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Next Generation Antibody–Drug Conjugates: Molecular Design Innovations And Overcoming Resistance – A Comprehensive Review

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ABSTRACT

Antibody–drug conjugates (ADCs) represent one of the most transformative advances in targeted cancer therapy, combining the high specificity of monoclonal antibodies with the potent cytotoxic activity of small-molecule drugs. While first- and second-generation ADCs have yielded significant clinical benefit, therapeutic resistance, limited payload delivery, and off-target toxicity remain major barriers. Next-generation ADCs integrate innovations in antibody engineering, linker chemistry, payload diversification, and site-specific conjugation technologies to enhance stability, therapeutic index, and tumour selectivity. Further, the emergence of antibody–drug conjugate combinations, immune-stimulating ADCs, and conditionally activated ADCs is reshaping clinical strategies. This review discusses current advances in molecular design, mechanisms of resistance, and contemporary approaches to overcome therapeutic limitations, highlighting the future direction of ADC-based oncology.

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INTRODUCTION

Antibody–drug conjugates (ADCs) are complex, hybrid biopharmaceuticals that combine the high specificity of monoclonal antibodies (mAbs) with the potent cytotoxicity of small-molecule drugs. Structurally, an ADC is composed of three interconnected components: a monoclonal antibody that recognises a tumour-associated antigen, a cytotoxic payload capable of inducing cell death at picomolar concentrations, and a chemical linker that ensures controlled, tumour-specific drug release. This rational, modular architecture enables ADCs to selectively deliver potent chemotherapeutic agents to antigen-expressing cancer cells while minimising systemic exposure and toxicity to healthy tissues. The concept of an ADC, therefore, merges principles of immunotherapy, targeted therapy, and traditional chemotherapy into a single therapeutic platform.

The clinical success of first- and second-generation ADCs—such as brentuximab vedotin (targeting CD30) and ado-trastuzumab emtansine (T-DM1, targeting HER2)—validated this approach and catalysed rapid expansion of the field. Since their approval, more than a dozen ADCs have reached the market, and over 100 candidates are in various stages of clinical development. These agents have demonstrated efficacy across a wide spectrum of malignancies, including haematological cancers, breast cancer, urothelial carcinoma, gastric cancer, and lung cancer. Their success highlights the therapeutic potential of delivering ultrapotent cytotoxic molecules with improved selectivity and reduced systemic burden.

However, despite these major advancements, several challenges continue to limit the full therapeutic potential of ADCs. Tumour cells frequently develop intrinsic or acquired resistance through mechanisms such as antigen downregulation, impaired antigen–antibody internalisation, lysosomal dysfunction, and upregulation of efflux transporters that expel the payload. Additionally, antigen heterogeneity within solid tumours often leads to incomplete targeting, reducing overall therapeutic efficacy. On the structural side, early ADCs faced issues including hydrophobic payload-induced aggregation, unstable linkers that released drugs prematurely in circulation, and inconsistent drug-to-antibody ratios (DAR) resulting from random conjugation chemistry. These issues not only reduced the therapeutic index but also contributed to dose-limiting toxicities such as hepatotoxicity, neutropenia,

and peripheral neuropathy.

To address these limitations, next-generation ADCs integrate advances across all three core components. Improvements in antibody engineering—such as bispecific constructs, biparatopic antibodies, and antibody fragments—enhance binding specificity, internalisation rates, and tumour penetration. Innovations in linker chemistry, including conditionally activated, enzyme-cleavable, pH-responsive, and self-immolative linkers, have markedly improved plasma stability and controlled payload release. The diversification of cytotoxic payloads, ranging from microtubule inhibitors to DNA alkylators, topoisomerase I inhibitors, immune-modulating agents, and even protein-degrading PROTAC payloads, has further expanded the therapeutic landscape. In parallel, site-specific conjugation technologies now enable precise DAR control, reducing heterogeneity and improving stability, efficacy, and safety.

Collectively, these advancements define the era of next-generation ADCs—agents designed not only for enhanced potency and selectivity but also to overcome the multifactorial resistance mechanisms seen with earlier constructs. As the field continues to evolve, next-generation ADCs are increasingly positioned as a central component of modern oncology therapeutics.

