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Recent advances in antibody–drug conjugates

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Antibody–drug conjugates (ADCs) combine the target specificity of antibodies with the potency of small-molecule drugs. Over the last few years, advances in antibody engineering, site-selective bioconjugation, linker design, and payload development have driven significant clinical success, culminating in multiple FDA approvals. In this opinion piece, we highlight recent innovations that we believe will define the next generation of ADCs, with a particular focus on site-selective conjugation strategies, linker technologies that enable higher drug-to-antibody ratios (DARs), and emerging payload classes with novel mechanisms of action. We also discuss the expanding scope of ADCs beyond oncology and outline key challenges that must be addressed to fully realise their therapeutic potential.

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Introduction

With six new ADCs approved by the FDA since 2020 [1], Antibody–drug conjugates (ADCs) have emerged as one of the most successful examples of how chemical biology can be applied to therapeutic design. Research in the field has matured from simply aiming to produce potent but heterogenous ADCs towards ADCs with greater control over the structure and integration of the roles of each of the components that comprise ADCs (Figure 1).

Early generations of ADCs were hindered by several challenges, including heterogeneous conjugation, insufficient stability in circulation, limited tumour penetration, off-target toxicity, and suboptimal therapeutic windows [2,3]. In our view, many of the recent advances in the field can be understood as systematic efforts to address these limitations through improved molecular control. Integral to this has been the development of new chemical technologies that enable site selective modification of antibodies to afford increasingly homogeneous ADCs, next-generation linker strategies which offer improved stability and tuneable release mechanisms for the ADCs, and the expansion of payloads beyond the core highly cytotoxic molecules such as monomethyl auristatin E (MMAE).

Antibody structure and implications for conjugation

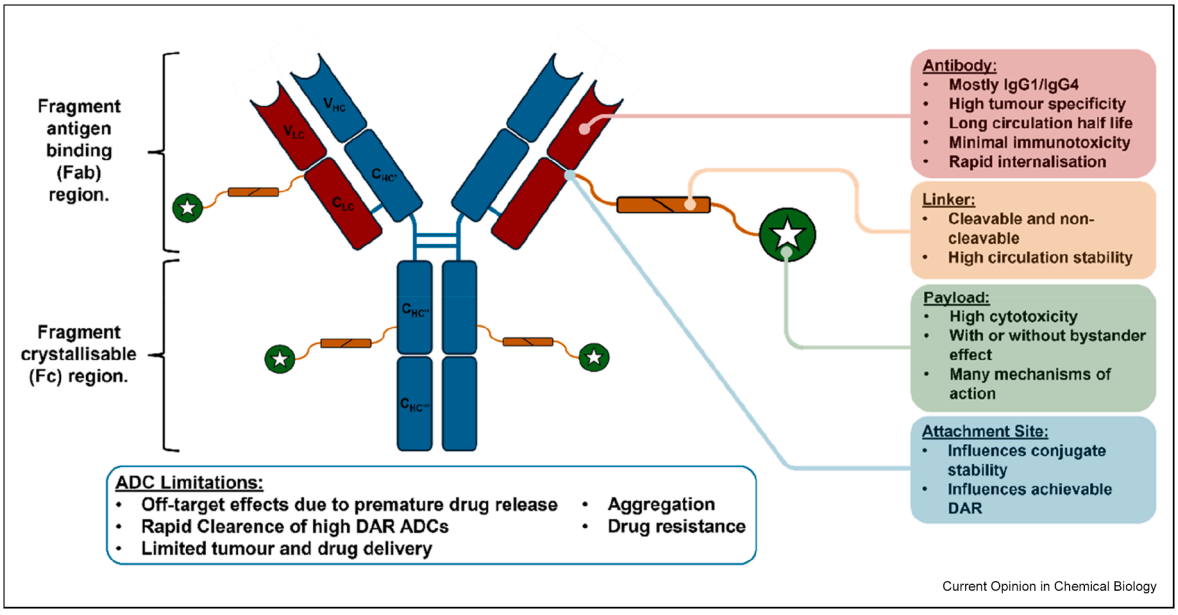
Most clinically approved ADCs are based on immunoglobulin G (IgG) antibodies, with trastuzumab representing one of the most widely used scaffolds. IgG antibodies are approximately 150 kDa in size and consist of two identical heavy chains and two identical light chains, assembled through non-covalent interactions and inter-chain disulfide bonds [4]. In humans, IgG is divided into four subclasses (IgG1–4), which differ primarily in their hinge regions and their capacity to engage immune effector functions [5].

