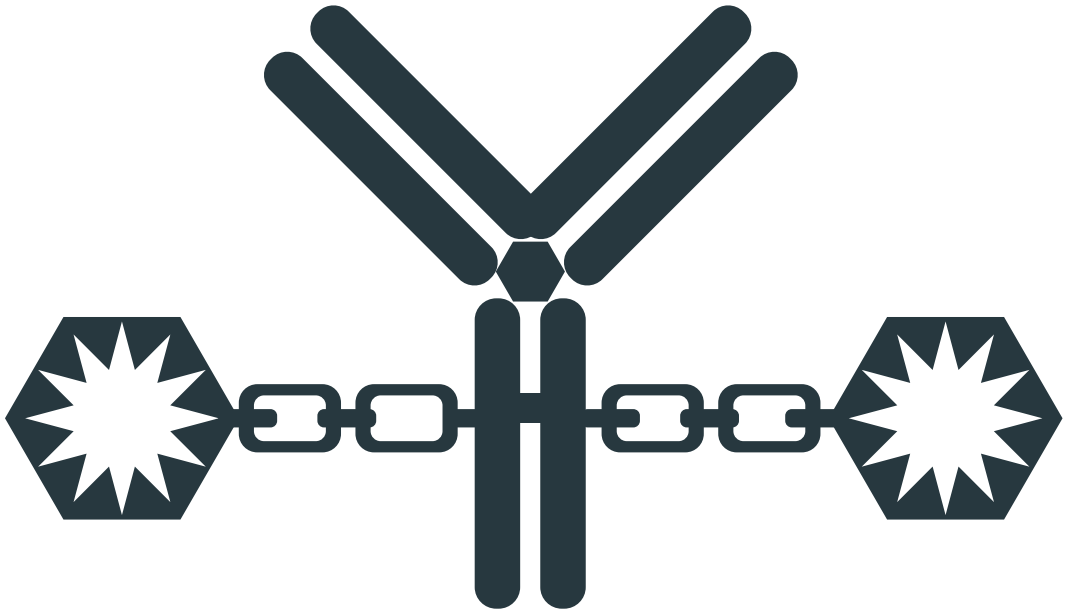


RECENT ADVANCES IN ADCs

December 2025

This review article is periodically updated and can be downloaded from

https://njbio.com/antibody-drug-conjugates/

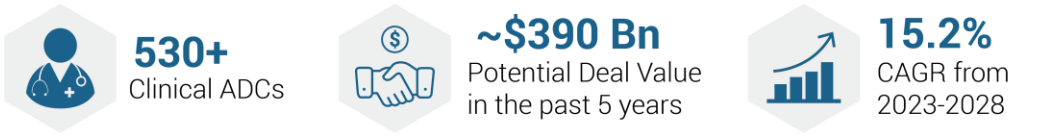
Contents

Review Article

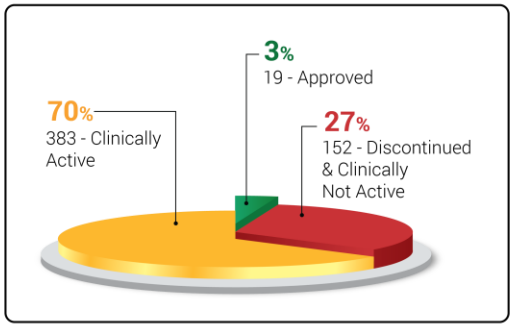
Recent Advances in ADCs

Abstract: Antibody-Drug Conjugates (ADCs) represent an innovative class of chemotherapeutics, which combines the precision of monoclonal antibodies (mAbs) with potent cytotoxic agents. Each generation of ADC has steadily progressed closer to the goal of targeted cancer therapy, with enhanced efficacy and reduced off-target toxicity. Notably, there have been 14 FDA approvals, till date, and over 2000 ADCs are currently in various stages of development. The momentum of this field is underscored by several billion-dollar industry deals, and the global sales exceeding $12 billion in 2024.

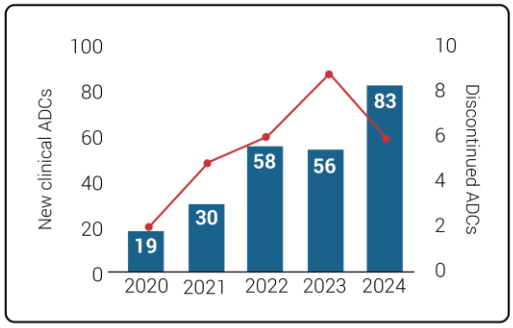
This review navigates the complex ADC landscape by focusing on critical aspects of ADCs, including – mechanisms of action, bioconjugation techniques, and the selection of linkers, cytotoxins, and linker-payload combinations. The review provides an in-depth overview of approved and clinical candidates, while examining significant business activities, including mergers and acquisitions, offering a comprehensive resource on both the scientific and commercial landscapes. It also addresses ADC toxicity mechanisms and reasons behind discontinuation of various clinical drugs, further explaining strategies to overcome these challenges and providing insights into the future direction of research and development of next-generation ADCs.



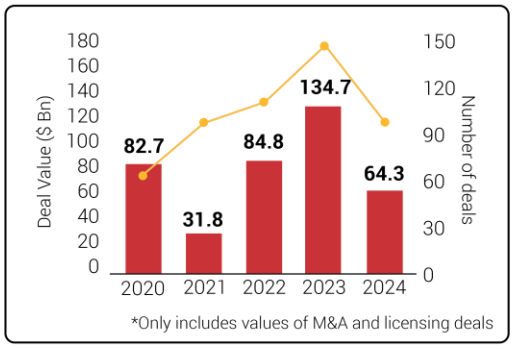
ADC Development Stages



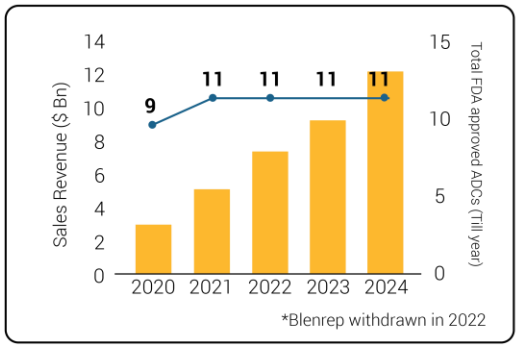
Clinical Landscape



Business Landscape of ADCs



ADC Sales Revenue



Keywords: antibody-drug conjugates, chemotherapy, payloads, bioconjugation, linker, cytotoxin

1. Introduction

After the initial success of auristatin and maytansinoid-based ADCs (Kadcyla® & Adcetris®), there were multiple setbacks in terms of project discontinuations and withdrawal of clinical candidates. The approval of Padcev®, Enhertu® and Trodelvy® in 2019-2020 renewed hope for the therapeutic applications of ADCs in oncology and other disease indications. Designed with chemistry to match the targets more precisely, rather than a one-size-fits all strategy, these ADCs have shown remarkable clinical outcomes. Enhertu and Trodelvy showed a 37%[1] and 59%[2] reduction in the risk of disease progression or death for patients with breast cancer respectively. Resurgence in the ADC space is highlighted by a significant rise in the number of ADCs (~270)[3] undergoing clinical trials, substantial business investments and a wave of mergers and acquisitions (M&A). Also, in terms of revenue, the global ADC market reached an estimated value of $9.7 billion in 2023 and is projected to exhibit a CAGR of 15.2% from 2023 to 2028.[4]

Even after 19 approvals globally and success of treatments like Kadcyla (with a median OS of 30.9 months; ORR of 43.6%)[5] and Enhertu (with a median OS of 29.1 months; ORR of 62.0%),[6] the ADC landscape remains challenging. Discontinuation rates are still high across multiple payload mechanisms, notably auristatins, maytansinoids, and PBD-dimers. As of December 2025, 88 ADC projects have been discontinued[3], and several other projects are currently inactive, highlighting the inherent complexities and difficulties involved in matching the linker-payload and mAb specifically to the target.

Off-target toxicity in ADCs can limit dosing to levels below those necessary for optimal anti-cancer efficacy. This toxicity may arise from factors such as target expression on healthy cells, premature drug release, and off-target binding. The maximum tolerated dose (MTD) thus needs to be lowered to prevent significant harm to the patient. However, reducing the dose below the optimal therapeutic range can lead to suboptimal cancer treatment. Even among FDA-approved ADCs, a considerable fraction of treated patients requires supportive care to manage ADC-associated toxicities, often leading to dose reductions, treatment delays, or discontinuations. The conventional "one-size-fits-all" or "copy-paste" approach, which focuses on repurposing established targets and linker-payload combinations, can frequently be unsuccessful. Achieving the right balance between efficacy and safety requires the careful design of ADCs, focusing on better target selection, improved linkers, and optimized payloads thus making it crucial to explore and implement diverse translational strategies in ADC development. Creating a focused approach based on past failures and successes can guide the development of an optimal clinical candidate. Since every cancer and target is unique the right combination would be required. The emergence of site-specific conjugation technologies and innovative payload-linker strategies, coupled with the identification of new target compounds, has fueled the evolution of ADCs over the past two decades, and is helping move the field towards fourth generation and beyond successes.

To address the challenge of high project discontinuation rates, a "data-driven approach" is essential. A thorough understanding of the mechanism of action, advancements, and obstacles in the field of ADCs can help in making informed decisions and in effective progress of drug development programs. It is imperative to embrace innovative approaches based on years of research data and leverage technological advancements to develop next-generation ADCs.

In this review, we offer an in-depth exploration of recent advancements in the field while covering essential aspects such as the mechanism of action, a summary of approved drugs

and ongoing clinical studies, the underlying mechanisms of ADC toxicity, current research trends, and insights into the business landscape of ADCs. The technological progress discussed here holds promise for addressing challenges in drug discovery and advancing ADC development across established and emerging therapeutic areas.

