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Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2023.v15.i02.pp79-88

ANTIBODY-DRUG CONJUGATES: LINKER CHEMISTRY AND CLINICAL ADVANCES

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Article info

Received date:10-01-2023
Accepted date:17-05-2023
Published date:15-09-2023
ISSN;0975-8216

Keywords:

Antibody-drug conjugates, Linker chemistry, Payload release, Bystander effect, Targeted chemotherapy

Abstract

Antibody-drug conjugates join a monoclonal antibody to a cytotoxic payload through a chemical linker, and the linker largely decides whether the drug stays inert in blood and acts only inside the target cell. This mini review summarises published work on cleavable and non-cleavable linkers, conjugation sites, drug loading and payload properties, and relates these design choices to pharmacokinetics, toxicity and clinical results in haematological and solid tumours. The literature shows that stable linkers, controlled loading and membrane-permeable payloads have widened the therapeutic index, with several agents now giving survival benefit. Gaps remain in resistance, heterogeneous antigen expression and comparative data. The article is a narrative review and reports no new data.

1. INTRODUCTION

Paul Ehrlich imagined a magic bullet that would carry a poison straight to diseased cells and leave everything else alone [1]. Monoclonal antibodies gave that idea a physical form, yet naked antibodies rarely kill tumour cells on their own. Cytotoxic drugs do kill them, but at doses that damage normal tissue as well. Joining the two, so that the antibody steers and the drug does the harm, became the logic behind antibody-drug conjugates (ADCs) [2, 3]. Early attempts in the 1980s and 1990s used conventional anticancer drugs of modest potency, and most failed because too little drug reached each antigen-positive cell to matter. The concept

was sound. The chemistry was not yet good enough.

The turn came when payloads became far more potent and the chemistry that connected them became more careful. Auristatins, maytansinoids and calicheamicins kill at sub-nanomolar concentrations, so even the small number of antibody molecules that actually reach a tumour can deliver a lethal dose [2, 4]. That potency cuts both ways. A conjugate that sheds its payload in the bloodstream behaves like a systemic poison with the long half-life of an antibody, and it explains why linker behaviour has become the central design question for the field rather than a technical afterthought [5, 6, 7].

Earlier conjugates were handicapped by the immunogenicity of murine antibodies, by unstable linkers and by payloads that were too weak. A frequently cited example paired a chimeric antibody with doxorubicin and needed very large doses to achieve any effect on tumour growth, which in the clinical setting meant gastrointestinal toxicity before any antitumour activity. Reviews of this period conclude that the three components had to be improved together, since a better antibody alone, or a better drug alone, left the same limit in place [2, 3, 6]. Without such changes the technology would probably have remained a curiosity.

The first ADC to reach patients, gemtuzumab ozogamicin, was approved in 2000, withdrawn after confirmatory trial concerns, and later returned at a lower, fractionated dose [8, 9]. Brentuximab vedotin followed and showed that a stable, enzyme-cleavable linker could give durable responses in lymphoma [10]. Ado-trastuzumab emtansine brought the approach to solid tumours [11], and trastuzumab deruxtecan has since extended it to patients whose cancers express only low levels of the target [12, 13]. Recent counts of the pipeline list well over a hundred candidates in clinical development, with a growing share built on newer linker platforms [14, 15, 16].

This mini review follows the chemistry from the bench to the clinic. It describes how the three components fit together, compares cleavable and non-cleavable linkers, considers conjugation site and drug loading, and links those choices to pharmacokinetics and toxicity before summarising clinical results and open problems. Selected findings are collected in table 1, and the distribution of the evidence by theme is shown in fig. 1. The review reports no new data. It draws on published reviews, preclinical papers and clinical trials available up to 2023, and it does not attempt a comprehensive catalogue of every agent in development [7, 17].

Readers new to the topic may find it helpful to keep one idea in mind throughout. An ADC is a prodrug in the strict sense, because the payload should be pharmacologically inactive until the antibody has been internalised and the linker has opened. Almost every design variable discussed below, from the length of a spacer to the position of a single engineered cysteine, serves that one aim of keeping the conjugate quiet in plasma and loud in the lysosome. When a design fails clinically, the failure can usually be traced to a breach of that principle somewhere along the way [5, 18].