From a structural perspective, IgG antibodies can be divided into the fragment crystallisable (Fc) region and the fragment antigen-binding (Fab) regions [5]. The Fc region interacts with the neonatal Fc receptor (FcRn), causing long serum half-lives of approximately 21 days, whereas the Fab regions contain the variable domains responsible for antigen recognition [6]. Importantly for ADC development, both regions present potential chemical handles for bioconjugation, including solvent-accessible lysine residues and inter-chain disulfide bonds. How these handles are exploited has a profound impact on ADC homogeneity, pharmacokinetics, and ultimately clinical performance.

Bioconjugation techniques

Traditional lysine-based bioconjugation strategies rely on the inherent nucleophilicity of lysine side chains but typically result in heterogeneous mixtures due to the high abundance of lysine residues on IgG antibodies (Figure 2a) [7,8]. Such stochastic modification leads to broad DAR distributions and batch-to-batch variability, complicating both manufacturing and clinical translation.

Figure 1



General structure of an antibody–drug conjugate (ADC), highlighting key components and limitations of early-generation ADCs.

It is now widely accepted that greater control over conjugation site and stoichiometry improves pharmacokinetic predictability and reduces off-target toxicity [2,8].

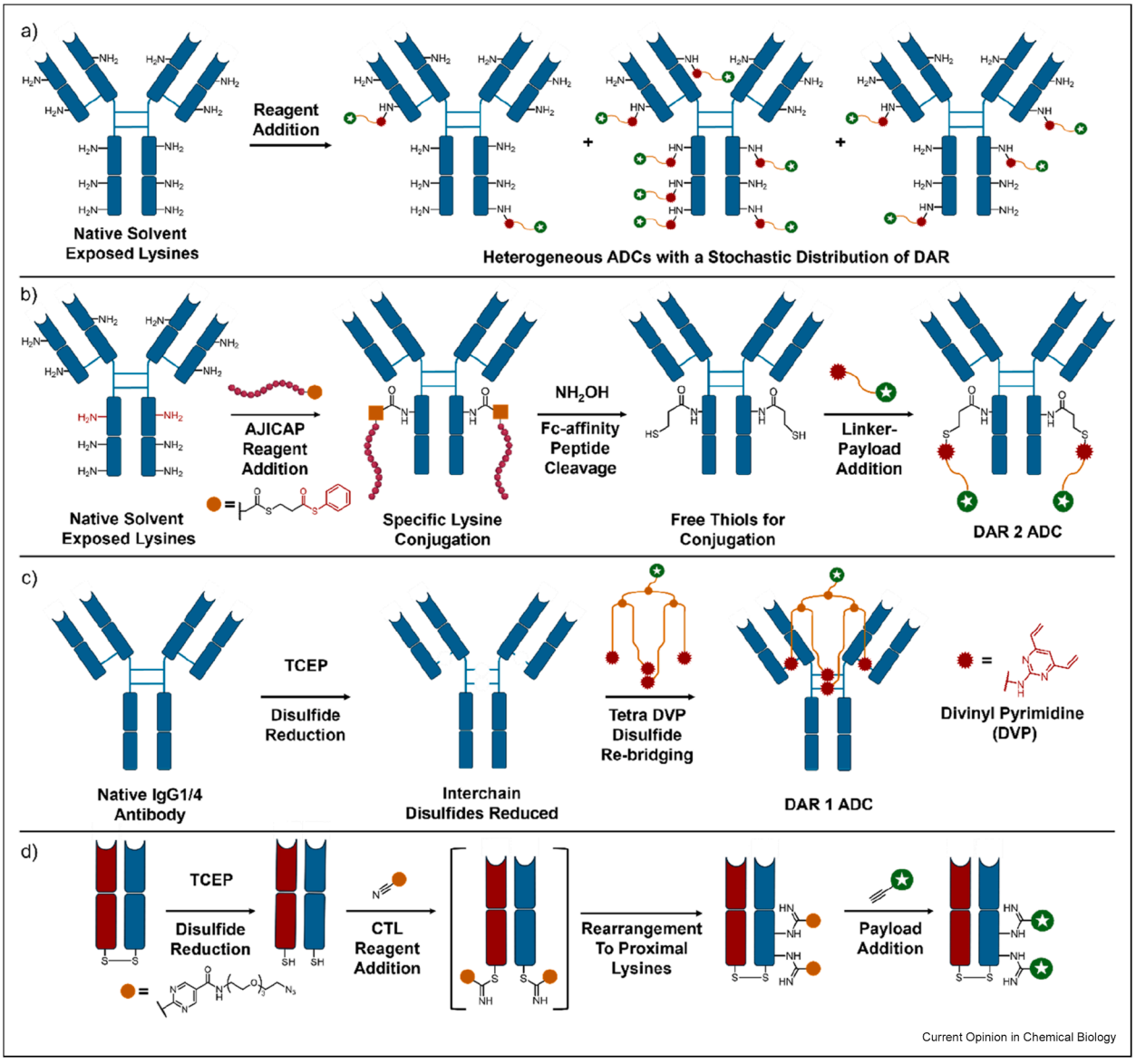
A notable advance in this area is the development of affinity-guided lysine conjugation strategies, exemplified by the AJICAP technology introduced by Yamada and co-workers in 2019 [9,10]. This approach employs Fc-binding peptide reagents to selectively modify specific lysine residues, most notably Lys248, on native IgG antibodies, affording ADCs with narrowly distributed DARs of approximately 1.8–1.9 (Figure 2b). In comparative studies, AJICAP-derived ADCs demonstrated improved therapeutic windows relative to first–generation conjugates such as trastuzumab emtansine (Kadcyla) [9].