2. The Evolution of Antibody-Drug Conjugates from Inception to Innovation

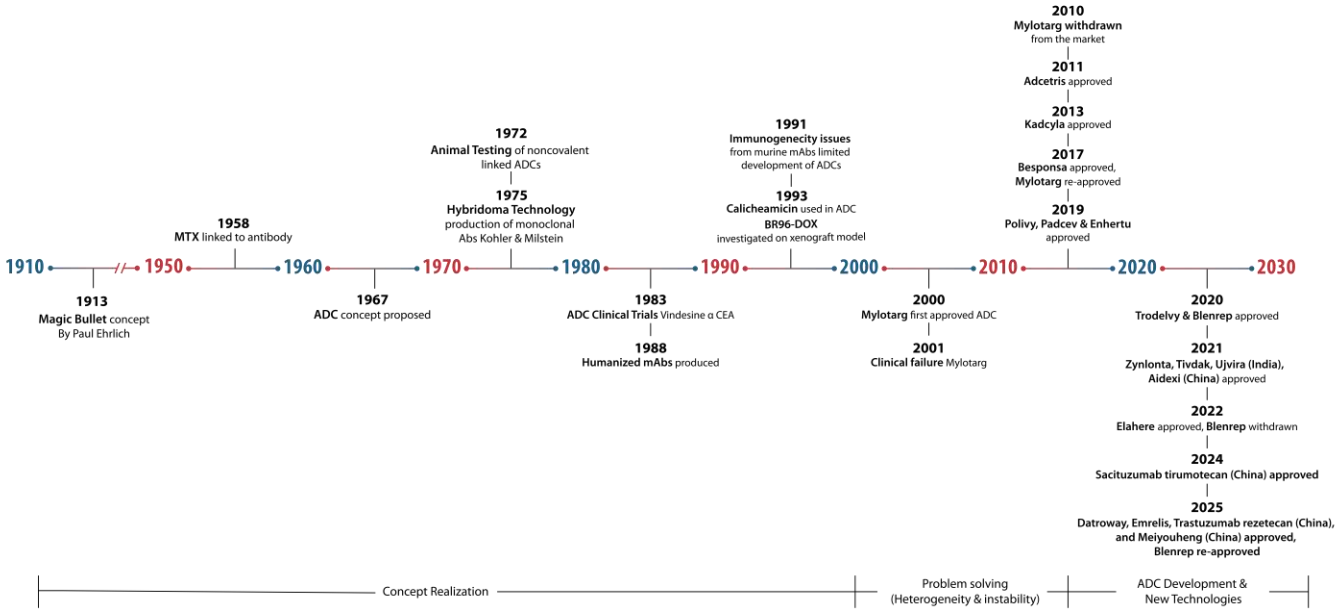


Figure 1. Timeline of Antibody-Drug Conjugates[3,7]

It has taken several decades from the inception of the concept of ADCs to its realization, signifying that the process is highly complex as compared to small-molecule drugs. Development of a successful ADC candidate requires proper integration of the receptor (target), antibody, linker, and payload. Challenges in any of these components can lead to clinical failure and withdrawal of the drug program. We will address each one of these key elements in detail in the later sections.

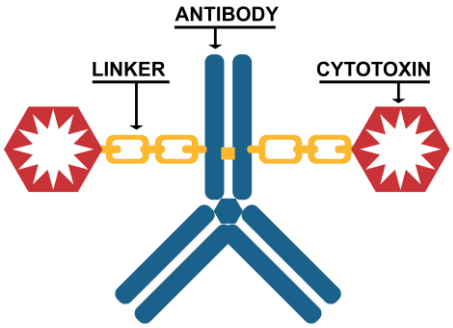


Figure 2: Anatomy of an ADC[8]

Ever since the development of the hybridoma technology (1975), the pace of research in this field has gained considerable momentum. Initial *in vitro* studies utilized antibodies conjugated to radioactive isotopes or cytotoxic drugs to target cancer cells. Issues such as low

DAR (drug-to-antibody ratio), unstable linkers, and poor pharmacokinetics slowed down progress. The development of mAbs by Kohler and Milstein (1970) allowed the production of large volumes of a single antibody clone, with pre-selected specificity, enhancing its potential to be used for research and clinical applications.[9] This paved the way for critical advances like humanization and production of engineered mAbs to recognize various target antigens for chemotherapy.[10]

In 1983, the first human trial of an ADC (anti-carcinoembryonic antigen antibody and vindesine), was deemed safe and effective in eight patients with advanced metastatic carcinomas.[11,12] Gemtuzumab ozogamicin (Mylotarg), was the first FDA approved ADC (2000) targeting hematologic cancers with a CD33 monoclonal antibody conjugated to calicheamicin.[13] A decade later, trastuzumab emtansine (Kadcyla®) was approved for treating HER2-positive breast cancer, demonstrating the potential of ADCs beyond hematologic malignancies.[14]

The approval of trastuzumab emtansine and its successful clinical outcomes catalyzed significant investments and excitement in ADC research. However, not all ADCs shared this success. Some faced substantial hurdles during clinical development and commercialization, including safety or efficacy concerns. For example, Mylotarg was withdrawn after subsequent trials failed to confirm its clinical benefit and highlighted safety issues, including high early death rates in group of patients who received the drug compared to those receiving standard chemotherapy alone.[15] It was later reintroduced to the market in 2017 with an alteration in the dosage regime.[16]

Over three generations, ADC development has undergone significant changes driven by innovative technologies. Site-specific conjugation methods have enabled more precise control over the DAR, while maintaining the binding affinity and specificity of the antibody. Novel linkers and their associated triggers, designed to improve the specificity and safety of ADCs allow for the controlled release of cytotoxic drugs in the tumor microenvironment, minimizing off-target toxicity. Newer strategies include – Fe (II)-responsive linkers (respond to the higher levels of ferrous iron in tumors) and enzyme-cleavable linkers (glycosidases and phosphatases), photo-responsive linkers (light exposure), bio-orthogonal linkers (require bio-orthogonal cleavage pairs such as Cu(I)-BTTAA)[17] and dual-enzyme cleavable linkers.[18] Advances in antibody engineering and selection have also enhanced the binding affinity, and pharmacokinetics, increasing the potency and efficacy of the ADC.

Overall, these technological advancements have addressed many challenges in ADC development, highlighted by an increase in the number of clinical trials and growing investments in the field.

Table 1. Comparison of different generations of ADCs[7]

	First-generation ADCs	**Second-generation ADCs**	**Third-generation ADCs**
Antibodies	Mouse-original or chimeric humanized antibodies	Humanized antibodies	Fully humanized antibodies or Fabs
Linkers	Unstable Monovalent Non-cleavable Acid-labile	Improved stability (Cleavable/ Non-cleavable) Monovalent	Stable in circulation
Payloads	Low potency (duocarmycin, doxorubicin)	Improved potency (auristatins, maytansinoids)	Low potency (camptothecins & novel payloads like immunomodulators)

	First-generation ADCs	Second-generation ADCs	Third-generation ADCs
Conjugation methods	Random Lysines	Random Lysines and Reduced Interchain Cysteines	Site-Specific Conjugation
DAR	Heterogeneous (generally 0-8)	Heterogeneous (generally, 4-8)	Homogeneous (generally 2, 4, 8)
Advantages	Specific targeting Slightly increased therapeutic window	Improved specific targeting More potent payloads Lower immunogenicity	Higher efficacy Improved DAR and improved stability
Disadvantages	Heterogeneity Lack of efficacy Narrow therapeutic index Off-target toxicity due to premature release of drug High Immunogenicity	Heterogeneity Fast clearance for high DAR ADCs Off-target toxicity (premature drug release) Drug resistance	Potential toxicity due to high potency payloads Catabolism difference across species Drug Resistance
Examples of Approved ADCs	Mylotarg®, Besponsa®	Kadcyla®, Adcetris®, Padcev®, Elahere®	Enhertu®, Trodelvy®

3. Mechanism of action of Antibody-Drug Conjugates

From the initial approval of Mylotarg in 2000 to the subsequent approvals of Adcetris (2011), Kadcyla (2013) and Besponsa (2017), the development of ADCs has experienced a slow start, suggestive of an extended and challenging learning phase.[19] However, since 2019, the number of approved ADCs has more than doubled, with five approvals between 2019 and 2020, reflecting a significant advancement in the understanding of both the biology and chemistry of ADCs. **Figure 3** highlights the five critical elements in the design of effective ADCs – target antigen; targeting moiety; linker; conjugation method; and cytotoxic payload.

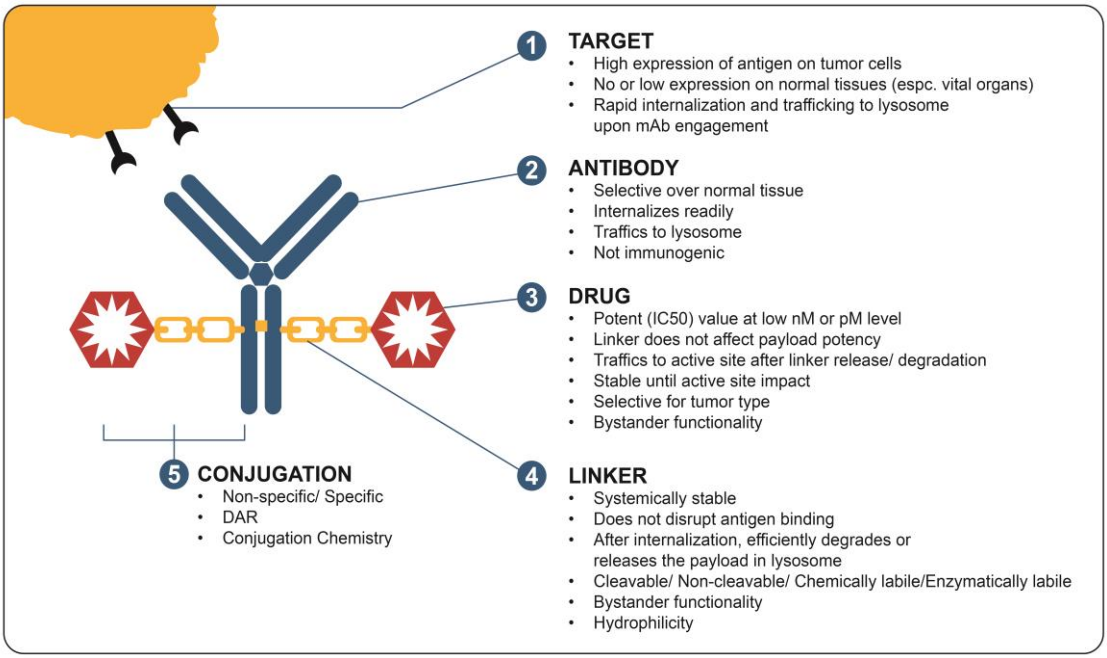


Figure 3. Aspects of ADC Design[10]

Mechanistically, an ADC functions by binding to the target antigen on the cell surface, undergoing internalization through antigen-mediated endocytosis, and trafficking into the lysosome. Here the payload releases or is cleaved resulting in toxin-mediated chemotherapy.[20] The ADC approach enhances specificity, thereby increasing therapeutic efficacy while minimizing toxicity and reducing the required dosage. **Figure 4** below describes the steps that lead to ADC activity.