Table 1: Linker designs and clinical examples reported for antibody-drug conjugates

Linker or design	Reported feature or outcome	Ref.
Hydrazone acid-labile	Hydrolyses in acidic endosomes; limited plasma stability contributed to premature release with early calicheamicin conjugates.	[8, 19]
Valine-citrulline-PAB cathepsin-cleavable	Lysosomal cathepsin B releases unmodified MMAE; stable in human plasma and used in brentuximab and polatuzumab vedotin.	[20, 21, 22]
Hindered disulfide glutathione-reduced	Reduced inside cells; steric hindrance tunes stability and gives bystander killing of neighbouring cells.	[6, 23]
Tetrapeptide GGFG deruxtecan	Cleavable linker with a permeable topoisomerase I payload; activity extends to HER2-low breast cancer.	[13, 24]
CL2A carbonate pH-sensitive	Slowly hydrolysing linker releases SN-38 inside and outside cells in Trop-2 positive tumours.	[25, 26]

Linker or design	Reported feature or outcome	Ref.
SMCC thioether non-cleavable	Needs lysosomal antibody degradation; charged catabolite limits bystander effect and off-target exposure.	[11, 27]
Maleimide exchange retro-Michael	Thiol exchange with albumin removes payload; succinimide ring hydrolysis stabilises the linkage.	[28, 29]
Engineered cysteines THIOMAB	Homogeneous loading and site-dependent stability improved the therapeutic index in animal models.	[29, 30, 31]
Hydrophilic spacers PEG	Reduces hydrophobicity and clearance of highly loaded conjugates, widening the therapeutic index.	[32, 33]
Gemtuzumab ozogamicin CD33	Fractionated dosing with chemotherapy improved event-free survival in acute myeloid leukaemia.	[9]
Trastuzumab deruxtecan HER2	Benefit in HER2-positive and HER2-low breast cancer; interstitial lung disease requires monitoring.	[12, 13]

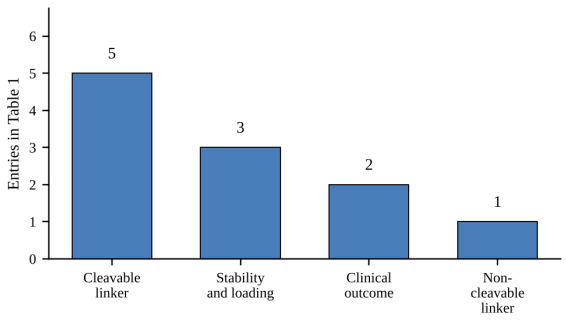


Fig. 1: Number of entries in table 1 by linker class and evidence type

2. COMPONENTS AND MECHANISM

An ADC has three parts. The antibody is usually a humanised or human IgG1 chosen for its affinity to a surface antigen that is abundant on tumour cells, sparse on vital tissue, and internalised after binding [2, 3]. The payload is a cytotoxic small molecule, typically a tubulin inhibitor or a DNA-damaging agent. The linker sits between them and has to meet two conflicting demands: it must survive circulation for days, yet it must release the drug quickly once the conjugate is inside the cell [6, 7]. Few other drug classes ask one small chemical group to do both jobs, which is why so many different linker solutions have been tried and why none has proved universal.

Target selection comes first, and it remains the hardest part to get right. A good antigen is expressed at high density on tumour cells, shows limited expression in essential tissues, and is internalised efficiently. Few antigens meet all three conditions, and the tolerable level of normal-tissue expression depends on the payload. HER2, CD30, CD33, CD19, CD22, CD79b and Trop-2 have each been exploited, with different compromises [3, 18]. Antigen density interacts with the linker as well, since low-density targets need either a more potent payload or a mechanism that spreads beyond the antigen-positive cell [2, 34].

The sequence of events after injection is well described. The ADC binds its antigen, the complex is taken up by receptor-mediated endocytosis, and the vesicle matures through early endosomes towards lysosomes. There the antibody is degraded and the payload is liberated, either by cleavage of the linker or by catabolism of the whole antibody to an amino acid-linked fragment [2, 34]. Trafficking speed matters a great deal. An antigen that recycles to the cell surface instead of travelling to the lysosome gives poor release whatever the linker chemistry, and an antigen that is shed into the circulation acts as a sink that mops up conjugate before it reaches the tumour [18, 34].

Not every tumour cell expresses the antigen, and a payload that is trapped inside the first cell it kills offers no help to its neighbours. Payloads that can cross membranes escape and kill adjacent antigen-negative cells, a phenomenon called the bystander effect [23, 34]. It is attractive in heterogeneous solid tumours, but it can also spread damage to healthy cells near the tumour. Whether bystander killing is a benefit or a hazard therefore depends on the tissue and the disease. It is decided in large part by the chemistry of the species that is finally released, and so it leads straight back to the linker [23, 34].