Despite these advantages, early implementations of AJICAP suffered from relatively long reaction sequences and increased aggregation compared to approved ADCs [9]. Subsequent refinements, including the replacement of *N*-succinimide esters with more stable thiophenyl esters and the use of alkylthioester linkages to avoid redox steps, significantly streamlined the process [10]. These improvements reduced reaction time, minimised purification steps, and enabled the rapid synthesis of diverse ADC libraries with controlled DARs and low aggregation levels (1.8%–3.2%) [10]. Alongside AJICAP, other affinity-guided technologies have been developed [11–13], such as AbTis' AbClick, which has afforded the AT-211 currently in Phase I/IIa clinical trials against gastric and pancreatic cancers. Affinity-guided conjugation represents a promising strategy for achieving site-selective modification of native antibodies without the need for genetic engineering, although scalability and manufacturing robustness will ultimately determine its clinical impact.

Cysteine modification remains one of the most widely used approaches for ADC construction, largely due to the presence of inter-chain disulfide bonds in IgG1 antibodies. Reduction of these disulfides generates up to eight reactive cysteine residues, enabling the preparation of ADCs with DARs ranging from 2 to 8. While early cysteine-based strategies often produced heterogeneous products, with linker stability issues [14,15], more recently there has been the development of disulfide re-bridging reagents and new mono-reactive reagents that significantly improved control over conjugation site and DAR [16–18]. A few interesting new methods will be explored further here but to learn more about exciting homogeneous ADCs innovations, please read the review by Fan et al. which discusses the topic in more detail [19].

Despite these advancements, there are still some major limitations such as the fact the DAR is always a multiple of two which limits the tuning that can be achieved. To address this, several methods have been developed to access DAR 1 ADC species [20–25]. Recently, Huang and co-workers described a method utilising Fc engineering to ensure only a single N-glycosylation site was

