstrate the diversity of target antigens, linker systems and payload mechanisms. Brentuximab vedotin targets CD30 and carries MMAE through a protease-cleavable linker. Trastuzumab emtansine targets HER2 and uses DM1 attached through a non-cleavable linker. Gemtuzumab ozogamicin and inotuzumab ozogamicin use calicheamicin derivatives directed against CD33 and CD22, respectively. These products illustrate how target biology and payload mechanism can be matched to haematological or solid tumour indications [33].

More recent clinically important examples include trastuzumab deruxtecan, which targets HER2 and delivers a topoisomerase-I inhibitor payload through a cleavable linker, and sacituzumab govitecan, which targets Trop-2 and delivers SN-38. Enfortumab vedotin targets nectin-4 and delivers MMAE, while mirvetuximab soravtansine targets folate receptor alpha and delivers the maytansinoid DM4. These products have contributed to the expansion of ADC treatment across breast, lung, urothelial, ovarian and other malignancies. Their approved indications vary by jurisdiction and may change; prescribing information should therefore be consulted for current clinical use [34].

Clinical activity must be interpreted alongside safety. ADC toxicities may arise from target expression in normal tissues, premature payload release, uptake by non-target cells, Fc-mediated processes or the intrinsic pharmacology of the payload. Examples of clinically relevant adverse events across ADCs include

peripheral neuropathy, myelosuppression, hepatotoxicity, ocular toxicity, interstitial lung disease/pneumonitis and gastrointestinal effects. The pattern and severity are product-specific, and monitoring recommendations should follow the relevant product label [35].

Table 3. Selected clinically established ADCs and their design features (illustrative, not a complete global approval list).[35]

ADC	Target	Payload	Linker / conjugation feature	Representative clinical context
Brentuximab vedotin	CD30	MMAE	Protease-cleavable peptide linker	CD30-positive lymphomas
Trastuzumab emtansine (T-DM1)	HER2	DM1	Non-cleavable thioether linker; lysine conjugation	HER2-positive breast cancer
Gemtuzumab ozogamicin	CD33	Calicheamicin derivative	Acid-labile hydrazone-containing linker	Acute myeloid leukaemia
Inotuzumab ozogamicin	CD22	Calicheamicin derivative	Acid-labile hydrazone-containing linker	B-cell acute lymphoblastic leukaemia
Trastuzumab deruxtecan	HER2	DXd	Cleavable peptide linker; high average DAR	HER2-expressing solid tumours; indication-specific
Sacituzumab govitecan	Trop-2	SN-38	Hydrolysable linker architecture	Trop-2-expressing epithelial cancers
Enfortumab vedotin	Nectin-4	MMAE	Protease-cleavable peptide linker	Urothelial carcinoma
Mirvetuximab soravtansine	FRα	DM4	Cleavable disulfide-containing linker	FRα-positive ovarian cancer

IX. RESISTANCE MECHANISMS AND SAFETY CHALLENGES

Resistance to ADCs can occur at several stages of the delivery pathway. Tumour cells may reduce or lose target-antigen expression, alter antigen accessibility, decrease internalization or redirect internalized ADCs away from productive lysosomal processing. Changes in lysosomal function may reduce payload liberation, while increased expression of drug-efflux transporters can lower intracellular payload concentration. Alterations in tubulin, topoisomerase-I, DNA-damage responses or apoptotic signalling may further reduce sensitivity to particular payload classes [23].

Toxicity is influenced by the antibody target, linker stability, payload class, DAR, conjugation distribution and patient-related factors. On-target/off-tumour toxicity can occur when the antigen is present in healthy tissues. Off-target toxicity may result from premature release of free payload or non-specific uptake of the conjugate. Payload-related adverse effects may also occur even when the ADC is appropriately targeted, because a fraction of the administered dose can reach non-tumour tissues or undergo systemic catabolism [18].

The development of safer ADCs requires integrated evaluation of pharmacokinetics, tissue distribution, free payload exposure, target expression in normal organs, immune responses and organ-specific toxicity. Biomarker strategies should consider not only antigen positivity but also antigen density, spatial heterogeneity, internalization and relevant resistance mechanisms. Combination therapy may improve activity in selected settings, but it can also compound toxicity and should be supported by clinical evidence [22].

X. RECENT ADVANCES AND FUTURE PERSPECTIVES

Next-generation ADC design is moving towards greater molecular homogeneity, tunable drug loading and rational control of payload release. Site-specific conjugation can reduce variability in attachment position and DAR distribution, while hydrophilic linkers and spacer engineering may improve the developability of constructs carrying hydrophobic payloads. These technologies offer opportunities to improve pharmacokinetics and therapeutic index, but their value must be established for each antibody–linker–payload combination rather than assumed from chemical novelty alone [26].

