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Next Generation Antibody Drug Conjugates: Molecular Design Innovations and Overcoming Resistance

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ABSTRACT
Antibody drug conjugates (ADCs) represent the relevant merger between targeted therapy and cytotoxic pharmacology, which supports the targeted destruction of cancerous cells as a result of antibody-mediated identification of antigens attached to tumors. This effect is also central to the engineering of antibodies, linker stability, and an additional benefit of payload design based on the requirements of target sites, which have generally increased the precision and safety of ADCs in cancer biology. Nonetheless, the issues of resistant mechanisms, non-homogeneous expression of antigens, and inefficient intracellular delivery keep affecting their clinical performance.
We selected a systematic review of the recent developments in next-generation ADC development in this review, with a particular focus on site-specific conjugation innovations, adaptive linker technologies, and dual-payload structures to surpass tumor heterogeneity and drug resistance. Furthermore, we discussed the newly emerging artificial intelligence (AI) based molecular modeling and computational optimization that assist in the creation of potential ADCs by enhancing payload-antibody integration. As a set, these interdisciplinary advances augment the ability of ADCs to be translational by shedding light on the realization of more efficient, adaptive, and patient-centered therapeutic solutions in oncology.

Introduction

ADCs represent a revolutionary type of biopharmaceuticals, which combine highly selective monoclonal antibodies with potent cytotoxic small molecule scaffolds. This design enables the selective destruction of cancer cell with the capability to spare the destruction or even death of the healthy tissues. ADCs are now found in at least 19 available worldwide as of 2025, with more than 20 years of FDA approval history of gemtuzumab ozogamicin, targeting breast, urothelial, gastric, lymphoma, and non-small-cell lung cancer [1].

The recent approvals, such as trastuzumab deruxtecan (Enhertu) and sacituzumab govitecan (Trodelvy) inform about the necessity of improved conjugation chemistries and optimal linker designs to achieve enhanced therapeutic effects and safety. Indicatively, the improved linker-payload design of trastuzumab deruxtecan enables efficient delivery of the drug and a robust bystander effect in tumors

expressing HER2, thus leading to considerable survival improvements in advanced breast cancer patients [2].

The majority of contemporary ADCs employ humanized or entirely human antibodies with high target affinity and stability, and have cleavable or non-cleavable linkers that liberate the payload into the cancer cells selectively [3]. The site specific conjugation methods have also been established so that more uniform ADC candidates with well controlled drug to antibody ratios can be produced, thereby allowing improvement of pharmacokinetic parameters with reduced toxicity can be accomplished [4].

The effect of antigen heterogeneity, defective internalization, drug efflux, and poor lysosomal obstruction are all potential resistance mechanisms that can impair ADC efficacy. Toxicity dose limitations, especially in the hematologic and hepatic systems, also require careful molecular engineering that will enable an improved expansion of the therapeutic range. These issues have led to the generation of ADCs of the next-generation such as dual-payload constructs, bispecific antibodies, and AI-assisted design approaches to enhance efficacy by overcoming resistance [5].

The issue of molecular refinement directed by computational modeling, aimed at transforming the cytotoxicity of ADCs to future clinical advantage, not only over the broad range of cancers but also in non-oncology contexts is being pursued by researchers [6].

Basic Components and Mechanism of Action of ADCs

ADCs are advanced biopharmaceuticals composed of three primary components: an antibody, a linker, and a cytotoxic payload. Each element plays a crucial role in ensuring the specificity, stability, and efficacy of the therapeutic agent [7].

The Antibody

The antibody is used as a targeting carrier, which is usually a monoclonal antibody with a high degree of affinity and specificity to an antigen on a specific tumor [8]. They are produced in mammalian systems like Chinese hamster ovary (CHO) cells to develop these antibodies to maintain the correct binding and post-translational modification. When it is administered intravenously, the antibody is in the bloodstream until it identifies and interacts with its specific antigen, which is mainly found on cancerous cells.

The Linker

The connecting object is the one that links the antibody with the cytotoxic payload. Its significant role is to provide stability during circulation, prevent premature release of the drug, and release its payload at the targeted tumor sites with high efficiency. These linkers become stimuli-responsive, cleaving under possible intracellular conditions, e.g., acidic pH, enzymatic activity (e.g., Cathepsin B) or reductive environment. Depending on the conjugation chemistry, different conjugation chemistries can be employed to conjugate the linker to reactive amino acid residues like cysteine or lysine on the antibody [9].