ARCHITECTURE OF MODERN ADCS

The therapeutic performance of antibody–drug conjugates (ADCs) is fundamentally dictated by the interplay of their three structural components—the antibody, the linker, and the cytotoxic payload. Continuous innovation in each domain has been critical for enhancing specificity, stability, potency, and safety. Next-generation ADCs employ sophisticated molecular engineering to optimise binding, internalisation, intracellular trafficking, and controlled drug release, ultimately improving therapeutic index and overcoming resistance mechanisms seen in earlier designs.

Antibody Component

The antibody portion serves as the targeting scaffold that directs the cytotoxic payload specifically to tumour cells. Early ADCs relied primarily on murine or chimeric antibodies, which carried a high risk of immunogenicity, reducing therapeutic durability. Modern ADCs predominantly employ humanised or fully human monoclonal antibodies, significantly lowering the risk of anti-drug antibody (ADA) responses and improving pharmacokinetic profiles.

Innovations in Antibody Engineering

1. **Bispecific Antibodies (bsADCs):** Bispecific antibodies can bind two distinct antigens simultaneously—such as a primary tumour antigen and a co-expressed surface marker—enhancing avidity and ensuring sustained targeting even when antigen expression is heterogeneous or downregulated. This design is particularly valuable for resistant or heterogeneous tumours where single-antigen targeting is insufficient.
2. **Biparatopic Antibodies:** These antibodies bind two different epitopes on the same antigen, improving internalisation rates and enhancing lysosomal trafficking, ultimately increasing intracellular payload accumulation.
3. **Fragment-Based ADCs (Fab, scFv, Nanobodies):** Smaller antibody formats improve tumour penetration, especially in dense solid tumours with stromal barriers. Nanobody-based ADCs further offer high stability, rapid tissue distribution, and access to less accessible epitopes.
4. **Fc Engineering:** Modifications to the Fc region can modulate half-life (via FcRn interaction), enhance internalisation, or reduce Fc-mediated effector functions to minimise non-specific immune activation.

Together, these innovations expand the versatility, tumour selectivity, and pharmacodynamic precision of ADC therapies.

Linker Chemistry

The linker is the molecular “bridge” connecting antibody to payload and is crucial for balancing plasma stability with efficient intracellular release. Linker design is one of the most rapidly advancing aspects of ADC technology.

Key Categories and Innovations

1. **Enzyme-Cleavable Linkers:** Activated by tumour-associated enzymes such as cathepsin B, β-glucuronidase, and sulfatases, these linkers allow payload release specifically in the lysosomal or tumour microenvironment. They enable potent bystander killing due to their capacity to generate membrane-permeable released drugs.
2. **pH-Sensitive Linkers:** Based on hydrazone or maleic acid derivatives, these linkers exploit the acidic conditions of endosomes and lysosomes (pH ~5–6) to trigger controlled release. While earlier hydrazone linkers suffered from plasma instability, modern analogues have improved specificity.
3. **Self-Immolative Spacers:** These linkers incorporate a cleavage-triggered cascade that cleanly releases the free drug in its active form. They ensure high efficiency of payload liberation after enzymatic or chemical cleavage.
4. **Non-Cleavable Linkers:** These rely on antibody degradation rather than chemical cleavage. Their enhanced stability minimises systemic toxicity but limits bystander killing. ADCs like T-DM1 utilise this mechanism effectively.
5. **Conditionally Activated Linkers:** Next-generation linkers respond to tumour-specific stimuli such as hypoxia, reactive oxygen species (ROS), matrix metalloproteases (MMPs), or glutathione levels, providing exceptional precision in payload release while avoiding premature drug liberation in circulation.

These innovations collectively improve pharmacokinetic stability, tumour specificity, and therapeutic index.

Payload Evolution

The payload determines the cytotoxic potency of the ADC. Traditional payloads were largely limited to microtubule inhibitors such as MMAE and DM1. However, next-generation ADCs now utilise a broader landscape of payloads designed to overcome

drug resistance and target diverse cellular vulnerabilities.