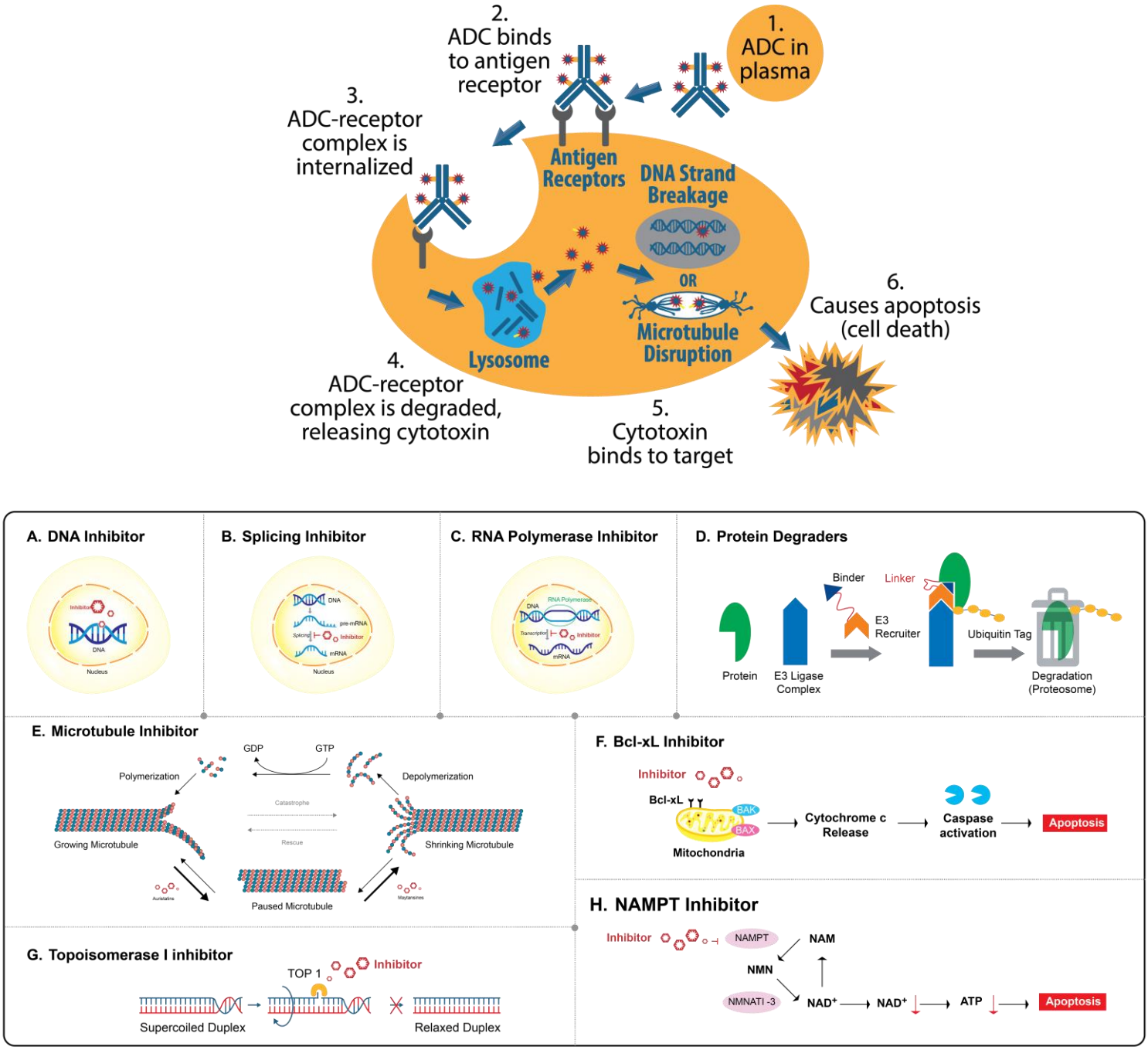


Figure 4. Mechanism of action of an ADC.[8,21,22]

The following discussion will focus on the conjugation and linker-payload portions of ADCs Once the payload is released from the lysosome, the type of payload used will determine which cell death program is triggered. **Figure 4 (A-H)** highlights mechanisms of different payload types. **Figure 4** - (A) DNA inhibitor; (B) Splicing inhibitor; (C) RNA polymerase inhibitor; (D) Protein Degrader; (E) Microtubule inhibitor; (F) Bcl-xL inhibitor; (G) Topoisomerase inhibitor; (H) NAMPT inhibitor.

4. Strategies for Enhanced Efficacy and Safety in ADCs

Over the past few years, extensive research has focused on the five critical elements of ADC design.[7] Numerous failures and successes in preclinical and clinical programs have led to the development of innovative strategies aimed at improving and advancing the chemistry of these elements to create next-generation ADCs.

4.1 Target Antigen

Recent advancements in ADC research are focused on identifying cell surface antigens that are either overexpressed or uniquely expressed on cancer cells. This approach aims to enhance treatment specificity and minimize toxicity concerns. Additionally, researchers are exploring targeting components of the tumor microenvironment, such as stromal cells or vasculature, to disrupt tumor growth and metastasis. Novel antibody formats enable simultaneous targeting of multiple antigens, enhancing the efficacy of ADCs.[7] Tumor-associated glycoproteins, such as mucins[23] and glycosylated proteins,[24] are also gaining attention due to their specific expression patterns in tumors. Next-generation ADCs are being developed to target a wide array of cell-membrane receptors and proteins. The most explored target antigens are highlighted in **Table 2**.

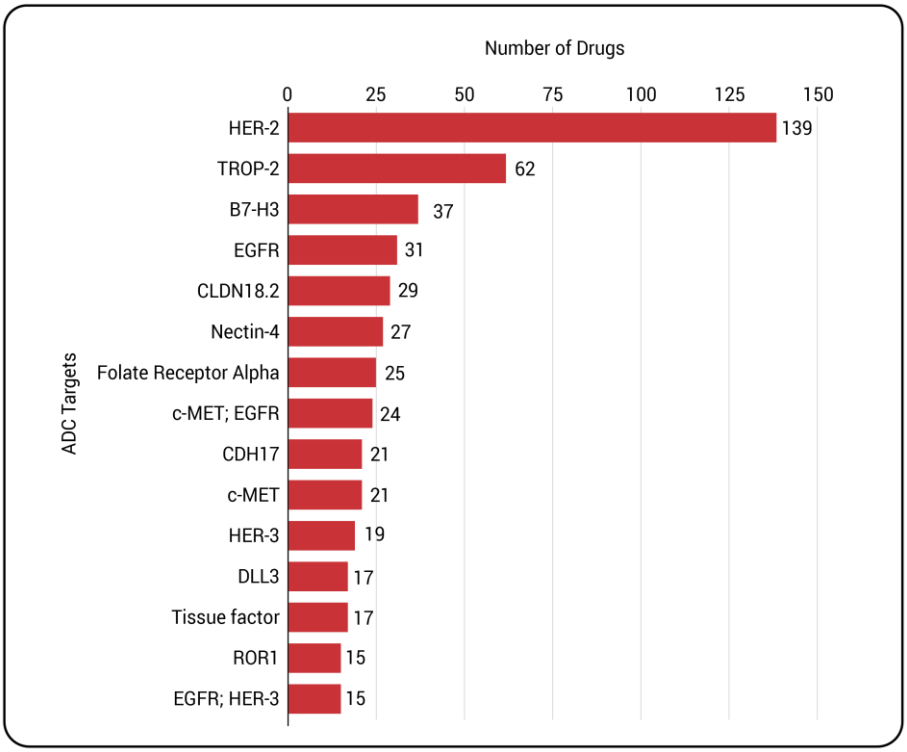


Figure 5. Top disclosed ADC Targets[3]

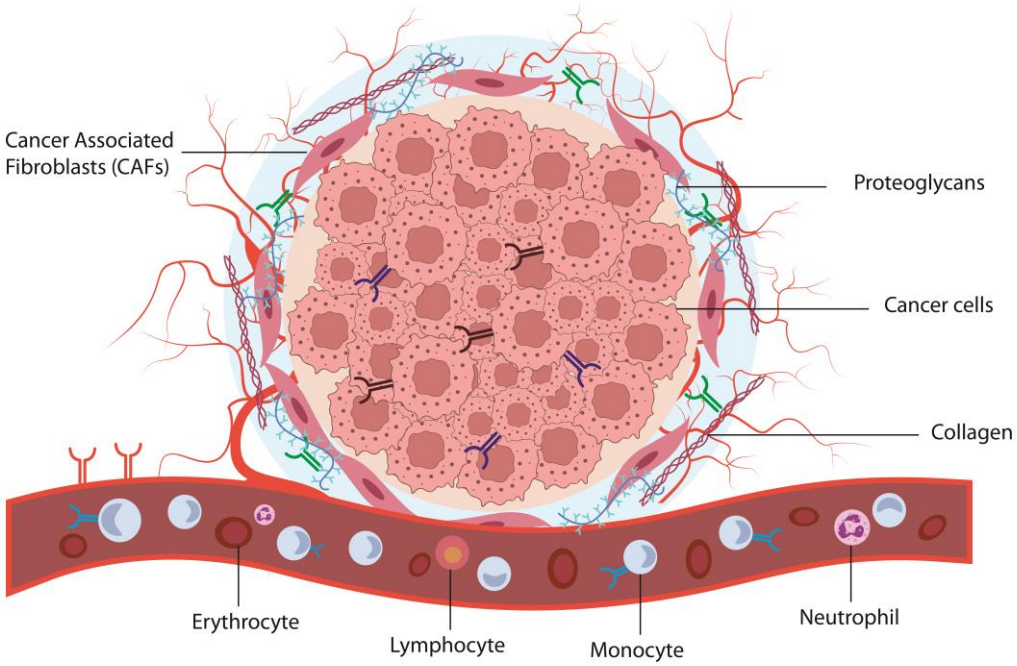


Figure 6. Targets for ADCs[7]

Table 2. Common target antigens for different disease indications[7,25]

	Driver Oncogenes	HER2, EGFR
	Target Antigens in tumor vasculature	EDB (Fibronectin, extra-domain B), ETB (Endothelium receptor), PSMA, VEGFR2, ROB04, Tissue Factor
	Target Antigens in tumor stroma	Collagen IV, Periostin, Tenascin C
	Target Antigens overexpressed in cancer cells	GPNMB, CD70, CD56 (NCAM), Trop-2 (TACSTD2), Folate receptor alpha, Tissue factor, ENPP3, p-Cadherin, Mesothelin, STEAP1, CEACAM5, Mucin1, Nectin 4, SLC44A4, PSMA, LIV1 (ZIP6), 5T4, SC-16, Guanylyl cylcase C, SLITRK6
	Target Antigens in hematological malignancies	CD30, CD22, CD79b, CD19, CD138, CD74, CD37, CD33, CD98

4.2 Targeting moiety

Antibodies used are exclusively of the IgG class (subclass IgG1, IgG2, IgG3, and IgG4) which have a unique profile with respect to the length of hinge region, the number of inter-chain disulfide bonds, and Fc-effector functions.