Figure 2



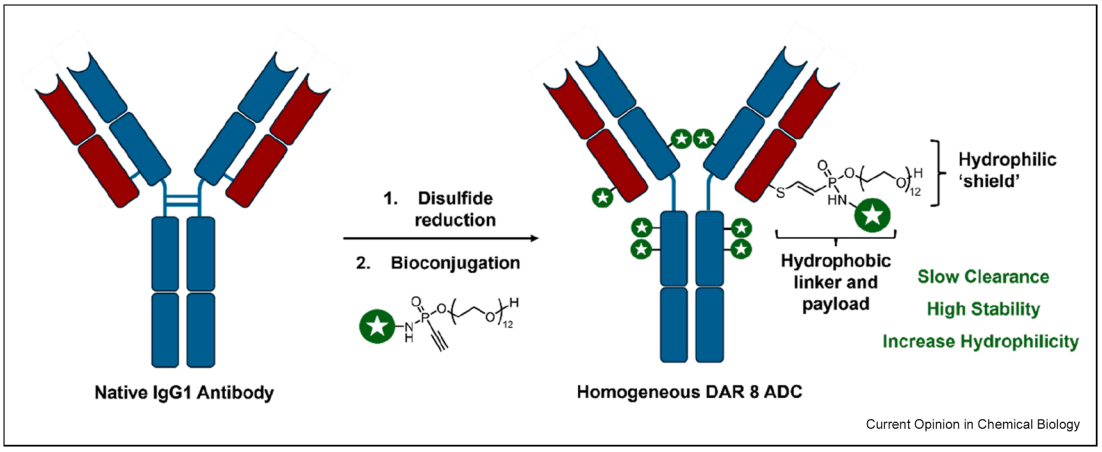
Pictorial representation of several ADC bioconjugation techniques. a) Lysine targeting bioconjugation which affords stochastic modification and a wide distribution of DARs; b) AJICAP™ modification of antibodies uses an Fc-affinity peptide reagent to target specific lysine residues to afford DAR ~2 ADCs [9,10]; c) Tetra-DVP complete re-bridging of all interchain disulfide bonds affords homogenous DAR ~1 ADCs without the need for glycan or genetic engineering [23–25]; d) CTL transfer modification of Fab units affords conjugates with the disulfide bond reformed maintaining the integrity of the original protein [26,27].

present, this then allowed glycosite-specific chemoenzymatic conjugation to be used to add on a single payload to the antibody [22].

Another method is to re-bridge all the disulfide bridges in an antibody with a single construct (Figure 2c). TetraDVP represents one of the only methods to successfully accomplish this and allows access to DAR 1 species on native antibodies without the need for glycan or genetic engineering [23–25,58].

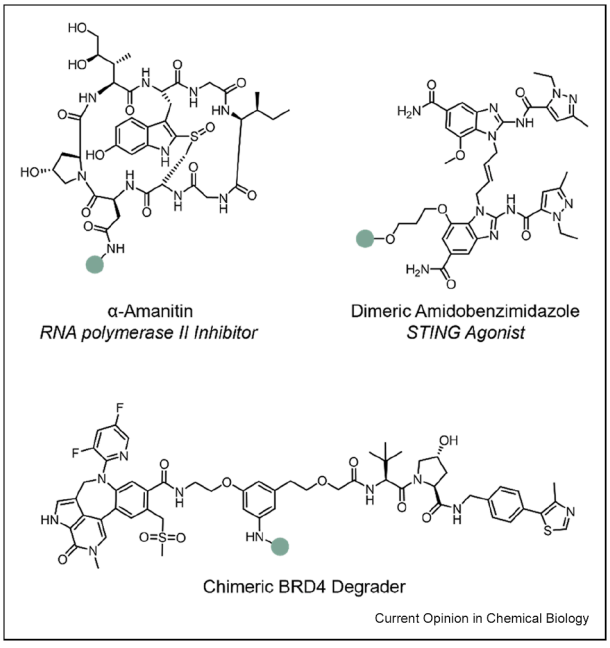
An intriguing hybrid approach that bridges lysine and cysteine chemistry is the cysteine-to-lysine transfer (CLT) strategy reported by Baker and co-workers [26,27]. In the first generation of CLT reagents, alkyl thioesters selectively acylated cysteine residues within Fab fragments, followed by intramolecular transfer of the acyl group to proximal lysine residues [26]. This process enabled selective modification of a small number of lysines with minimal competing hydrolysis of the cysteine appended intermediate [26]. This

Figure 3



The development of PEG-shielded linkers enables the reproducible synthesis of high-DAR ADCs that demonstrate lower serum clearance and improved tumour regression compared with earlier high-DAR constructs [31].

Figure 4



Examples of emerging payload classes being explored for use in ADC. Linker attachment point denoted by grey circle.

proximity-driven strategy enables selective lysine targeting without the need for large sacrificial peptides by confining conjugation to a small, proximal subset of lysine residues near a defined cysteine, affording DAR ~1.8 conjugates that leverage cysteine targeting while yielding a more stable amide linkage in the final product. More recently, a second class of CLT reagents based on electron-poor aryl nitriles was introduced (Figure 2d) [27]. The second-generation approach minimises competing hydrolysis of the acyl donor, enabling higher effective transfer efficiency and more reproducible DARs. Although CLT has so far been demonstrated primarily on Fab fragments, its extension to full-length antibodies could provide a powerful route to highly homogeneous ADCs that combine the advantages of cysteine selectivity with lysine stability. Whether this approach can be translated to higher-DAR ADCs without compromising stability remains an open and important question.