The Payload

The cytotoxic agent is a strong payload, and it is highly toxic when not combined with other agents. It is therefore linked to antibodies to cause the cancerous cells to die. Payloads are chosen due to their capacity to interfere with essential cellular processes, e.g., microtubule dynamics, DNA integrity, or immune modulation. The payload used affects the cell-killing mechanism and the general efficacy of the ADC as a therapeutic agent [10]..

Mechanism of Action

The typical mechanism involves several sequential steps [11]:

1. **Target Binding:** The antibody component detects and binds to a specific antigen expressed on the surface of a tumor cell.
2. **Intracellular Uptake:** The ADC-antigen complex is incorporated into cells through endocytosis, forming an intracellular vesicle.
3. **Linker Cleavage and Payload Release:** In the tumor cell, the linker is cleaved through enzymatic activity or the microenvironmental conditions, releasing the cytotoxic payload.
4. **Cell Death:** The released payload counteracts with intracellular targets, inducing apoptosis or cell cycle arrest, thereby killing the cancer cell.

In some cases, particularly with cleavable linkers, payloads can diffuse into neighboring cells, exhibiting a bystander effect, further enhancing tumor eradication.

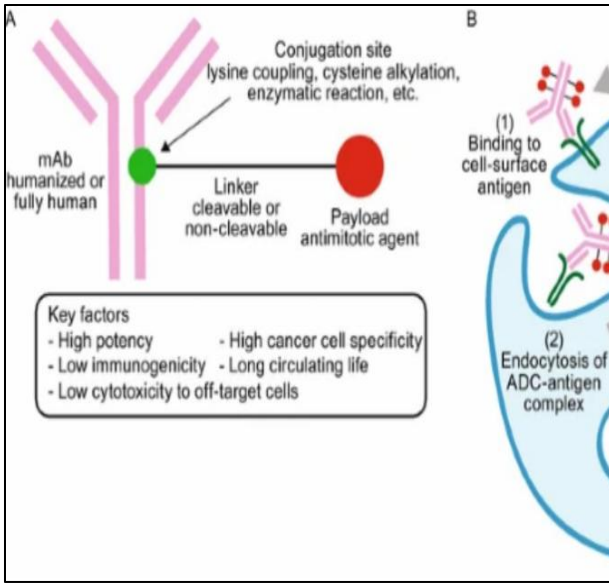

Fig.1: Mechanism and key components of antibody ADCs illustrating targeted delivery, cellular uptake, payload release, and cancer cell killing.

Linker Chemistry in Antibody–Drug Conjugates

The linker in an ADC plays a pivotal role by connecting the monoclonal antibody to its cytotoxic payload. It is a key element of the ADC's therapeutic performance, as it maintains balance, ensuring stability in the bloodstream to prevent premature drug release while allowing efficient release of the cytotoxin upon the cellular uptake of the ADC by the target cells [12].

Classification of Linkers

Linkers are broadly classified into cleavable and non-cleavable classes based on their release mechanism [13]:

1. The cleavage linkers are made in such a way that they react to certain conditions in the intracellular tumor cells. Such stimuli are acidic pH, high levels of enzyme activity (especially, lysosomal cathepsin B) as well as redox alterations related to increased glutathione concentration in cancer cells. The hydrazone linkers are acid-sensitive to promote pH-dependent cleavage, with the limitation of early degradation in plasma, which is overcome by using them primarily through hematologic cancers. The reductive environment of tumors exploits the application of disulfide linkers, which can be selectively released with increased intracellular glutathione. Intracellular proteases cleave enzyme-sensitive peptide linkers, including valine-citrulline dipeptides, which provide high specificity and the foundation of a number of clinically approved ADCs [14].

2. Non-cleavable linkers, on the other hand, create a stable covalent bond between the antibody and payload, propagating the entire proteolytic degradation of the antibody within the lysosome for drug release. This approach generally results in a payload-linker complex that remains inside the cell, improving plasma stability and minimizing off-target effects. A well-known example is the SMCC linker used in ado-trastuzumab emtansine, which has been widely applied in the treatment of solid tumors [15].