Next-Generation Payload Classes

1. **DNA-Damaging Agents**
   - **Pyrrolobenzodiazepine (PBD) dimers:** Ultra-potent DNA crosslinkers capable of killing quiescent and resistant tumour cells.
   - **Indolinobenzodiazepine (IGN) alkylators:** Highly effective with reduced off-target toxicity.
2. **Topoisomerase I Inhibitors**
   - Deruxtecan and SN-38 payloads exhibit strong bystander effects and are highly effective in solid tumours, especially those with heterogeneous antigen expression.
3. **Immune-Modulating Payloads:** Incorporating STING agonists, TLR agonists, or other immunostimulatory molecules allows ADCs to convert "cold" tumours into "hot" immunogenic environments, enabling synergistic effects with immunotherapy.
4. **Protein Degraders (PROTAC Payloads):** PROTAC-based ADCs deliver degradation-inducing ligands directly into tumour cells to target otherwise "undruggable" proteins. These constructs represent a major frontier in ADC payload design.
5. **Metabolism-Targeting Payloads:** Agents that induce excessive ROS, disrupt mitochondrial respiration, or target tubulin isotypes provide novel mechanisms to overcome resistance to canonical chemotherapy.

Overall, payload diversification expands the spectrum of tumours amenable to ADC therapy and reduces the likelihood of cross-resistance.

Site-Specific Conjugation

Traditional ADCs used random conjugation to lysine or cysteine residues, resulting in heterogeneous mixtures with variable drug-to-antibody ratios (DARs). This heterogeneity compromised stability, efficacy, and safety.

Advances in Precision Conjugation

1. **Engineered Cysteine Residues (THIOMABs):** Site-directed insertion of cysteine residues enables controlled, predictable conjugation, yielding homogeneous ADC populations with defined DAR values and improved stability.
2. **Enzymatic Conjugation Technologies**
   - **Transglutaminase-mediated coupling:** Targets glutamine residues for precise attachment.
   - **Sortase A ligation:** Adds payloads to the C-terminal LPXTG motif.
   - **Glycan remodelling:** Introduces reactive groups into the Fc glycan for uniform conjugation.
3. **Click Chemistry Approaches:** Copper-free azide–alkyne cycloaddition allows rapid, selective, bio-orthogonal conjugation under mild conditions, producing highly stable linkages.
4. **Chemo-Enzymatic Hybrid Methods:** Combine enzymatic specificity with the flexibility of chemical reactions, enabling high precision even with structurally complex payloads.

These advances enhance batch consistency, pharmacokinetics, and therapeutic index, paving the way for safer and more effective next-generation ADCs.

Table 1. Evolution of Antibody–Drug Conjugates (ADCs)

Generation	Key Features	Limitations
First Generation	Random conjugation, unstable hydrazone linkers, and limited payloads	High toxicity, low DAR control
Second Generation	Stable cleavable linkers, MMAE/DM1 payloads, improved mAbs	Drug efflux resistance, antigen heterogeneity
Third Generation (Next Gen)	Site-specific conjugation, conditionally activated linkers, potent DNA payloads	Complex production; emerging resistance
Fourth Generation (Future)	PROTAC payloads, immune-stimulating ADCs, bispecific ADCs	Under investigation

NEXT-GENERATION ADC MODALITIES

Bispecific ADCs (bsADCs)

Targeting two antigens increases tumour selectivity and reduces dependence on a single epitope. Examples under investigation include HER2/HER3 or CD7/CD3 bispecific ADCs.

Immune-Stimulating ADCs (ISACs)

ISACs attach immune-activating payloads instead of classical cytotoxins, stimulating innate immunity and improving immunotherapy response.

Probody ADCs (masked ADCs)

Antibodies are masked with peptides cleaved only in the protease-rich tumour microenvironment, reducing systemic toxicity.

ADC–Radiopharmaceutical Hybrids (Radio-ADCs)
Deliver radionuclides for dual cytotoxic effect and diagnostic imaging.

Antibody–Drug Conjugate Nanoparticles
Nanocarrier-based ADCs improve payload loading and modulate pharmacokinetics.