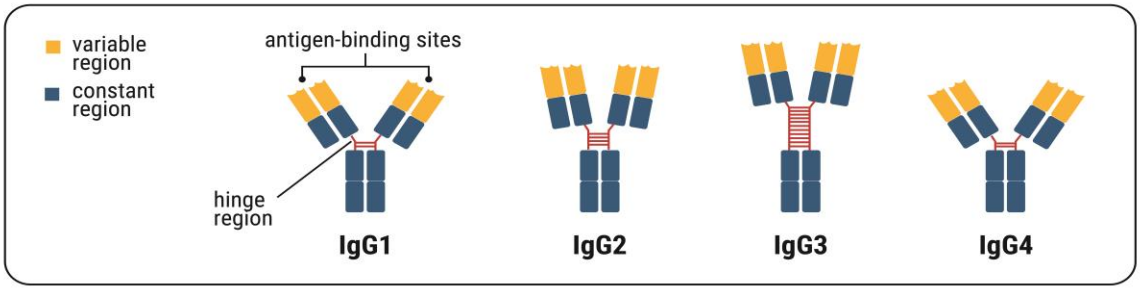


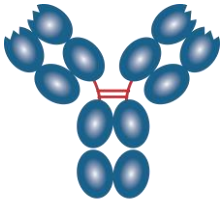
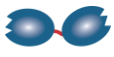
Figure 7. Immunoglobulin G (IgG) subtypes

Table 3. Comparison chart of IgG subtypes[3,26,27]

	IgG1	IgG2	IgG3	IgG4
Molecular mass (kD)	146	146	170	146
Amino acids in hinge region	15	12	62	12
Inter-heavy chain disulfide bonds	2	4	11	2
Serum half-life	~21 days	~21 days	~7 days	~21 days
Complement activation (C1q binding)	++	+	+++	–
Specifications	Induces strong effector functions such as ADCC, ADCP & CDC by high binding affinity with Fc receptor	Potential for more conjugation sites (Increased cytotoxic payload)	More efficient at inducing tumor cell lysis	Ability to form half antibodies and swap fragments with other IgG4 units (hybrid bispecific compounds)
Approved ADCs	Kadcyla®, Enhertu®, Trodelvy®, Adcetris®, Polivy®, Padcev®, Elahere®, Aidexi®, Ujvira™, Zynlonta®, Tivdak®, Datroway®, Sacituzumab tirumotecan, Blenrep, Emrelis™, Aveda®	N/A	N/A	Mylotarg®, Besponsa®
Candidates in clinical trial	160	2	N/A	4

Hematologic indications account for 8 out of 19 approved ADCs, while the remaining 11 ADCs target various solid tumors including breast, cervical, and lung cancers. However, inadequate penetration of tumor cells remains a concern limiting the drug's efficacy for solid tumors. Research on alternative delivery systems like smaller targeting moieties can address the issue of poor penetration associated with large ADCs. Novel small-format drug conjugates are emerging at the preclinical stage, ranging from antibody-fragment drug conjugates (e.g., Fab, diabody, and scFv) to small protein scaffold-drug conjugates (e.g., Affibody, etc.) and are summarized in **Table 4.**

Table 4. Small-format Drug Conjugates[28,29,30]

Small -format drug conjugate	Mass	Structure	Advantage(s)	Drawback(s)
 IgG	150 kDa	Disulfide linked, two heavy + two light chains	Longer half-life and better drug accumulation at tumor site; Ability to carry a higher load of drugs molecules; Triggers immune-mediated effector functions (ADCC, CDC)	Drug resistance, off-target toxicity, low penetration
 Bivalent fragment	~ 75-80 kDa	Two fragments linked at hinge region	Better penetration than mAbs due to smaller size	Shorter half-life
 Fab	~50 kDa	Disulfide linked, one heavy + one light chain	Block targets (receptors & signaling pathways) without cross-linking	Not very potent in vivo; modest reduction in tumor growth
 Diabody	~50 kDa	Two Fv domains connected by peptide linker	Rapid tumor penetration and accumulation due to smaller size	Higher dose needed to match potency of ADC
 ScFv	~25-27 kDa	Variable region of heavy and light chain joined by peptide linker	Successful for applications where time critical elimination was necessary	Low delivery rate
 V-domain	12.5 - 25 kDa	Lacks a light chain and heavy chain CH1 domain	Highly soluble and more stable than conventional antibodies	Slower and lesser internalization

Small -format drug conjugate	Mass	Structure	Advantage(s)	Drawback(s)
 Scaffold	10-25 kDa	Monomeric proteins with stable tertiary structures	Small size, high affinity, excellent specificity, and stability	Requires use of protein engineering to ensure continuous exposure after dosing
 Cys-knot	~ 3.5-5 kDa	Protein motif containing 3 disulfide bridges (formed from pairs of cysteine residues)	3 disulfide bonds provide remarkable stability against chemical denaturation, and proteolysis	Less potent than free payload
 Peptide	< 5 kDa	Short chain of amino acids	Enhanced binding, diversity & capability to cross the cell membrane	Poor intrinsic pharmacokinetic properties of peptide; shorter half-life
 Bicycle	~ 1.5-2 kDa	Intramolecular disulfide bond & bicyclization of the peptides	High affinity binding and specificity to protein target, greater conformational rigidity, and metabolic stability	Poor physicochemical properties

4.3 Linker Chemistry and Synthesis

More than 80% of the clinically approved ADCs (16 out of 19) and >50% of those in clinical development employ cleavable linkers.[3] Cleavable linkers come in a variety of motifs and release mechanisms, but all have a bond that is custom designed to be broken at either a lower pH, with an enzyme or in the presence of thiols. The cleavable linkers will release a metabolite that can have membrane permeability. Membrane permeability usually will mean that the cytotoxin will have bystander activity, which is the ability to diffuse to neighboring cells and have an effect.

On the other hand, a non-cleavable linker is a linker that does not contain any biologically or chemically labile bond and an active catabolite is released by the complete degradation of the antibody. The released catabolite will contain the amino acid from the antibody to which the linker-payload was conjugated. Catabolites from non-cleavable linkers do not cross membranes passively and thus do not distribute within a tissue. The two most common non-cleavable linkers that are used are maleimidocaproyl (mc) and succinimidyl trans-4-(maleimidylmethyl) cyclohexane-1-carboxylate (SMCC). In general, a non-cleavable linker is better tolerated but less efficacious.[31]

The most popular linker is the protease cleavable linker that contains a valine-citrulline-para-aminobenzyl-carbamate moiety (vc-PABC).[32] This is a traceless linker that allows the release of amine containing cytotoxins. Many di-, tri-, and tetra-peptide sequences are cleaved by proteases and changing the sequence can facilitate the synthesis of the linker-payload and improve the properties of the ADC construct. There are also traceless cleavable linkers that get cleaved by glucuronidases that offer higher water solubility.[33] The advantages of cleavable

linkers are that they have good plasma stability and robust activity in a variety of cell lines and preclinical models.[34]

Another means of releasing cytotoxin is to use the acidic environment found in the tumor microenvironment and in the lysosome. Hydrazones and carbonates are two commonly used motifs for pH-sensitive linkers. These acid labile linkers shed cytotoxins in circulation but are still powerful linker motifs.[11] Finally, the last type of cleavable linker discussed will be the one containing reducible bonds. These are usually identified by their disulfide bond which breaks in half in the presence of cysteine or glutathione. The advantages of disulfide linkers are that the kinetics of release can be controlled by steric bulk.[35]

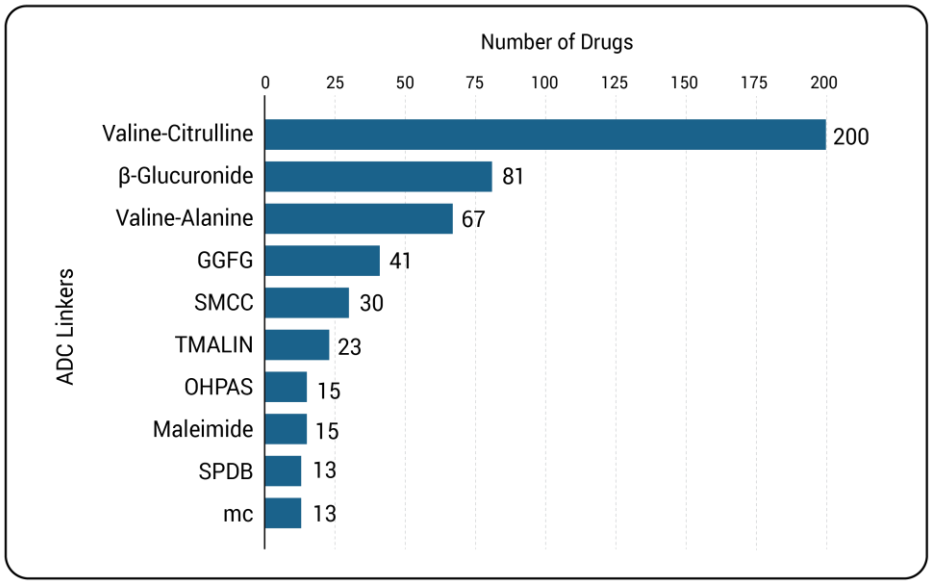


Figure 8. Top Disclosed ADC Linkers[3]

Non-specific payload release is a common problem encountered with the usage of existing linkers. The resulting off-target toxicity becomes a prime cause for limiting the therapeutic window.[17] ADC stability and safety is primarily affected by factors such as the linker length, hydrophilicity, site of conjugation, conjugation method and steric hindrance around the site of the linker.[36] While designing an ADC it could be considered that if, for example, the tumor has consistent expression throughout the tissue then one could consider non-cleavable linkers to lower toxicity. If there is heterogeneous expression, then a cleavable linker generating a membrane permeable catabolite (with bystander activity) would be advantageous. But if there is low expression, then a potent cytotoxin will be required. With this information in hand, one can start testing the linker-payload that has the best chance of success and begin refining the ADC from the data generated.

4.4 Conjugation Technologies

DAR is a critical quality parameter which influences the overall efficacy, pharmacokinetics, and safety profile of an ADC molecule. This ratio is typically determined by the conjugation method employed during the development stage. The DAR is measured by a variety of analytical techniques, which should give similar results but almost never the same number.[37] Hence the usage of two different methods to determine the DAR is highly recommended. As

the field evolves, finding orthogonal methods for DAR determination is becoming more routine.[38] The distribution of stochastic conjugations is usually referred to as heterogeneous, that is a mixture of populations (DAR 0 – 8) is obtained to give an average DAR (e.g., DAR 4), or homogeneous when the population is mostly one species (e.g., mostly DAR 2).[39]

IgG molecules generally possess multiple intrinsic sites that can be engineered by introducing electrophilic handles to create reactive sites for bioconjugation. Non-specific or stochastic conjugation methods utilize natural nucleophilic amino acids found on the antibody, particularly lysine and cysteine residues and do not require antibody engineering.

There are 80 lysine residues in an IgG molecule, among which 20 are located in highly solvent-accessible positions.[40] Lysine-based conjugations are carried out by mixing the mAb with an activated ester. This generally results in a DAR distribution between 0 and 9 with an average DAR of 3.5. In contrast, cysteine residues are less abundant but are uniformly distributed throughout the antibody structure thus reducing heterogeneity as compared to lysine conjugation. There are 16 pairs of cysteines, which comprise of 12 intrachain disulfide bonds and 4 interchain bonds. Cysteine conjugation generally involves partial reduction of these 4 interchain bonds to form reactive cysteine thiol groups. These thiols are then available to react with thiol-specific maleimide linkers. The DAR is typically controlled by the amount of reducing agent used at the reduction stage. The standard conjugation using cysteine aims for a DAR around 4 with a DAR distribution between 0-8 for IgG1 antibodies. Currently, most ADCs employ cysteine conjugation for the attachment of the linker-payloads.[39,41]