Conjugation Strategies and Linker Design Considerations

The bioconjugation technique is the essential element of ADC technology and can often be called the main structural backbone. Traditional conjugation on the antibody cysteine (thiol) or lysine (ε-amino) residue side chains (through maleimide or amide coupling) is the prevalently employed method [16]. Depending on the number of available residues typically present on a mAb (80–90 for lysine, 40 of which are generally modifiable, and 8 total disulfide bonds), the probable random payload coupling rationally produces variable DARs (0–8). Though these structural similarities possess potential advantages of relatively quick reaction kinetics, the inherent heterogeneity of the obtained ADC conjugates develops different therapeutic indices, PK, and stability profiles [17]. Moreover, the second notable weakness of the conjugates made with maleimides is that they are prone to retro-Michael deconjugation and early release of the payload when thiols are present in the blood. These restrictions have been sufficiently blamed in the event of clinical failures, which can result in the withdrawal of a few compounds [18].

The conjugation strategies provide insight into the reactive sites of the antibody, which can be lysine residues or designed cysteines. Site-specific conjugation with engineered cysteines provides more accurate control of drug loading to generate more stable ADC candidates. This

will enhance the pharmacokinetics and decrease the chance of immunogenicity relative to traditional, random lysine-based conjugation [19].

Linker designs mainly use hydrophilic spacers, such as polyethylene glycol (PEG) chains, to increase solubility and minimize aggregation. The chemical characteristics of the linker, including its length, flexibility, and charge, further influence ADC stability, circulation time, and the efficiency of intracellular transportation [20].

Table 1: Different types of linkers and their applications [21].

Linker Type	**Examples**	**Applications**	**Limitations**
Cleavable Linkers			
Acid-Sensitive (Hydrazone)	Gemtuzumab ozogamicin, Inotuzumab ozogamicin	Used in hematologic malignancies; payload release triggered by acidic lysosomal pH	Premature hydrolysis in plasma; limited stability
Disulfide Linkers	Brentuximab vedotin	Payload release triggered by an intracellular reductive environment (glutathione)	Susceptible to premature cleavage; less stable in circulation
Peptide Linkers (e.g., Val-Cit, Ala-Ala)	Brentuximab vedotin, Polatuzumab vedotin	Lysosomal enzyme (cathepsin B)-mediated cleavage; effective in many solid tumors	Possible variability in enzyme expression impacting efficacy
Non-Cleavable Linkers			
Thioether Linkers	Ado-trastuzumab emtansine	Stable bond; payload released after antibody degradation; enhanced plasma stability	Payload remains conjugated to linker residue; potentially altered intracellular behavior
Maleimidocaproyl (MC)	Brentuximab vedotin	Stable linker chemistry, improved pharmacokinetics	Requires complete proteolytic degradation for payload release
Other Innovations	Platinum-based conjugations	Site-specific, high stability conjugation	Limited but promising in preclinical phases

Payload Diversification and Novel Strategies in ADCs

1. Tubulin Inhibitors

Early ADCs mainly used tubulin inhibitors like auristatins (MMAE) and maytansines (DM1). By disrupting microtubules, they inhibit cell division and induce cancer cell death, with high potency at a very small or even nanomolar range. These payloads laid a solid foundation for many advanced ADCs [22].

2. DNA-Damaging Agents

DNA-targeting payloads, including pyrrolobenzodiazepines (PBDs) and calicheamicins, produce DNA cross-links or break the strands and are highly potent even at smaller concentrations [23]. They are especially useful against resistant tumors, as seen with the PBD-based ADC, loncastuximab tesirine. Topoisomerase inhibitors, such as exatecan derivatives used in trastuzumab deruxtecan, block DNA replication and transcription, showing strong clinical activity in HER2-positive breast cancer [24].

3. Immunomodulatory Payloads

There are ADCs that have gained the ability to integrate cytotoxicity with immune activation.

Toll-like receptor (TLR) and STING agonists have the ability to alter the tumor microenvironment's shape and enhance the antitumor immune response, providing a two-fold approach to cancer control [25].

4. Dual-Payload ADCs

Dual-payload ADCs are cytotoxins with different mechanisms that are conjugated to a single antibody, and they attack multiple pathways in cells simultaneously. This approach will enable it to defeat tumor heterogeneity and drug resistance that are common with other conventional measures. The optimization of the drug-to-antibody ratio (DAR) should be performed carefully to achieve efficacy and safety. According to preclinical investigations, it is probable that dual-payload ADCs can be superior than single-payload ADCs or traditional combination therapies [26].