Linker technology

Linker design plays a central role in determining ADC stability, pharmacokinetics, and tolerability [2]. Many clinically approved ADCs employ cleavable dipeptide linkers, such as the valine–citrulline (Val-Cit) motif, which enable payload release in the lysosomal environment [1]. However, these linkers, in combination with hydrophobic payloads, have been implicated in aggregation and rapid clearance, particularly at higher DARs [28,29]. Coupled with heterogeneity, hydrophobicity is also implicated with increased bone marrow toxicity which has led to dose limitations in clinical trials [30]. As hydrophobicity tends to rise with the number of payloads attached, to enable the higher potency possible with DAR 8 ADCs, methods for mitigating hydrophobicity must be used. One strategy to address this challenge involves the incorporation of hydrophilic shielding elements into the linker architecture to mask payload hydrophobicity [30–33].

Hackenberger and co-workers reported a phosphonamidate-based conjugation handle featuring a

branched hydrophilic polyethylene glycol (PEG) substituent positioned alongside the cleavable trigger and payload [31] (Figure 3). Using these new linkers, the authors were able to synthesise stable DAR 4 and 8 derivatives of the FDA-approved ADC Adcetris (DAR 4). The higher stability of the linkage reduces the amount of drug that is prematurely liberated, ensuring a controlled payload release only near the target cells. The higher-DAR ADCs exhibited slower serum clearance in rats and improved tumour regression compared to their lower-DAR, commercial counterparts. These results are promising, and with two ADCs in Phase 1/2 clinicals trials (as of April 2026) the effectiveness of this technology will soon be revealed in a clinical setting.

Simmons et al. opted for a more traditional linker architecture, combining maleimide conjugation with a branched PEG linker to generate a melanotransferrin targeting DAR 8 ADC [30]. The ADC (SGN-CD228A) enabled 3—8 fold increases in intracellular MMAE concentration compared to a DAR 4 version, though the authors note that this only led to mild increases in cytotoxicity in high antigen-expressing cell lines. This finding highlights that whilst DAR 8 promises to double the concentration of drug delivered on-paper, this doesn't necessarily translate *in vitro*. Nevertheless, the properties of the ADC changed depending on the PEG size of the linker branch. It was found that SGN-CD228A (with a 12 PEG-unit branch) led to slower clearance and c. 50% less off-target MMAE uptake by bone marrow cells compared to an ADC with no PEG branch. The authors argue that the higher hydrophilicity of the ADC led to less non-specific cell uptake, lowering the amount of MMAE that accumulated in bone marrow cells. The ADC is currently in Phase I clinical trials for the treatment of solid tumours where is it hoped the hydrophobic mask will translate into lower haematological toxicity and therefore improved patient outcomes.

Alongside the PEG shields incorporated by Hackenberger and co-workers, and Simmons et al., there are innovations using branching polysarcosine chains and peptide linkers which have shown improved hydrophilicity and reduced aggregation [32,33]. All in all, hydrophobic masking has shown promise in mitigating the hydrophobicity of payloads *in vitro*, with ongoing clinical trials posed to demonstrate the effect on patients.

Future linker designs must balance stability, cleavability, and hydrophilicity to unlock the full therapeutic window of high-DAR constructs.

Payloads

Currently approved ADCs rely on a relatively small number of payload classes, primarily tubulin inhibitors (e.g. MMAE and MMAF) and DNA-damaging agents (e.g. calicheamicin, pyrrolobenzodiazepines, and topoisomerase I inhibitors such as SN-38 and Dxd) [34]. While these payloads are highly potent, their limited mechanisms of action raise concerns about the emergence of drug resistance [35].

To address this limitation, recent research has been focused on the development of payloads with novel biological targets (Figure 4). One promising example is α-amanitin, a cyclic octapeptide that selectively inhibits RNA polymerase II [36—38]. Studies have demonstrated that α-amanitin-based ADCs can induce apoptosis through transcriptional shutdown and may overcome both adhesion-mediated and drug-mediated resistance mechanisms. However, much of this work remains at the clinical trial or preprint stage, and careful evaluation of therapeutic index will be critical [37,38].