Payload diversification is another important direction. New cytotoxic mechanisms may overcome resistance to established microtubule or topoisomerase inhibitors, while immune-modulating payloads may

help reshape the tumour microenvironment. Bispecific antibodies, biparatopic formats and alternative antibody fragments are being explored to improve antigen engagement, internalization or tumour penetration. These approaches add molecular and manufacturing complexity and require careful assessment of stability, immunogenicity and biological activity [30].

Computational approaches may support antigen selection, linker–payload matching, prediction of conjugate developability and analysis of clinical response. Machine-learning methods can integrate molecular descriptors, antigen expression, pharmacokinetic data and toxicity outcomes; however, their predictive value depends on the quality, representativeness and standardization of the underlying datasets. Experimental validation and clinical evidence remain essential [36].

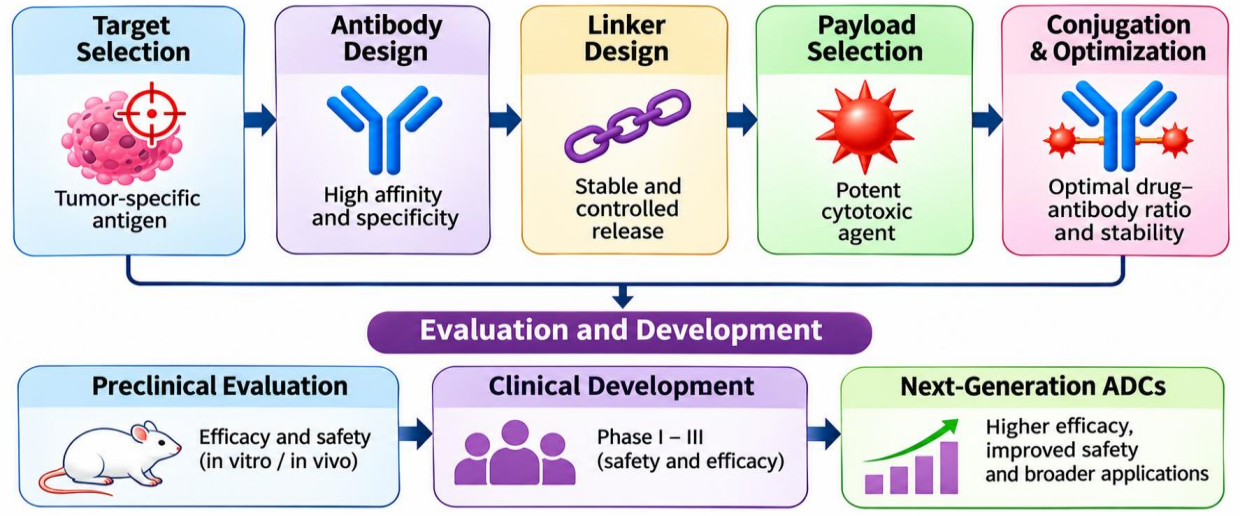


Figure 4. Integrated design and optimization workflow for next-generation ADC development.[35]

Future ADC development should prioritize a translational framework that links target biology to molecular design, analytical characterization, nonclinical pharmacology and biomarker-informed clinical evaluation. The most effective design may not maximize payload potency or DAR in isolation; it should instead balance tumour delivery, intracellular drug release, bystander activity, systemic stability, tolerability and manufacturability. This integrated approach is likely to be central to improving the consistency and clinical value of ADCs [37].

XI. CONCLUSION

Antibody–drug conjugates have become an important therapeutic platform by combining antibody-mediated target recognition with the potent pharmacology of small-molecule drugs. Their performance is determined by the coordinated optimization of antibody, linker, payload, conjugation site and target biology. Advances in protease-sensitive and non-cleavable linkers, self-immolative spacers, hydrophilic linker architectures, site-specific conjugation and topoisomerase-I inhibitor payloads have broadened the possibilities for targeted drug delivery. At the same time, tumour heterogeneity, limited penetration, acquired resistance, off-target toxicity and manufacturing complexity remain important challenges. Future progress will require rational molecular design, robust analytical control, biomarker-guided patient selection and careful clinical evaluation. ADCs should therefore be viewed not as a single technology but as a versatile and evolving family of precision medicines whose therapeutic index depends on the quality of the complete molecular system [12].

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