A further point is easy to overlook, namely the antibody itself. Fc function is usually

retained, so some conjugates also trigger antibody-dependent cellular cytotoxicity, and Fc-mediated uptake by macrophages and liver cells may contribute to off-target toxicity [17, 35]. Trastuzumab keeps its HER2 signalling blockade when it carries emtansine, and this dual action is thought to add to the activity of the conjugate [11, 27]. These antibody-driven effects are rarely separated from payload effects in clinical reports, so the contribution of each is often a matter of inference and not of direct measurement, and dedicated studies with unconjugated antibody would be needed to settle it.

3. CLEAVABLE LINKERS

Cleavable linkers exploit a difference between plasma and the inside of a cell. Three triggers have been used in practice: acidity, reducing conditions and lysosomal proteases. Acid-labile hydrazones were the earliest. They were designed to hydrolyse in endosomes at about pH 5 and were used in gemtuzumab and inotuzumab ozogamicin. In practice the hydrazone bond proved only moderately stable at the pH of blood, and slow release of calicheamicin in circulation is thought to have contributed to the toxicity seen with the first-generation agent [8, 19]. For that reason hydrazones have largely given way to more stable alternatives in newer designs.

Disulfide linkers are reduced by glutathione, which reaches millimolar concentrations inside cells against micromolar levels in plasma. Their weakness is that thiol-disulfide exchange with free cysteine and albumin can also occur in blood. Placing methyl groups next to the disulfide adds steric hindrance and slows that exchange, so the degree of hindrance can be tuned to balance plasma stability against intracellular release [6, 23]. Maytansinoid conjugates built this way release lipophilic metabolites that diffuse out of the target cell, and they showed strong bystander killing in mixed-antigen tumour models [23].

The most widely adopted trigger is the dipeptide valine-citrulline, joined to the payload through a self-immolating p-aminobenzyl carbamate spacer. Cathepsin B and related lysosomal proteases cut the amide bond, the spacer collapses spontaneously, and the free drug emerges without a residual linker fragment [20]. The chemistry was first shown with doxorubicin conjugates and then applied to monomethyl auristatin E (MMAE) in brentuximab vedotin [4, 20, 21]. Stability in human plasma is excellent. In mouse plasma it is poor, because a carboxylesterase cleaves the linker, a species difference that complicates the interpretation of rodent efficacy and safety studies [31, 35].

Payload class shapes what the linker has to do. MMAE is membrane permeable and produces a clear bystander effect, whereas a charged auristatin analogue is trapped inside the cell and spares neighbours [34]. Maytansinoids, calicheamicins and topoisomerase I inhibitors each differ in permeability, potency and mechanism, and the same linker can behave differently with each. The clinical lesson is that linker and payload are best treated as a pair, with permeability and potency chosen to suit the biology of the target tumour and with the toxicity profile of the payload in mind [34, 35].

Peptide-linked auristatin conjugates of the anti-CD30 antibody were shown to be potent and selective in animal models [21], and the same conjugate then went into a pivotal single-arm trial in relapsed Hodgkin lymphoma [10]. Polatuzumab vedotin uses the same valine-citrulline-MMAE system against CD79b and produced high response rates in B-cell lymphoma models and then in patients [22, 36]. A related line of work gave the tetrapeptide linker glycine-glycine-phenylalanine-glycine, cleaved by lysosomal cathepsins and carrying a topoisomerase I inhibitor in trastuzumab deruxtecan [24]. That linker keeps the conjugate stable in plasma even at a drug-to-antibody ratio (DAR) close to eight, which is unusually high.

A different strategy was chosen for sacituzumab govitecan. Its CL2A linker is a pH-sensitive carbonate that hydrolyses slowly, releasing SN-38 both inside cells and in the tumour microenvironment, and this moderately stable design is deliberately less rigid than the peptide linkers [25, 26]. The

approach works because SN-38 is membrane permeable and because the target Trop-2 is widely expressed, so some release outside the cell is tolerated. The price is a higher rate of neutropenia and diarrhoea, which echo the toxicity of irinotecan, the parent compound of SN-38 [25, 37]. Here a leakier linker was a considered choice and not an engineering failure.