Another emerging class of payloads comprises Stimulator of Interferon Genes (STING) agonists. Rather than directly inducing cytotoxicity, these molecules activate innate immune signalling pathways, effectively flagging tumour cells for immune-mediated clearance [39,40]. STING agonism has shown encouraging responses in clinical trials but often requires direct administration into the tumour and adverse events have been observed in the clinic, which can limit application. ADC-based delivery of STING agonists offers a potential solution to the dosing and localisation challenges that have limited their clinical application to intratumoural administration; however, caution needs to be taken, with deaths related to adverse effects having been observed for some ADCs using STING agonists such as XMT-2056 [41]. Immune-modulating payloads may mark a conceptual shift in ADC design, moving the field beyond direct cytotoxicity toward targeted immune activation.

Proteolysis-targeting chimeras (PROTACs) represent a further innovative payload class [42—46]. By inducing the degradation rather than inhibition of intracellular targets, PROTACs offer access to previously undruggable proteins. Antibody—PROTAC conjugates have shown encouraging activity against targets such as EGFR [46], HER2 [44,45], and other proteins [44,45], demonstrating that targeted protein degradation can be successfully integrated into ADC architectures.

As well as exciting evidence for the use of PROTACs as payloads, recent research has shown that co-dosing ADCs and PROTACs that target the same cell-surface receptor can increase ADC internalisation by 1.4—1.9-fold [47]. This suggests that the co-dosing of PROTACs with current ADCs could lead to improved drug delivery, however more research is needed.

Beyond the three classes mentioned in the review, there are more exciting payloads being investigated such as *N*-

Myristoyltransferase (NMT) inhibitors [48], ecteinascidins [49], and radioactive payloads [50]. These are further developments that the authors hope will help address the issues of emergence drug resistance and improve the imaging of cancers. Exploring many different new payload classes is key due to difficulty associated with getting new payloads clinically approved. However, the lack of data about new payload classes, and therefore the unknown risks associated with their incorporation into ADCs, has hampered their utilisation. If a novel antibody is discovered, it is far more risk-averse to use tried and tested payloads such as MMAE. Therefore, we believe that full clinical validation and FDA approval of an ADC containing a novel payload is effectively a requirement before a payload will be used more widely.

ADCs beyond oncology

To date, all FDA-approved ADCs have been developed for oncology indications. However, the fundamental principle of targeted drug delivery has clear relevance beyond cancer. Infectious diseases represent an attractive but challenging frontier for ADC technology.

Early attempts to combine antibiotics with antibodies were limited by unfavourable pharmacokinetics and toxicity [51]. More recent studies have demonstrated that ADCs can be designed to selectively eliminate bacterial pathogens such as *Staphylococcus aureus*, both in extracellular biofilms and within intracellular reservoirs [52,53]. These approaches exploit either extracellular release of antibacterial agents at infection sites or intracellular delivery following phagocytic uptake.

Research has also been undertaken to implement ADCs for the treatment of inflammatory diseases with some exciting phase 1 clinical trial data being observed [54,55]. Although still early-stage, these approaches illustrate the broader versatility of ADC platforms beyond oncology.

Conclusion

The past few years have witnessed rapid maturation of ADC chemistry, driven by increasingly precise control over conjugation site, linker architecture, and payload mechanism. The convergence of site-selective bioconjugation, hydrophilic linker engineering, and mechanistically diverse payloads is transforming ADCs from empirical constructs into rationally engineered therapeutics. Whilst ADC homogeneity has been widely reported to improve pharmacokinetics (PK) and therapeutic index [56,57], direct clinical trial analyses explicitly demonstrating improved properties solely attributable to homogeneity remain limited, because clinical variability is also driven by target burden, disease state, Fc-mediated disposition, payload metabolism, and patient-specific factors. Therefore, whilst homogeneity is expected to reduce inter-patient variability and has been shown preclinically to improve PK properties and the therapeutic index, further data is required to prove the benefits clinically.

Looking ahead, we believe that the next generation of ADCs will be defined not only by improved chemistry but also by an expanded biological scope. Novel payloads that modulate transcription, immune signalling, or protein stability have the potential to overcome resistance mechanisms and broaden clinical utility. However, significant challenges remain, particularly with respect to manufacturing scalability, therapeutic index, and cost. Addressing these challenges will determine whether ADCs evolve from specialised oncology tools into broadly deployable precision medicines across multiple therapeutic areas.

Declarations

There are no conflicts of interest to declare.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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