MECHANISMS OF RESISTANCE TO ADCS
Tumour cells may become resistant through several pathways:

Antigen-Related Resistance
- Downregulation, mutation, or loss of the target antigen.
- Heterogeneous expression across tumour mass.
- Impaired antigen recycling or internalisation.

Linker or Payload-Related Resistance
- Premature linker breakdown or insufficient intracellular cleavage.
- Increased drug efflux (ABC transporters).
- Detoxification pathways (glutathione, aldehyde dehydrogenase).

Tumour Microenvironment (TME)–Derived Resistance
- Hypoxia, high interstitial pressure, and dense stroma limit ADC penetration.
- Stromal cells may sequester ADCs.
- Immune suppression reduces ISAC efficacy.

Intracellular Trafficking Defects
- Impaired endosomal–lysosomal transport.
- Altered autophagy affecting payload release.

Table 2. Mechanisms of ADC Resistance

Mechanism	Description
Antigen Downregulation	Tumour cells reduce antigen density to evade targeting
Efflux Pump Upregulation	ABC transporters efflux payloads (P-gp, BCRP)
Altered Trafficking	Impaired lysosomal transport reduces payload release
Microenvironment Barriers	Hypoxia, fibrosis, poor perfusion
Payload Resistance	DNA repair activation, altered tubulin isoforms

STRATEGIES TO OVERCOME RESISTANCE
Enhanced Antigen Targeting
- Use of **bispecific or biparatopic antibodies**.
- Targeting multiple epitopes on the same antigen.
- Exploitation of **pan-cancer antigens** (HER3, TROP2, B7-H3).

Improved Linker Stability and Conditional Activation
- Protease, ROS, or hypoxia-sensitive linkers ensure tumor-restricted activation.
- Non-cleavable linkers reduce off-target toxicity.

Novel Payloads to Circumvent Efflux
- Topoisomerase-I inhibitors and DNA crosslinkers show reduced efflux susceptibility.
- Use of **dual payloads** with different mechanisms to prevent escape.

Rational Drug-Antibody Ratio Optimisation
- DAR tuning reduces hydrophobicity and improves penetration.

Combination Therapies
- ADC + checkpoint inhibitors (PD-1/PD-L1).
- ADC + PARP inhibitors (synergy with DNA-damaging payloads).
- ADC + anti-angiogenic therapy to enhance tumour perfusion.

Biomarker-Guided Patient Selection
- Quantitative antigen scoring.

- Gene expression signatures predicting internalisation efficiency.
- Companion diagnostics (e.g., IHC, molecular imaging).

Table 3. Strategies to Overcome ADC Resistance

Strategy	Examples
Biparatopic & bispecific ADCs	HER2/HER3; CD7/CD3
Dual payload ADCs	MMAE + DNA payload combinations
Novel linkers	ROS-sensitive, protease-cleavable, self-immolative
Next-gen payloads	PBD dimers, deruxtecan, IGN alkylators
Combination therapy	ADC + checkpoint inhibitors; ADC + PARP inhibitors
Probody (Masked) ADCs	Protease-activated in tumours only

CURRENT CLINICAL LANDSCAPE AND RECENT APPROVALS

Antibody–drug conjugates (ADCs) have transformed oncology by combining the antigen specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule payloads. Over the last decade, rapid advances in linker chemistry, payload potency, and antibody engineering have enabled the approval of multiple next-generation ADCs with improved efficacy and manageable toxicity. Recent FDA approvals and late-stage clinical candidates highlight expanding therapeutic potential across solid tumors and hematologic malignancies.

Breakthrough ADCs

1. Trastuzumab deruxtecan (T-DXd)

- **Target: HER2**
- **Payload: Deruxtecan, a potent topoisomerase I inhibitor.**
- **Key Features:**
  - High DAR (~8) enables delivery of more cytotoxic molecules per antibody.
  - Cleavable tetrapeptide linker that is selectively hydrolyzed in tumor microenvironments rich in lysosomal enzymes.
  - Strong bystander killing effect due to membrane-permeable payload, allowing killing of adjacent low-HER2 cells.
- **Clinical Impact:**
  - Demonstrated unprecedented response rates in HER2-positive metastaticbreast cancer.
  - Showed significant benefits in HER2-low tumors, redefining HER2 biology and expanding patient populations.
  - Approved for breast, gastric, and HER2-mutant lung cancers.