4. NON-CLEAVABLE LINKERS AND CONJUGATION SITE

Non-cleavable linkers contain no designed breakpoint. The payload is released only after the antibody is degraded completely in the lysosome, leaving the drug attached to the linker and to the amino acid residue that carried it. Ado-trastuzumab emtansine (T-DM1) is the standard example. It joins the maytansinoid DM1 to lysine side chains of trastuzumab through the thioether linker SMCC, and the active catabolite is lysine-SMCC-DM1 [27]. That species is charged, so it crosses membranes poorly and shows little bystander killing [27, 34]. In effect the design trades reach for restraint.

The practical gain is plasma stability and lower off-target exposure. The clinical result is well known. In the EMILIA trial, T-DM1 improved progression-free and overall survival over lapatinib plus capecitabine in HER2-positive metastatic breast cancer, with a toxicity profile dominated by thrombocytopenia and raised liver enzymes rather than the neuropathy and hair loss associated with taxanes [11, 37]. The trade-off is that a non-cleavable conjugate depends entirely on antigen-positive cells doing the killing, which makes it less suited to tumours with patchy expression of the target [23, 34]. That stability also simplifies pharmacokinetic modelling, since little free drug is expected in the circulation.

The maleimide group used to attach payloads to reduced cysteines raises a separate problem. The resulting thiosuccinimide can undergo a retro-Michael reaction in plasma, and the freed maleimide-linked drug then transfers to albumin and other thiols, which both lowers delivery to the tumour and spreads exposure to other tissues [6, 29]. Hydrolysis of the succinimide ring to the ring-opened form locks the linkage in place. Chemistry that drives this hydrolysis under mild conditions improved potency, exposure and efficacy of the conjugates in animal models, without damaging the antibody [28]. Whether such stabilisation is needed for every maleimide conjugate is still debated, because some exchange may be tolerable.

Where the linker is attached matters nearly as much as what it is made of. Conventional conjugation to interchain cysteines or lysines yields mixtures with drug-to-antibody ratios from zero to eight, and the species with high loading clear faster and are more toxic [32, 33]. Engineering cysteines at chosen positions, the THIOMAB approach, gives homogeneous conjugates with defined loading and a better therapeutic index than the stochastic product made from the same antibody and drug [30]. Conjugation site also altered plasma stability, and sites with partial solvent exposure and favourable local charge protected the maleimide linkage from exchange [29, 31].

Characterising what has actually been made is a task in its own right. Hydrophobic interaction chromatography, mass spectrometry of the intact or reduced protein and peptide mapping are used to determine average DAR, the distribution of species and the sites of attachment, and each method has blind spots. For stochastic conjugates the product is always a mixture, and the proportion of high-loaded species affects clearance and toxicity out of proportion to its abundance [33, 38]. Control of that distribution is a regulatory requirement as much as a scientific one [17].

Hydrophobic payloads make highly loaded conjugates aggregate and clear quickly. Lyon and colleagues showed that masking hydrophobicity with polyethylene glycol (PEG) side chains allowed a homogeneous DAR 8 conjugate to circulate much like a DAR 2 to 4 conjugate, keeping potency while extending exposure [32]. This prompted the use of hydrophilic spacers and charged sulfonate groups in later designs, an approach that increases the amount of drug that can be carried without loss of pharmacokinetic quality [7, 32]. Earlier work had already shown that more drug per antibody did not

automatically mean a better therapeutic index [33].

5. PHARMACOKINETICS AND SAFETY

Pharmacokinetic assessment of an ADC is awkward because several analytes circulate together: intact conjugate, total antibody, free payload and payload metabolites. Each has its own half-life and its own assay. Deconjugation shifts the average DAR down over time, and the practical approach is to measure conjugated antibody, total antibody and unconjugated drug in parallel [38]. Intact ADCs generally show the long half-life expected of an IgG, and clearance rises with drug loading, as the early loading studies on auristatin conjugates showed [33, 38]. Bioanalytical choices also affect the numbers reported, which makes cross-study comparison hazardous and calls for careful reading of any pooled estimate of half-life or clearance.

The toxicity of an ADC is shaped more by its payload than by its target, a recurring and slightly uncomfortable finding. Reviews of preclinical and clinical data report that conjugates carrying MMAE are associated with neutropenia and peripheral neuropathy, DM1 conjugates with thrombocytopenia and hepatic effects, and calicheamicin conjugates with hepatotoxicity including veno-occlusive disease [35, 37]. Such toxicities arise even when the antigen is absent from the affected organ, which points to nonspecific uptake and to premature release as the likely mechanisms [7, 35]. Practical consequences follow: a prescriber can anticipate the adverse events from the payload alone.