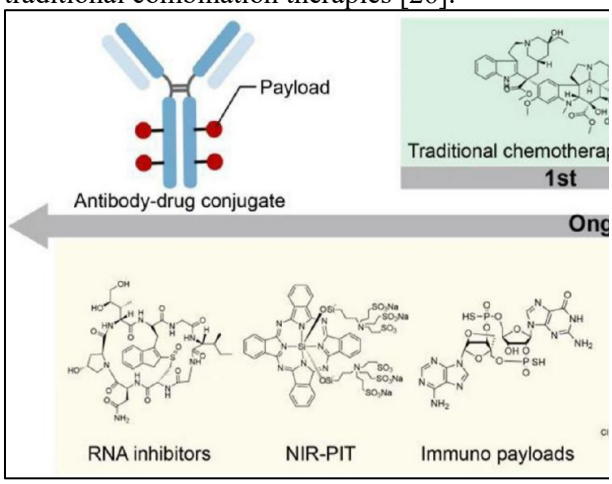

Fig.2: Evolution and Diversification of Antibody–Drug Conjugate (ADC) Payloads

Advances in Site-Specific Conjugation

The current trends in ADC technology are centered on site-specific conjugation; hence, specific payloads are attached to particular sites with high accuracy on the antibody. This approach decreases the variations observed in the case of traditional random conjugation, whereby more homogeneous ADCs are produced with similar proportions of drugs and antibodies (DARs) [27]. The higher the homogeneity, the better the pharmacokinetics, bioavailability, and safety. Approaches frequently adopted include enzymatic conjugation, where enzymes such as transglutaminase are used, genetic engineering to, in effect, add reactive cysteine residues, and special chemical reactions that are site-specific. These methods have also been found to be important and reproducible in preclinical and clinical applications, resulting more controlled ADC production [28].

Innovations in Linker Chemistry

In the design of linkers, advancements have focused on obtaining delivery of the payload in a more selective and precise manner to tumor environments. Recent linker generations are designed to react to a particular intracellular signal like acidic pH, enzyme (cathepsin B) or reducing environment, which allows regulated release of the payload into cancer cells. These linkers are multi-stimuli-responsive and improve therapeutic efficacy without compromising stability in the bloodstream, while reducing off-target effects [29]. Additionally, adding hydrophilic spacers enhances solubility, decreases aggregation, and improves the overall therapeutic index.

Artificial Intelligence in ADC Design

The use of artificial intelligence (AI) and machine learning is already becoming a very prevalent technique in the engineering of antibody-drug conjugates (ADCs) [30]. These technologies assist investigators in confirming the most appropriate combinations of antibodies, linkers, and payloads, and also foresee future immune responses and the actions of the drug in the body. Rather than solely relying on trial and-errorexperiments, AI can be used to design and test ADC candidates more quickly and efficiently. It is able to determine the intimate correlation between the molecular structure and function, proposing the ideal ratio of drug to antibody to reduce the potential off-target effects. One such example is the use of AI models to predict linker stability and payload release efficacy, which helps to select ADC constructs with a better therapeutic window [31]. As a tool to make decisions based on the evidence of the data, AI is capable of accelerating the development process and enhancing the safety and efficacy of new ADCs, which makes it a crucial component of contemporary cancer drug design.

Clinical Translation of Next-Generation ADCs

Next-generation ADCs, including telisotuzumab vedotin and datopotamab deruxtecan, are showing promising results in cancers that are poorly responsive to conventional treatments, such as non-small-cell lung cancer and hormone receptor-positive breast cancer [32]. These outcomes reflect improvised antibody design, more stable linkers, and diverse payload strategies, including dual-payload and immune-activating agents that often can provide

promising benefits to patients. Such successes illustrate the practical impact of these technological advances and shed light on the growing potential of next-generation ADCs to offer new treatment options across a variety of cancers.

Table 2: Comparison of Next-Generation ADCs: Targets, Payloads, and Clinical Status [33].