2. Sacituzumab govitecan

- **Target: TROP-2**
- **Payload: SN-38, the active metabolite of irinotecan.**
- **Key Features:**
  - Utilizes a hydrolyzable, moderately stable linker allowing controlled release of SN-38.
  - Higher DAR (~7.6) compared to earlier ADCs.tumours
  - Capable of bystander killing, increasing efficacy in heterogeneous tumors.
- **Clinical Impact:**
  - Approved for metastatic triple-negative breast cancer (TNBC) and HR-positive/HER2-negative breast cancer.
  - Demonstrated survival benefit in heavily pretreated patient groups.

3. Enfortumab vedotin

- **Target: Nectin-4**
- **Payload: MMAE (monomethyl auristatin E), a microtubule inhibitor.**
- **Key Features:**
  - Employs a cleavable cathepsin-sensitive linker for selective intracellular release.
  - Strong internalization and potent cell-killing ability.
- **Clinical Impact:**
  - First ADC approved for locally advanced or metastatic urothelial carcinoma post-platinum and immune checkpoint therapy.
  - Demonstrated durable responses across Nectin-4–expressing tumors.

4. Disitamab vedotin (RC48)

- **Target: HER2**
- **Payload: MMAE**
- **Key Features:**

  - Designed for HER2-low and heterogeneous tumors where traditional HER2-targeted therapies show limited efficacy.
  - High internalisation efficiency and favourable pharmacokinetics.
- **Clinical Impact:**
  - Approved in China for gastric cancer.
  - Showing promising activity in HER2-low breast and urothelial cancers, expanding HER2-directed therapy eligibility.

ADCs Under Investigation

Targets Expanding Beyond Traditional Antigens

A diverse range of novel tumour-associated antigens is being exploited to enhance selectivity and overcome resistance to existing therapies:

- **HER3:** Highly expressed in resistant breast and lung cancers. HER3-DKI (patritumab deruxtecan) shows strong efficacy in EGFR-mutant NSCLC.
- **B7-H3:** Broadly overexpressed in solid tumours; ADCs show potent antitumor activity with limited normal tissue expression.
- **TROP2 (next-generation):** Multiple improved TROP2-targeting ADCs with optimised linker–payload combinations are in mid-stage trials.
- **ROR1:** A stem-cell–associated receptor seen in triple-negative breast cancer and leukaemias.
- **GPR20:** Highly expressed in gastrointestinal stromal tumours (GIST), offering a new precision-targeted option.
- **CLDN18.2:** A gastric-specific tight junction protein; several CLDN18.2 ADCs are in early trials for gastric and pancreatic cancers.

Emerging ADC Engineering Concepts

1. Dual-payload ADCs

- Combine two different cytotoxic agents (e.g., DNA-damaging + microtubule-inhibiting) to:
  - Overcome multidrug resistance
  - Target diverse tumor subpopulations
  - Prevent adaptive resistance pathways
- Examples include MEDI4276, SYD985, and novel proprietary platforms under translation.

2. Bispecific ADCs

- Use dual-antigen recognition to enhance tumor selectivity.
- Advantages include:
  - Better uptake in antigen-low tumors
  - Reduced off-target binding
  - Synergistic receptor clustering leading to enhanced internalization
- Early candidates target combinations such as HER2 × HER3, TROP2 × CEACAM5, and EGFR × MET.

3. Site-specific and homogeneous ADCs

- Ensure uniform DAR and controlled pharmacokinetics.
- Reduce premature payload release and systemic toxicity.
- Platforms include THIOMAB, engineered cysteine, enzymatic conjugation, and click chemistry.

FUTURE DIRECTIONS IN ADC DEVELOPMENT

Conditional Activation Approaches

Modern ADCs are increasingly designed to remain *inactive* in circulation and become activated only within the tumor microenvironment (TME). This strategy enhances tumor specificity and reduces systemic toxicity.

• Protease-Activated ADCs

- Tumors often overexpress proteases such as cathepsin B, MMPs, or ADAM family enzymes.
- ADCs with protease-cleavable linkers (e.g., Val-Cit, Gly-Phe) remain stable in blood but release the payload only when cleaved by tumor proteases.
- This limits off-target exposure and improves therapeutic index.