Potency makes the safety margin narrow. Payloads in current use kill cells at picomolar to nanomolar concentrations, a thousand times below what conventional chemotherapy needs, so the fraction of the dose that reaches the tumour is small and the fraction that goes elsewhere can still be harmful [2, 39]. Experience suggests that the maximum tolerated dose is often set by payload toxicity in the bone marrow or liver, and that a better therapeutic index is more likely to come from changes in linker stability and loading than from changes in the antibody [35, 37].

Hepatic veno-occlusive disease deserves special mention. It was observed with gemtuzumab and inotuzumab ozogamicin and became the main safety concern in the INO-VATE comparison with standard chemotherapy in adult acute lymphoblastic leukaemia, particularly in patients who went on to transplantation [9, 40]. Interstitial lung disease is a more recent concern with trastuzumab deruxtecan. In the registration phase II study it affected a minority of patients, but some cases were fatal, and close monitoring with early corticosteroids is now part of routine care [12, 13]. Both examples show how a rare toxicity can define the clinical use of a drug.

Dose and schedule are further levers. Fractionating gemtuzumab ozogamicin into three small doses cut peak exposure and made the drug tolerable alongside induction chemotherapy [9]. Other work stresses that tumour penetration depends on dose, because high-affinity conjugates are trapped at the perivascular edge of a tumour unless the dose is high enough to saturate binding sites. That is an argument for dose optimisation based on pharmacology instead of the maximum tolerated dose alone [38, 39]. Regulators have also emphasised developability, comparability and control of the heterogeneous product as part of the quality case [17].

6. CLINICAL ADVANCES

Haematological malignancies were the proving ground. Brentuximab vedotin gave objective responses in about three-quarters of patients with relapsed Hodgkin lymphoma in the registration single-arm study, with a notable fraction reaching complete remission [10]. In relapsed systemic anaplastic large-cell lymphoma the response rate was higher still [41]. Peripheral neuropathy was the characteristic adverse effect, and it is a direct reflection of the MMAE payload as noted above [37, 41]. These results arrived in diseases where the options after failure of standard therapy had been poor. Longer follow-up has since confirmed that some patients remain in remission for years.

Polatuzumab vedotin was first tested alone in a phase I study of relapsed B-cell

non-Hodgkin lymphoma and chronic lymphocytic leukaemia. Objective responses were recorded in diffuse large B-cell lymphoma and in indolent lymphoma, with neutropenia and peripheral neuropathy the main toxicities [22]. Gemtuzumab ozogamicin then returned through the ALFA-0701 trial, in which three fractionated doses added to daunorubicin and cytarabine improved event-free survival in adults with previously untreated acute myeloid leukaemia [9]. Inotuzumab ozogamicin raised remission rates in relapsed or refractory acute lymphoblastic leukaemia [40]. These trials also confirmed that ADCs can be added to existing regimens without prohibitive toxicity.

In solid tumours the story belongs mainly to breast cancer. After T-DM1 showed a survival advantage in HER2-positive disease [11], trastuzumab deruxtecan achieved a high response rate in heavily pretreated patients, with an objective response of around 60% [12]. The DESTINY-Breast04 trial then did something new. In HER2-low metastatic breast cancer, a group previously labelled HER2-negative, the conjugate extended progression-free and overall survival compared with physician's choice chemotherapy [13]. The bystander effect of its permeable payload is the leading explanation for activity at such low antigen density [13, 24]. These results shifted the standard of care in lines of therapy where chemotherapy alone had given short remissions.

Sacituzumab govitecan targets Trop-2, an antigen found on many epithelial cancers. In the ASCENT trial of previously treated metastatic triple-negative breast cancer it improved both progression-free and overall survival over single-agent chemotherapy of the physician's choice [25]. Reviews of the solid-tumour experience also describe enfortumab vedotin in urothelial cancer, tisotumab vedotin in cervical cancer and mirvetuximab soravtansine in ovarian cancer, all of which pair a validated surface antigen with an auristatin or maytansinoid payload [15, 42]. The pattern across tumour types is consistent: where a good antigen exists, an ADC can be built to reach it, although the supply of such antigens is not unlimited.

Taken across these studies, the linker-payload combination appears to predict the clinical profile at least as well as the antigen does. Cleavable linkers with permeable payloads are favoured when expression is heterogeneous, while stable non-cleavable systems suit homogeneous targets such as HER2 in amplified tumours [16, 23, 42]. Agents, linker designs and their reported behaviour are compared in table 1, and fig. 1 shows how the entries divide between cleavable linkers, non-cleavable chemistry, stabilisation strategies and clinical outcomes [15, 16]. The table is a synthesis of published findings and not a ranking of products.