ADC Name	Target Antigen	Payload Type	Linker Type	C M
Telisotuzumab vedotin	c-Met	Microtubule inhibitor	Cleavable peptide	S cy
Datopotamab deruxtecan	TROP2	Topoisomerase inhibitor	Cleavable peptide	S cy
Ado-trastuzumab emtansine	HER2	Maytansinoid	Non-cleavable thioether	R ly
Loncastuximab tesirine	CD19	DNA alkylator (PBD)	Cleavable peptide	S
KH815 (dual-payload)	TROP2	Topoisomerase I inhibitor + RNA polymerase II inhibitor	Dual cleavable	S

Challenges and Limitations of ADC Development

Tumor Heterogeneity and Microenvironment Variability: The variations in antigen expression, tumor shape, and other factors, such as hypoxia, can lower ADC penetration and even prevent the delivery of the payload. Drug efflux pumps and increased DNA repair are also barriers to effectiveness via resistance mechanisms [34].

Toxicity and Safety Issues: The therapeutic window can be narrowed due to off-target uptake, premature payload release, and inherent cytotoxicity;in this case, strict patient monitoring ought to be conducted with correct dosing [35].

Pharmacokinetic and Metabolic Complexity: There are various forms of ADCs, such as intact conjugates, free antibodies, and released payloads, with its own half-lives and distribution patterns. The changes in metabolism and clearance, particularly in patients with liver or kidney disease, complicate the dosing and its effect on clinical outcomes [36].

Manufacturing and Scalability Issues: ADC manufacturing needs a high degree of drug-to-antibody ratio (DAR) and site-specific conjugation. It is still technically complex and costly to ensure that production is consistent in batches and scales without succumbing to quality issues [37].

Analytical and Regulatory Issues: The amount of payload, stability, and post-translational modifications can be measured only with the help of sophisticated analytical tools. Additionally, clinical trials require patient selection based on biomarkers, and regulators that are both vigilant, which may slow development and approval [38].

Patient Selection Limitations: It is also difficult to determine which patients are best suited to respond based on antigen expression, tumor biology, and resistance profiles;these factors may limit the clinical success [39]**.**

Future Perspectives:

The future of antibody-drug conjugates (ADCs) concerns the development of the next-generation payloads, such as new cytotoxic agents, immunomodulators, as well as dual-payload approaches, which can be used to optimize therapeutic efficacy and overcome resistance. The development of more homogeneous and multifunctional ADCs with better pharmacokinetics and safety profiles is being encouraged by improved conjugation methods, including site-specific, dual, or bispecific. Equally, novel designs of linkers, such as multi-stimuli responsive, cleavable, and more stable linkers, are enhancing the release of targeted payloads with reduced off-target toxicity. The use of ADCs in combination with immune checkpoint inhibitors (or other targeted therapies) has potential synergies and the ability to treat refractory tumors. Lastly, the efforts to integrate biomarker-driven and personalized medicine approaches will maximize patient selection, whereby the ADC therapies would be tailored to fit the unique tumor characteristics to achieve the maximum clinical benefits.

Conclusion

Critically assessed in this review how antibody-drug conjugates (ADCs) have developed to be

one of the most promising types of targeted cancer therapy. ADCs provide an opportunity to target cancer cells and avoid healthy tissue destruction by combining the accuracy of monoclonal antibodies with the killing power of cytotoxic drugs. The recent developments in site-specific conjugation, enhanced linker chemistry, and novel payload structures, such as dual- payload and immunomodulatory approaches have significantly increased their stability, selectivity, and overall therapeutic performance. The AI-supported design has also contributed to faster development, whereby optimized combinations are prepared to enhance safety and efficacy. The increasing efficacy of these technologies in clinical oncology is reflected in the already meaningful results in cancers that are commonly hard to treat with next-generation ADCs, including telisotuzumab vedotin and datopotamab deruxtecan.

Nevertheless, a number of obstacles remain on the way to full exploitation of the therapeutic potential of ADCs. Variations in tumor biology, inconsistent microenvironments, tricky pharmacokinetics, and insufficient therapeutic indices still impact the precision of treatment and patient outcomes. The problems associated with manufacturing and mass production also present practical issues requiring strong control and high costs. To efficiently surmount all these obstacles, chemists, biologists, clinicians, and data scientists must work closely to deliver an orientation between molecular knowledge and translational studies, and eventually improve the creation of potential ADCs. In the future, it is likely that the use of innovative strategies will be used to establish safer, more effective, and personalized ADC therapy using bispecific ADCs, smart cleavable linkers, alternative payloads, combination approaches, and biomarker-directed therapy.

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