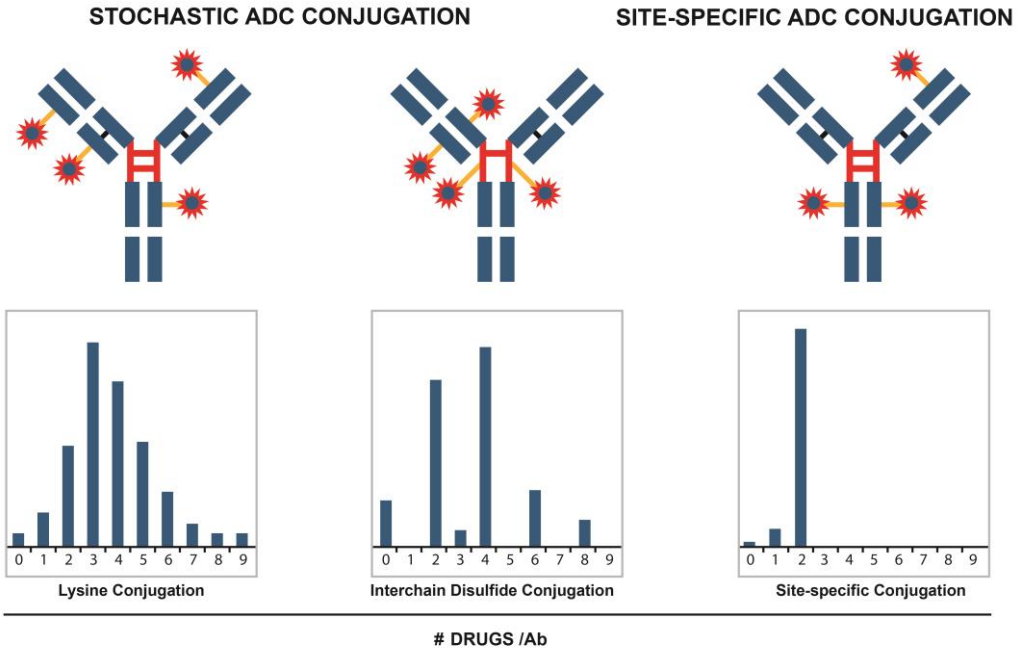


Figure 9. DAR Distribution between Heterogeneous (Stochastic) and Homogeneous Conjugations.[8]

This stochastic approach often leads to the generation of a heterogeneous population of different species with a widely distributed DAR. A low DAR could present significant challenges like reduced efficacy, higher dosage requirements and suboptimal tumor penetration. On the other hand, an ADC with a higher DAR is more susceptible to aggregation, rapid systemic clearance and toxicity concerns.[42] Since each of these generated subpopulations have different PK and efficacy profiles it could be hard to predict the effect of

all the different species during clinical trials. A small population of such species could be generating most of the toxicity observed, due to extensive antibody modification, which may also cause structural changes affecting the biological function.[43]

To address these challenges, several site-specific conjugation technologies have been developed. These strategies can create a more homogeneous ADC population with improved plasma stability, heightened tumor uptake, and enhanced binding efficiency.[43] The case of homogeneous ADCs into the clinic involved the modification of each interchain disulfide bonds (DAR8), enabling precise and site-specific conjugation, as demonstrated by trastuzumab deruxtecan (Enhertu®). This advancement allowed for more consistent DARs and improved therapeutic outcomes. In the past few years, numerous site-specific conjugation technologies have been developed. **Table 5** provides an overview of commonly employed strategies in developing ADC constructs with improved homogeneity and therapeutic index.

Among these numerous technologies, ConjuAll™ is a leading site-specific method developed by LigaChem Biosciences. It utilizes engineered antibodies and enzyme catalyzed modification steps via β-glucuronide linker. The linker adapts to higher DAR and wider payloads, such as degraders and small molecules. Another common technology platform is GlycoConnect™ which uses enzymatic remodeling and metal-free click chemistry to replace the glycan with a cytotoxic payload. **Figure 10** represents the top ten site specific technologies that are currently driving innovation in the ADC industry. [3]

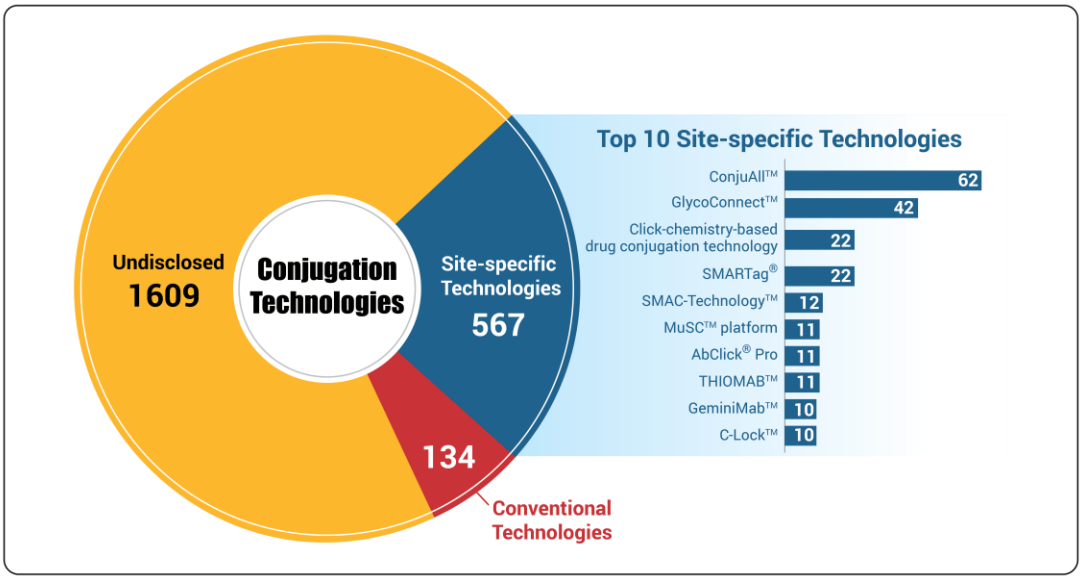


Figure 10. ADC Conjugation Technologies[3]

Table 5. List of ADC Conjugation Technologies

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
STOCHASTIC CONJUGATION				
Lysine sites		Heterogeneous ADC product	Activated ester groups undergo a stable covalent bond formation with primary amines found on the side chains of exposed lysine residues.	*Marketed*: Gemtuzumab ozogamicin (Mylotarg), Trastuzumab emtansine (Kadcyla), Inotuzumab ozogamicin (Besponsa), Mirvetuximab soravtansine (Elahere)
Cysteine sites		Heterogeneous ADC product	This approach utilizes cysteine residues generated through partial reduction of interchain disulfide bonds. Subsequent thiol-maleimide coupling involves a linker containing a maleimide group. This group reacts with the thiol (SH) groups of up to eight reduced cysteines in the IgG1 hinge region, typically engaged in four interchain disulfide bridges.	*Marketed*: Brentuximab vedotin (Adcetris), Polatuzumab vedotin(Polivy), Enfortumab vedotin (Padcev), Tisotumab vedotin (Tivdak), Disitamab vedotin (Aidexi), Loncastuximab tesirine (Zynlonta), Datopotamab deruxtecan (Datroway®)
SITE-SPECIFIC CONJUGATION				
Engineered Reactive Cysteines/ Cysteine Conjugation				
THIOMAB™	Genentech	2	The technology strategically introduces cysteine (cys) residues at specific positions within the heavy or light chains of antibodies. Drugs are selectively conjugated to the engineered cysteines, preserving the structural integrity of the disulfide bonds within the antibody.	*Phase 1/2:* HDP-101, *Phase 1:* DMUC4064A *Preclinical*: ITC-6102RO
Selenomab™	Scripps Research Institute		Selenomabs represent engineered mAbs with strategically incorporated selenocysteine residues through translational processes. The distinctive reactivity of selenocysteine's selenol group allows for precise drug conjugation at specific sites. Their high reactivity facilitates rapid, efficient, and single-step reactions, closely mirroring physiological conditions.	

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
Actibody	Kyowa Hakko Kirin Co., Ltd.		The Actibody (Active thiol antibody) has an LC-Q124C mutation positioned at a less exposed site. This occurs by substituting cysteine at Gln124 in the light chain of the targeted antibody.	
CYSMAB Technology	ImmunoGen	2	ADCs site specifically conjugated at HC-C442	*Phase 1/2*: Pivekimab Sunirine
Full Reduction of interchain disulfides	N/A	8	In the modification process of IgG1 antibodies, naturally occurring cysteine residues become accessible by reducing the four interchain disulfide bonds. This reduction reveals up to eight reactive thiol residues, and subsequently, the antibodies are conjugated with eight payloads, each attaching to one of the available cysteines. Reduction of interchain disulfides reveals thiol residues, reactive towards soft electrophilic reagents. Full reduction and complete reaction of all eight reactive cysteines results in DAR 8 conjugates.	*Marketed*: Sacituzumab govitecan (Trodelvy), Trastuzumab deruxtecan (Enhertu)
Flexible Antibody Conjugation Technology (FACT) Platform	Pyxis Oncology (in-licensed from Pfizer)		Technology involves the site-specific conjugation of the linker-payload to engineered cysteine residues, enhancing anti-tumor activity, safety, and tolerability.	*Phase 1/2*: PYX-201
ByonShieLD®	Byondis		Utilizing orthogonal cysteine activation and conjugation technology, this method produces consistent ByonZine® ADCs. The process involves shielding the hydrophobic payload, resulting in ADCs characterized by a superior therapeutic index and exceptional manufacturability.	*Phase 1*: BYON3521
RESPECT-L® (REsidue SPEcific Conjugation Technology)	Eisai	2	Rabbit antibodies exhibit a unique intrachain disulfide bond between the Vκ and Cκ domains. Preserving the Vκ cysteine (Cys80) in the humanization process results in an unpaired cysteine, which shows high conjugation efficiency.	*Preclinical*: MORAb-109
WuXiDARx™	WuXi Biologics	2,4,6	In this approach, a metal ion blocker is introduced into the antibody solution during the reduction phase, facilitating the targeted reduction of disulfide bonds. Thiol-reactive linker-payloads are then applied for conjugation with sulfohydryls	

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
			(-SH), followed by quenching and the restoration of the blocked hinge region through oxidative recovery. In the WuXiDAR2 and WuXiDAR6 platforms, native antibodies undergo a proprietary process without intermediate purification steps. This process results in the reduction of 1 or 3 disulfide bonds, yielding 2 or 6 thiol groups, respectively. Thiol-reactive linker-payloads are subsequently introduced for conjugation. This technology offers a narrow DAR distribution (composition of the desired DAR ≥ 70%)	
PermaLink™	Iksuda (Previously Glythera)		This approach can be used for cysteine-based heterogeneous conjugation with wild-type antibodies and homogeneous conjugation with antibodies featuring engineered cysteines. The vinyl segment of PermaLink, derived from its vinyl-pyridine-based chemistry, effectively interacts with the thiol group present in the amino acid cysteine.	*Preclinical*: IKS01
P5 Conjugation	Tubulis GmbH	8	This approach involves cysteine-selective chemistry and employs a process that utilizes disulfide bond reduction and Staudinger-induced Michael addition.	*Phase 1/2*: TUB-040
Unnatural Amino Acids (UAA) Engineering				
EuCODE™	Ambrx		This process involves the integration of non-natural amino acids into heterologous proteins. It is achieved by incorporating three non-natural components into the expression system including, non-natural amino acid, supplemented into the growth medium; orthogonal aminoacyl-tRNA synthetases (aaRS); and an orthogonal tRNA.	*Phase 2/3*: ARX788, *Phase 1:* ARX517
Xpress CF+™	Sutro Biopharma		This cell-free protein synthesis system generates antibodies incorporating non-natural amino acids. This capability allows for precise conjugation of uniform antibody drug conjugates (ADCs) through click chemistry at specific sites.	*Phase 2/3*: Luveltamab tazevibulin
SMARTag® Technology	Redwood Bioscience (Subsidiary of Catalent)	0 to 8	This approach involves incorporating formylglycine (fGly), a non-natural amino acid, into the protein sequence. A tagged construct is created by inserting a short consensus sequence (CxPxR) at the desired location. Co-expressing this construct with the formylglycine-generating	*Phase 1*: TRPH-222