By the end of 2022 more than ten ADCs held marketing approval in at least one major region, spread across lymphoma, leukaemia, urothelial, cervical, ovarian and breast cancers [14, 15, 16]. Not every approval has endured. Gemtuzumab ozogamicin was withdrawn and later reinstated, and other agents have been withdrawn or restricted after confirmatory studies failed to meet their end points. The history shows that early response rates in refractory disease do not always translate into survival advantage, and that the regulatory route for these hybrid products depends heavily on randomised confirmation [8, 17].

7. LIMITATIONS AND FUTURE DIRECTIONS

Resistance limits the benefit of every approved ADC. Mechanisms reported include loss or downregulation of the target antigen, altered trafficking that diverts the conjugate away from the lysosome, impaired lysosomal acidification or protease activity, and upregulation of efflux pumps such as P-glycoprotein that remove the payload before it can act [18, 39]. Sequential use of ADCs with different payloads is attractive in principle, but good data on whether a second ADC works after progression on a first are still sparse, and most evidence comes from small retrospective series [16, 39].

Several gaps stand out in the preclinical evidence as well. Mouse plasma cleaves valine-citrulline linkers that are stable in people, so murine pharmacokinetic and

tolerability data can mislead [31, 35]. Xenograft models usually express the antigen uniformly and lack an intact immune system, which flatters both efficacy and the bystander effect. Few studies compare linkers head to head with the same antibody, payload and loading, so that claims for one linker over another often rest on indirect comparison across different antigens and models [5, 7]. Companion animal and organoid models might narrow the gap in the future.

Future work is moving in three directions. One is new payloads with other mechanisms of action, including topoisomerase I inhibitors, which have already changed practice. Another is dual-payload and bispecific designs aimed at heterogeneous targets and resistance. The third is smarter linkers that open only in response to tumour-specific stimuli, such as enzymes overexpressed in the microenvironment [7, 16]. Whether any of these will surpass the current peptide linkers in the clinic is not yet known, and the field will need prospective comparisons and shared reporting of DAR distribution and plasma stability to find out [16, 39].

Manufacturing and cost deserve a plain mention. An ADC is made from three separately manufactured parts, one of them a highly potent compound that needs containment, and the conjugation step has to be controlled tightly so that every batch has a similar DAR distribution and a low level of aggregate. Process development is therefore demanding and expensive, and regulatory expectations for characterising the product are correspondingly high [7, 17]. Prices of approved agents are substantial, which will matter to health systems as indications widen and as the number of eligible patients grows [15].

8. CONCLUSION

The linker is the part of an ADC that most directly controls the balance between benefit and harm. Peptide and glycine-based cleavable linkers, hindered disulfides and stabilised thioethers each solve a different version of the same problem, which is how to hold a potent drug inactive for days and release it within hours of internalisation [5, 6, 7, 20]. Conjugation site, drug loading and hydrophilicity then determine how well that chemistry behaves in the whole animal, and the studies on engineered cysteines and PEG masking show that these variables can be changed deliberately and not left to chance [30, 32, 33].

Clinical results back the design logic. Stable, well-characterised conjugates have improved survival in breast cancer, lymphoma and leukaemia, and a permeable payload with a cleavable linker has made HER2-low disease treatable with an ADC [9, 11, 13, 25]. The unresolved issues are resistance, toxicity that follows the payload rather than the target, and the lack of head-to-head linker comparisons. Progress will probably come from rational combination of payload, linker and dosing, tested in models that predict human behaviour better than current ones, and from clearer rules for choosing patients by antigen level [16, 35, 39].

9. ABBREVIATIONS

ADC-Antibody-drug conjugate,
CL2A-Carbonate-based pH-sensitive linker,
DAR-Drug-to-antibody ratio, DM1-Mertansine, a maytansinoid,
GGFG-Glycine-glycine-phenylalanine-glycine,
HER2-Human epidermal growth factor receptor 2, MMAE-Monomethyl auristatin E,
PAB-p-Aminobenzyl carbamate,
PEG-Polyethylene glycol, SMCC-Succinimidyl trans-4-(maleimidylmethyl)cyclohexane-1-carboxylate, SN-38-Active metabolite of irinotecan,
T-DM1-Ado-trastuzumab emtansine,
Trop-2-Trophoblast cell-surface antigen 2

10. FUNDING

Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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