• Hypoxia-Activated ADCs

- Solid tumors exhibit low oxygen levels, which can be exploited using hypoxia-sensitive linkers (e.g., nitroimidazole-based linkers).
- These linkers undergo reduction only in hypoxic zones, triggering payload release where conventional therapies often fail.

• Light-Triggered ADCs

- Incorporate photo-cleavable linkers or photoactivatable moieties.

- External light (e.g., near-infrared) can precisely activate the ADC in superficial tumors or endoscopically accessible sites.
- Enables spatial control, minimizing healthy tissue exposure.

Integration with Synthetic Biology

Synthetic biology approaches are pushing ADCs beyond traditional protein conjugates, enabling programmable and interactive therapies.

• "Living Drug Factories" – CAR-T + ADC Hybrid Platforms

- Engineered CAR-T cells can be programmed to secrete ADC-like molecules, such as antibody–toxin fusions, only when they encounter tumor antigens.
- This turns immune cells into *localized drug producers*, reducing systemic exposure to cytotoxic agents.
- Alternatively, CAR-T cells may be modified to deliver ADC payloads directly into tumors, enhancing depth of penetration in solid tumors where CAR-T therapies usually underperform.

• Microbial Synthetic Biology

- Engineered bacteria capable of homing to hypoxic tumor regions can release nanobody-linked cytotoxins, functioning as "smart delivery vehicles" for ADC-like payloads.

PROTAC-ADCs (Targeted Protein Degradation ADCs)

A disruptive new ADC generation replaces traditional cytotoxic payloads with PROTACs (Proteolysis-Targeting Chimeras).

How They Work

- Instead of killing cells, PROTAC-ADCs trigger selective degradation of disease-driving proteins.
- PROTACs recruit E3 ubiquitin ligases to tag target proteins for proteasomal destruction.
- When delivered via an ADC, PROTACs can selectively degrade oncogenic drivers (e.g., HER2, BCL-xL, AR).

Advantages

- Effective even against non-dividing cells, unlike conventional cytotoxic payloads.
- Can overcome resistance arising from mutations that reduce sensitivity to chemotherapy.
- Lower risk of widespread toxicity since degradation is limited to antigen-positive cells.

Status

- Early-stage preclinical programs show promise in breast cancer, prostate cancer, and hematologic malignancies.

AI-Driven ADC Design

Artificial intelligence and machine learning (ML) are now central to ADC development, enabling rapid optimization of structure–activity relationships.

Applications of AI in ADC Engineering

1. **Linker Optimization**
   - Predicts linker stability, cleavability, hydrophobicity, and release kinetics.
   - Helps design tumor microenvironment–responsive linkers.
2. **Payload Selection**
   - ML algorithms screen libraries of cytotoxins to identify candidates with optimal potency, permeability, and metabolic stability.
3. **Antibody Internalisation Modelling**
   - Predicts antigen density, endocytosis rates, trafficking patterns, and recycling pathways.
   - Helps select optimal targets and antibody clones.
4. **TME-Responsive Trigger Design**
   - AI models mimic tumour conditions (pH, enzymes, ROS, hypoxia) to propose conditional activation elements.
5. **DAR and Conjugation Site Prediction**
   - In silico design ensures optimal DAR and homogeneous conjugation sites to improve pharmacokinetics.

Impact

AI dramatically reduces the time needed for discovery, enables personalized ADC design, and accelerates identification of best-in-class candidates by simulating thousands of conjugation strategies.

CONCLUSION

Next-generation ADCs represent a paradigm shift in precision oncology, integrating advances in antibody engineering, linker chemistry, and payload innovation. By addressing the core limitations of earlier designs—poor stability, heterogeneous conjugation, limited penetration, and treatment resistance—new ADCs offer improved therapeutic index and durable responses. Continued progress will emerge from biomarker-informed patient selection, rational combination therapies, and novel payload modalities such as immune activators and protein degraders. As these innovations mature, ADCs are poised to become foundational therapies across a wide spectrum of cancers.

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