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
			enzyme (FGE) in cells leads to the conversion of cysteine within the tag into fGly during translation, resulting in an antibody with two aldehyde tags per molecule. The aldehyde tags serve as chemical handles for bio-orthogonal conjugation. Using the Hydrazino-iso-Pictet-Spengler (HIPS) ligation, the cytotoxin payload is connected to fGly, forming a stable, covalent C−C bond between the payload and the antibody.	
			Enzyme Assisted Ligation	
BTG (Bacterial transglutamination)	MI Abs & Innate Pharma	2 or 4	The utilization of Bacterial transglutaminase (BTG) enables the attachment of payload-linkers at multiple positions in antibodies through the incorporation of an LLQGA tag.	*Preclinical*: Immunitas Therapeutics anti-CLEC2D-TLR9-ISAC
Tub-Tag®	Tubulis	2 or 4	Tubulin tyrosine ligase (TTL), and enzyme involved in intracellular regulation of microtubule stability, recognizes a 14-amino acid motif at the C-terminus of alpha-tubulin. When fused to an antibody, this recognition motif (Tub-tag) enables TTL to attach unnatural tyrosine derivatives that carry reactive groups, facilitating chemoselective conjugation.	*Preclinical*: TUB-010
SMAC™	NBE-Therapeutics		This method conjugates a pentaglycine-modified toxin to the C-termini of LPETG-tagged antibody heavy and light chains using sortase-mediated antibody conjugation.	*Phase 1/2*: SOT102, NBE-002
iGDC™ (Intelligent glycosyltransferase dependent conjugation)	Gene Quantum		This method involves employing immobilized engineered glycosyltransferase to achieve accurate and effective coupling of payloads to designated locations on antibodies.	*Preclinical*: BioMap-GeneQuantum ADC, GeneQuantum dpADC (iLDC™ and iGDC™)
iLDC™ (Intelligent Ligase Dependent Conjugation)	Gene Quantum	2	This approach uses immobilized engineered transpeptidase for the accurate and efficient conjugation of payloads to specific antibody sites.	*Phase 1/2*: GQ1001
RESPECT-H® (REsidue SPEcific Conjugation Technology)	Eisai		This C-terminal lysine-specific linkage technique utilizes the transglutaminase enzyme to catalyze the formation of a durable isopeptide bond. This bond forms between the γ-carboxyamide group (acyl donor) of a glutamine and the ε-amino group (acyl acceptor) of a lysine.	*Phase 2*: BB-1701

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
Peptide Asparaginyl Ligase (PAL) one-pot conjugation	Singzyme & Lonza	2, 4. 6, 8	This approach facilitates the site-specific attachment of payloads with peptidic linkers to antibody, using highly efficient peptide asparaginyl ligases (PAL). The mAbs undergo conjugation at C-termini of both their L and H chains to produce a DAR 4 bioconjugate. DAR 2 conjugates can be produced by labelling either the L or H chain only and DARs higher than 4 via dual N- and C- conjugation or by using a higher payload to linker ratio.	
ConjuAll™	LegoChem Biosciences	2	This approach utilizes novel linker chemistry combined with site-specific enzymatic conjugation.	*Phase 3*: FS-1502
Glycan Remodelling & Glycoconjugation				
GlycoConnect ™	Synaffix		This approach leverages the conserved N-glycosylation site to produce site-specific ADCs through enzymatic remodelling and click chemistry without the need for metal catalysts. The existing antibody glycan is replaced with a therapeutic payload.	*Phase 3*: MRG004a
GlycOBI™	OBI Pharma	DAR4, DAR8 or DARX	This method incorporates OBI's exclusive enzymatic technology, EndoSyme OBI™ and conjugates the hydrophilic linker-payload to the glycan site naturally present in the Fc region of the antibody.	*Preclinical*: OBI Pharma BsADC
GlyCLICK	Genovis AB	2	The process involves Fc-glycan remodeling achieved through the complete deglycosylation of the antibody. This method of site-specific conjugation is based on click-chemistry and is carried out through a two-step enzymatic procedure, transforming Fc-glycans on IgG monoclonal antibodies into two anchor points for conjugation with any alkyne-containing payload.	*Preclinical*: Genovis Glykos ADC
Short Peptide Tags				
NexMab™	Alteogen		This method employs motifs containing ligand-protected cysteines. It involves introducing peptide motifs with cysteine residues at the C-terminus of the heavy chain of an antibody.	*Phase 1*: ALT-P7
AbClick® Pro & AbClick® Standard	AbTis	2,4,6,8	This click-chemistry based approach relies on the proximity effect to conjugate payloads to lysine residues on the Fc site of antibodies. Cyclic peptides reversibly bind to the IgG Fc domain and the payload is attached. AbClick® Pro, equipped with a binding site for Ferna, leads to a	*Preclinical*: AbTis and WuXi XDC ADC, AbTis CD22 ADC

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
			comparatively prolonged half-life, while AbClick® Standard, lacking the FcRN binding site, exhibits a relatively shorter half-life.	
pClick Technology	Rice University & Peking University		This approach is based on the proximity-induced reactivity between an affinity peptide cross-linker and a nearby antibody lysine residue. Solid-phase peptide synthesis is employed to incorporate the FPheK moiety at a designated site within the affinity peptide. When the affinity peptide binds to the antibody, the presence of FPheK facilitates covalent attachment to a nearby lysine residue on the antibody through proximity-induced reactivity.	
			Native Cysteine Rebridging	
McSAF Inside®	McSAF and Lonza	2, 4	This is a cysteines rebridging technology platform conjugating the payload to the target protein at the native interchain disulfides.	*Preclinical*: ADCITMER®, McSAF 01
ThioBridge™	PolyTherics/ Abzena	4	Following the reduction of an intra-chain bond, two free cysteine thiols are generated. These can be specifically conjugated at the site with a bis-thiol alkylating reagent (ThioBridge), to which the payload is already attached via a releasable/non releasable linker. The ThioBridge disulfide-bridging reagent undergoes bis-alkylation to connect to both cysteine thiols derived from the reduced disulfide.	*Phase 1*: Oba01 *Phase 1/2:* MBRC-101; *Discontinued*: OBI-999
			Fc affinity Mediated	
AJICAP® site specific conjugation	Ajinomoto	2	This linker structural tuning approach enables site-specific modification of native IgGs at the novel conjugation site (Lys288)	*Preclinical*: AJICAP-ADCs
			Modification of N/ C Terminal of Antibody	
N terminal serine conjugation	ImmunoGen		Engineered serine residues can be strategically placed at four distinct N-terminal positions on the antibody. Modifying the N-terminus ensures that the attached payload is positioned far from the antibody's target binding sites in the variable region CDRs.	*Preclinical*: TSD101
N-terminal glutamate conjugation	N/A		N-terminal glutamate is selectively modified with aldehyde functionalised payloads	

Conjugation Method/ Platform	Developed by	DAR	Description/ Features	Example(s) of ADCs using the technology
N-terminal cysteine conjugation	N/A		N-terminal cysteine is selectively modified with aldehyde functionalised payloads	
π-clamp tag mediated	N/A		π-clamp peptide sequence selectively reacts with perfluoroaromatic probe	
DBCO tag mediated	N/A		DBCO (cysteine containing peptide) tagged antibody selectively reacts with DBCO reagents via. the thiol-yne reaction	
CD38 tag mediated	N/A		CD38 tag reacts with covalent inhibitor tagged payload, forming a stable arabinosyl ester	
NTERM Conjugation	ABL Bio	3.2 (weighted average)	In this approach, payloads were linked to the N-terminal of an antibody by creating amine bonds through reductive alkylation reactions.	*Preclinical*: TSD 101
Disulfide Bridging				
C-Lock™	Sorrento Therapeutics		This approach employs an innovative linker chemistry to re-connect the reduced disulfide bonds between the H and L chains of the antibody, simultaneously enabling the incorporation of a drug into each reconnected disulfide bond.	*Phase 1/2*: STI-6129
Linker Controlled Conjugation Technology				
K-Lock™	Sorrento Therapeutics		This technology is highly selective on one or two specific sites among the 80-90 lysine side chains present on an antibody. The generated ADCs exhibit reduced regioisomers and a lower DAR.	*Phase 3*: Trastuzumab botidotin
Others				
MuSC™ (Multifunctional Site-specific Conjugation)	Adcoris	2,4,6,8, 10	Enables the development of typical ADC and new-structure ADC, i.e., dual payload ADC and bispecific ADC. Offers CMC advantage, multifunctionality, low immunogenicity risk and pervasiveness	*Phase 1*: ADC2154, *Preclinical:* ADC2192

Note: For references supporting the content provided please visit https://njbio.com/antibody-drug-conjugates/

4.5 Novel Payload Strategies

To mitigate the issues of toxicity and reduced half-life it would be beneficial if we could keep the DAR below 4 while maintaining ADC efficacy. For this reason, selecting an appropriate payload for a specific disease indication and using it at the optimal concentration based on its IC50 value is crucial. Cytotoxic compounds have different permeabilities, hydrophobicity, potencies and mechanisms of action. Payloads have diversified over years of research and novel strategies like topoisomerase II inhibitors, transcription inhibitors, protein synthesis inhibitors, PROTACs, and immunomodulators have been developed. A diverse array of payloads including small molecules, protein toxins, radionuclides, cytolytic immunomodulatory proteins, biologically active peptides and enzymes are under preclinical

and clinical investigation.[20] **Table 6** summarizes both payloads that are in use or under investigation in ADC development.

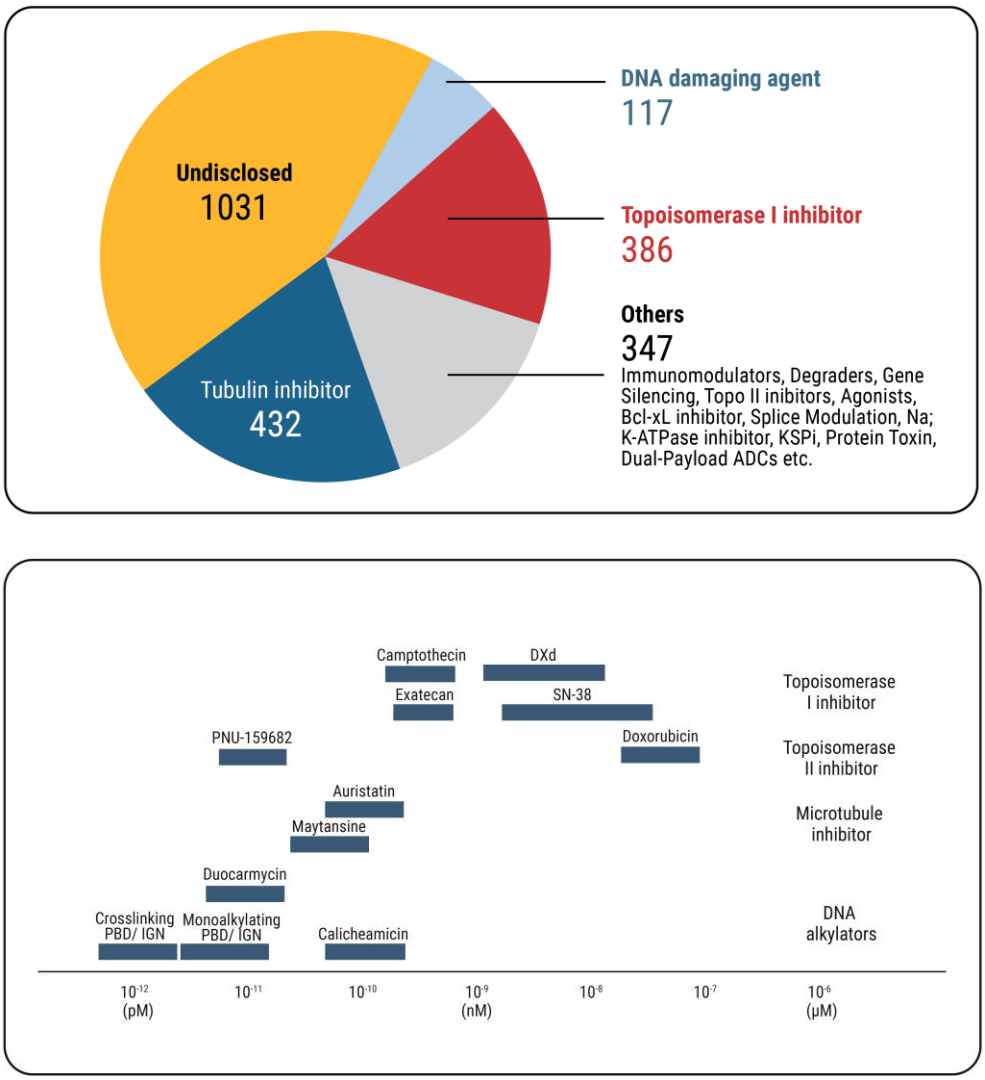


Figure 11. ADC Payloads by Mechanism of Action[3](top); IC50/ Potency of various payload types[3] [44,45](bottom)

Table 6. Conventional and novel ADC Payloads[3]

Payload Class	Payloads	Examples
Tubulin inhibitors	Auristatin	MMAE, MMAF, Duostatin5, Duostatin5.2, SHR152852, MMAD, LP2, PF-06380101/ Aur0101, Auristatin F-HPA, Auristatin W analog, F55443, MMAU, ZD02044, Amberstatin (AS269), AF-HEA
	Maytansine	DM4, DM1, DM21, M24
	Tubulysin	AZ13599185, Tubulysin A, Tub114, Tub201, Tub255, Tub196
	Others	Cytolysin, Eribulin, KSP inhibitor, PM050489, Cryptophycin, Paclitaxel, Docetaxel, DIACC2010, TAM470, AP052, Utidelone, VIP 716

Payload Class	Payloads	Examples
DNA Damaging Agents	Calicheamicin	--
	Duocarmycin	DUBA, NMS-P528, MED-A/DNAMGBA toxin
	Indolino-benzodiazepine dimer (IGN)	DGN549, DGN462, IGN-P1
	Pyrrolobenzodiazepine (PBD)	SG3199, SG3552, SG2000, D211, I-BiPs, SG2057, SGD1882, SC-DR003, SG3249, SG3376, LCB20-0187
	Pyridinobenzodiazepine (PDD)	FGX2-62, FGX20-75
	Others	Lidamycin, Azonafide, Thienoindole, Temozolomide, Cyclopropylpyrroloindole (CPI), dHBD, AxcynDOT™ (Trabectedin)
Topoisomer-ase inhibitors	Topoisomerase I inhibitors	SN-38, CPT-113, Exatecan, DXd/ DX8951, Camptothecin, ATI020, LMP517 (dual action), AZ14170132, Ed-04, Belotecan, Tubutecan, YL0010014, AMDCPT, BCPT02, D2102, Dxh, KLG10023, LD2, P1003, P1021, PBX-7, SHR9265, YL0014, ZD06519, SC3386, PL2202, MH30010008, MF-6, LDX2, GS-P-000, AZ14170133
	Topoisomerase II inhibitors	Doxorubicin, PNU-159682, Anthracycline
Immuno modulators	Agonists	STING agonist, TLR7 Agonist, TLR 7/8 agonist, TLR8 agonist, TLR9 agonist, TAK676, CRD5500, IMSA172, JAB-27670, Resiquimod (R848), SZU-101, Tacrolimus (FK506), Lenalidomide (Thalidomide)
Other Payload Classes	RNA polymerase II inhibitor	Amanitin, Triptolide, Thailanstatin
	Degradation	SMol006, GNE-987, PROTAC, PRT3789 (SMARCA2), GSPT1 degrader, BRD4 degrader, RIPK2 degrader, EBET-1055, EBET-1593, CDG0501
	Other Novel Payloads (Modulators)	siRNA, ASO, Bcl-xL inhibitor, Steroids, dmDNA31, Urease, Glucocorticoids, Na; K-ATPase inhibitor, Phosphonate, NMT inhibitor, TGFβR antagonist, CEN-106, CEN371, CLYP-71 (Lytic peptide), CpG ODNs, EBET-1055, Glucagon-like peptide-1 analogues, Granzyme B, MYX2339, N-linked glycosylation inhbitor-1, Saporin, siDUX4.6

4.6 Novel ADCs

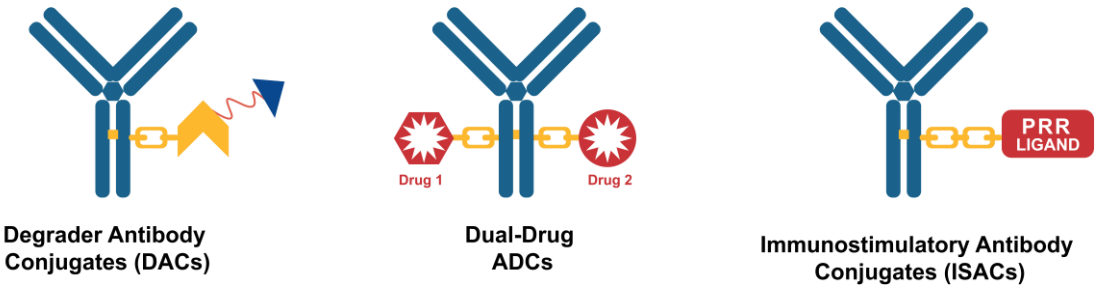


Figure 12. Novel ADCs

- Immunostimulatory Antibody Conjugates (ISACs)[46]

These conjugates are basically engineered mAbs linked with payloads that act as pattern recognition receptor (PRR) agonists. They work by enhancing the immune responses within the tumor microenvironment (TME) and further stimulate the adaptive immune system. Through the induction of pro-inflammatory cytokines and chemokines, they appear to be promising as monotherapies or in combination therapies and are currently in preclinical stages and early-phase clinical trials.

- Degrader Antibody Conjugates (DACs)

Degrader-Antibody Conjugates (DACs) combine the catalytic activity of proteolysis targeting chimera (PROTAC) payloads with the specificity of antibodies, [47] while overcoming the limitations of both ADCs and TPDs. DACs can recognize specific antigens and deliver degrader molecules to target tumors and tissues. These molecules have the potential to reduce toxicity associated with cytotoxic payloads while increasing the specificity of traditional degraders by linking them to highly specific mAbs.

Several DACs are currently being studied and have demonstrated superior *in vitro* and *in vivo* activity against target tumor cells. Using the BT474 xenograft model, the effect of ORM-5029 has reported superior single-dose activity as compared to Kadcyla® and similar to that of Enhertu®. ORM-6151, developed to selectively deliver catalytic GSPT1 protein degrader to SIGLEC3-expressing tumor cells, is currently in its Phase I clinical trial.[48]

Table 7. List of Preclinical and Clinical Degrader-Antibody Conjugates[3]

Drug Names	Highest Phase of Development	Drug Targets	Linker	Payload	Disease Indication
ORM-6151	1	GSPT1; SIGLEC3	β-Glucuronide	SMol006	Acute Myelogenous/Myeloid Leukemia (AML); Acute Myeloid Leukemia; Myelodysplastic Syndrome
3C Therapeutics Degrader-Antibody Conjugate (DAC)	Preclinical	Undisclosed	Undisclosed	Undisclosed	Undisclosed
84-EBET	Preclinical	BET (Bromodomain and Extraterminal Proteins); CEACAM6	Glycine-Glycine-Phenylalanine-Glycine (Gly-Gly-Phe-Gly) (GGFG)	EBET-1593	Breast Cancer; Colorectal Cancer; Lung Cancer; Pancreatic Cancer; Pancreatic Ductal Adenocarcinoma (PDAC)
AbTis DAC	Preclinical	Undisclosed	Undisclosed	Undisclosed	Undisclosed
AC4847	Preclinical	PI3Kα	Undisclosed	Undisclosed	Cancer

Drug Names	Highest Phase of Development	Drug Targets	Linker	Payload	Disease Indication
Accutar Biotechnology KIF11 DAC	Preclinical	KIF11; Undisclosed	Undisclosed	dKIF976	Cancer
BLB-201	Preclinical	Undisclosed	Undisclosed	Undisclosed	Acute Myelogenous/Myeloid Leukemia (AML)
BLB-202	Preclinical	HER-2	Undisclosed	Undisclosed	Breast Cancer; Solid Tumors
BLB-301	Preclinical	Undisclosed	Undisclosed	Undisclosed	Lung Cancer; Solid Tumors
Crossfire Oncology DAC platform	Preclinical	Undisclosed	Disclosed; Maleimide	Undisclosed	Cancer; Metastatic Castration-Resistant Prostate Cancer
CY006	Preclinical	Undisclosed	Undisclosed	Undisclosed	Autoimmune Disorders; Cancer
Cyrus Therapeutics DAC 1	Preclinical	GSPT1; Undisclosed	Undisclosed	Undisclosed	Solid Tumors
DAC-1522	Preclinical	TROP-2	Undisclosed	Undisclosed	Pancreatic Cancer
DC-D-134	Preclinical	Undisclosed	Disclosed	Undisclosed	Solid Tumors
Debiopharm Ubix Antibody Degraducer® Conjugates	Preclinical	Undisclosed	Undisclosed	Undisclosed	Cancer
FD-004	Preclinical	HER-2	Undisclosed	Undisclosed	Cancer
FD-005	Preclinical	SIGLEC3	Undisclosed	Undisclosed	Cancer
gDAC-A	Preclinical	Undisclosed	Undisclosed	Undisclosed	Autoimmune Disorders
HCB-WH101	Preclinical	Undisclosed	Undisclosed	Undisclosed	Alzheimer's Disease; Cancer
Hdz-C123A	Preclinical	GSPT1; IL-3R	Undisclosed	CDG0501	Acute Myeloid Leukemia
IL2401	Preclinical	Cyclin K; TROP-2	Undisclosed	Undisclosed	Solid Tumors
Jecho Antibody-PROTAC DAC	Preclinical	BRD4; ROR1	Dibenzocyclooctyne (DBCO)	MZ1	Solid Tumors
Kangpu Biopharmaceuticals DAC1	Preclinical	Undisclosed	Undisclosed	Undisclosed	Solid Tumors
Kangpu Biopharmaceuticals DAC2	Preclinical	Undisclosed	Undisclosed	Undisclosed	Hematological Malignancies

Drug Names	Highest Phase of Development	Drug Targets	Linker	Payload	Disease Indication
Merck Degrader-Antibody Conjugate	Preclinical	Undisclosed	Undisclosed	Undisclosed	Undisclosed
ORM-1023	Preclinical	GSPT1; Undisclosed (Antibody target)	Undisclosed	SMol006	Neuroendocrine Tumors (Solid Tumors); Small Cell Lung Cancer (SCLC)
ORM-1153	Preclinical	IL-3R	Undisclosed	SMol006	Hematological Malignancies
Polymed Biopharma DAC	Preclinical	Undisclosed	Undisclosed	Undisclosed	Solid Tumors
Polymed Biopharmaceuticals KRAS G12D Degrader Antibody Conjugate	Preclinical	KRAS G12D; Undisclosed (Antibody target)	Undisclosed	Undisclosed	Autoimmune Disorders; Solid Tumors
PRA0002	Preclinical	PSMA; SMARCA2; SMARCA4	Undisclosed	PRP0004	Hematological Malignancies; Prostate Cancer; Solid Tumors
Prelude Degrader Antibody Conjugate	Preclinical	CALR; CDK9; SMARCA2; SMARCA4	Undisclosed	Undisclosed	Myeloproliferative Neoplasm
PROTAb-0001	Preclinical	Undisclosed	Undisclosed	Undisclosed	Undisclosed
PTB600	Preclinical	GSPT1; Undisclosed	Undisclosed	Undisclosed	Hematological Malignancies; Solid Tumors
TRX-214-1002	Preclinical	GSPT1; SIGLEC3	Undisclosed	Undisclosed	Acute Myeloid Leukemia; Cancer
Vertex-Orum Therapeutics Degrader-Antibody Conjugate	Preclinical	Undisclosed	Undisclosed	Undisclosed	Undisclosed
Xiling Lab DACs	Preclinical	Undisclosed	Undisclosed	Undisclosed	Cancer
Y-Biologics-Ubix Therapeutics DAC	Preclinical	Undisclosed	Undisclosed	Undisclosed	Cancer

- Dual-Drug ADCs[49]

Dual-Drug or Dual-Payload ADCs (dpADCs) incorporate two distinct payloads with complementary mechanisms of action, aiming to deliver a more potent cytotoxic response to cancer cells. These drugs are currently in preclinical development as summarized in **Table 8**.

Table 8. ADCs with dual payloads in preclinical development [3,50]

Drug Name	Payload	Homogeneous Conjugate
GeneQuantum HER3 dual-payload ADC	Undisclosed (Topoisomerase I inhibitor; tyrosine kinase inhibitor)	Yes
CrossBridge Bio Dual-payload ADC (CB-120)	Undisclosed	Yes
Phrontline Biopharma Bispecific Dual Payload ADC (2by2 ADC)	Undisclosed	Undisclosed
SMP-Dual	Undisclosed	Yes
Tripartite Therapeutics Dual Payload ADC	Polarpeutic agonist	Yes
131I-HLX-58-Deruxtecan	131-Iodine (Radio-isotopes); DXd/DX8951 (MAAA-1181a) (Exatecan)	Undisclosed
[225Ac] Ac-Macropa-nimotuzumab-PEG6-DM1	225-Actinium (Radio-isotopes); DM1 (Maytansine)	Undisclosed
[225Ac] Ac-Macropa-pertuzumab-PEG6-DM1	225-Actinium (Radio-isotopes); DM1 (Maytansine)	Undisclosed
[225Ac] Ac-macropa-trastuzumab-PEG6-DM1	225-Actinium (Radio-isotopes); DM1 (Maytansine)	Undisclosed
ADC2192	Undisclosed	Yes
ADC2202	Undisclosed	Yes
Araris Biotech Anti-NaPi2b ADC	Exatecan (Camptothecin); Undisclosed	Yes
AT-01 Dual Payload ADC	AxcynDOT™ (Trabectedin)	Yes
BioCombo Therapeutics Dual-payload ADC	Undisclosed	Undisclosed
BR113	Undisclosed	Undisclosed
CATB-101 [Undisclosed novel MPC (Dual Payload)]	Undisclosed	Undisclosed
CATB-101(CATB-102 Dual Payload ADC)	Undisclosed	Undisclosed
CrossBridge Bio Dual Payload 1	Undisclosed	Yes
CrossBridge Bio Dual Payload 2	Undisclosed	Yes
CrossBridge Bio Dual-Payload ADC	Undisclosed	Yes
DCB Globo H ADC	MMAE (Auristatin)	Yes
DCB MSLN ADC	MMAE (Auristatin)	Yes
GeneQuantum dual Payload ADC	Undisclosed	Yes
HMBD-802	Undisclosed	Yes
Immunwork TRZ-4(MMAF+DXd) ADC	DXd/DX8951 (MAAA-1181a) (Exatecan); MMAF (Auristatin)	Yes
JSKN021	Undisclosed	Yes
MABS-02	Undisclosed	Undisclosed
MC001	Undisclosed	Undisclosed

Drug Name	Payload	Homogeneous Conjugate
OBI Pharma Dual Payload ADC	Undisclosed	Yes
Ohio University CD276 mAb-MMAF/IMQ	MMAF (Auristatin); Undisclosed	Yes
PRA0002	PRT3789 (SMARCA2); SMARCA4	Undisclosed
ShanghaiTech University Tras-DXd-MTL1	DXd/DX8951 (MAAA-1181a) (Exatecan); MTT-5	Undisclosed
STRO-00X Topo1i + anti-Tubulin Dual-payload ADC	MMAE (Auristatin); Undisclosed	Yes
STRO-00X Topo1i + PARPi Dual-payload ADC	Exatecan (Camptothecin); Talazoparib	Yes
Sutro Biopharma iADC 2	Hemiasterlin; Undisclosed	Yes
TJ102	PE-E2K, PY-4car2 (Camptothecin Derivatives)	Undisclosed

5. Toxicity concerns and mechanisms

Despite being designed to enhance the targeted delivery of cytotoxic payloads to specific cancer cells, ADCs often encounter challenges related to toxicity. First-generation ADC data revealed that only a small fraction (~0.003 – 0.08%) of the injected dose reached the intended tumor cell[51] leading to the distribution of a significant amount of cytotoxin to non-target tissues and subsequent adverse events.

The toxicity associated with ADCs can be broadly classified into on-target and off-target toxicity. On-target toxicity occurs when the ADC binds to the intended cell surface protein on healthy cells, leading to adverse effects (**Figure 13A**). Off-target toxicity involves non-specific endocytosis, binding of the ADC to Fc/C-type lectin receptors, or internalization of free payload by passive diffusion across the cell membrane (**Figure 13B** and **13C**).[52] The bystander toxicity effect is observed when cleavage of the payload from ADCs leads to the diffusion of free payload into neighboring healthy cells.[53]

While ADCs with the same class of payload-linkers share similar toxicity profiles, using the same ADC to treat different cancers may result in varied toxicities. Common adverse events associated in late-stage clinical and marketed ADCs outlined in **Table 9**, can vary in severity, with some reaching grade 3 or higher. Among commonly used payload classes, peripheral neutropenia or thrombocytopenia is reported as the most common toxicity, followed by peripheral neuropathy, hepatotoxicity, skin rash, ocular toxicity, and toxicity of the gastrointestinal tract.[54]

Various strategies have been explored recently to address these challenges and reduce ADC-associated toxicities. These strategies include modifying conjugation technology or payload-linker chemistry, making antibody modifications, adjusting dosage regimens, and implementing inverse targeting strategies.[52]

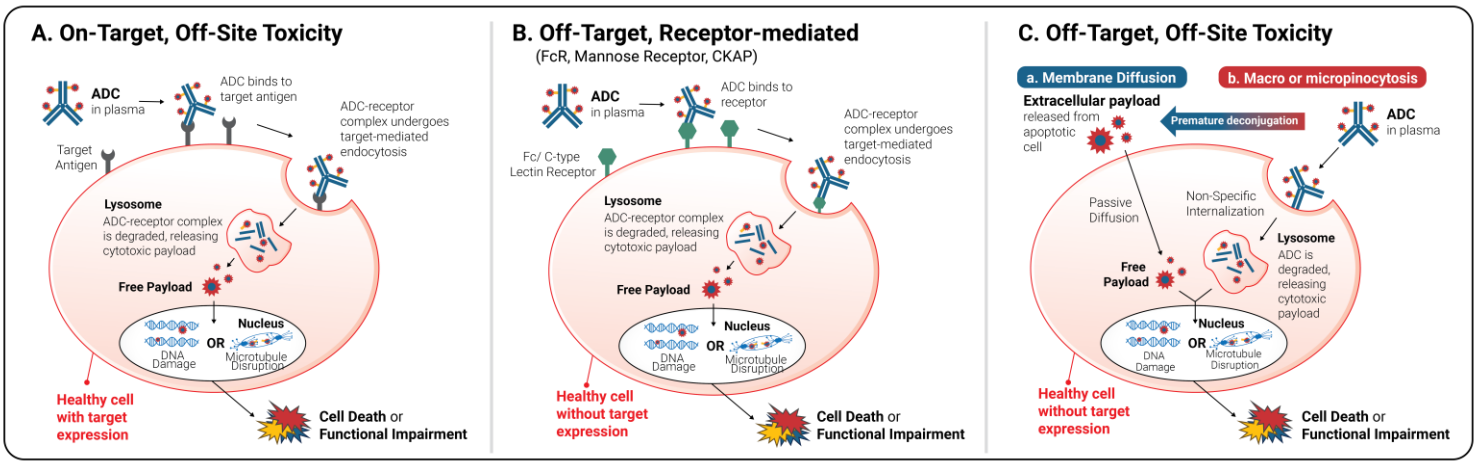


Figure 13. Mechanism of ADC Toxicity[52]

Table 9. Common adverse effects associated with different payload classes.

Payload Class	Payload	Approved ADCs	ADCs in phase III of clinical trials	Linker Type	Key Toxicities/ Adverse side effects
Tubulin inhibitors	MMAE	Adcetris®, Polivy®, Padcev®, Tivdak®, Aidexi®, Meiyouheng®, Emrelis™	9MW2821, CMG901, Sigvotatug vedotin, TPX-4589, Trastuzumab envedotin, Trastuzumab vedotin	Valine Citrulline (Cleavable)	Neutropenia, neuropathy, anemia, skin toxicities
	MMAF	Blenrep®	FS-1502	mc (Non-cleavable)	Thrombocytopenia, ocular toxicity, hepatic toxicity
	DM1	Kadcyla®, Ujvira™	N/A	SMCC (Non-cleavable	Thrombocytopenia, hepatic toxicity
	DM4	Elahere®	N/A	s-SPDB or SPDB (Cleavable)	Neutropenia, anemia, neuropathy, ocular toxicity
	Amberstatin269	N/A	ARX788	Oxime (Non-cleavable)	Ocular toxicity, anemia, pneumonitis

Payload Class	Payload	Approved ADCs	ADCs in phase III of clinical trials	Linker Type	Key Toxicities/ Adverse side effects
	Auristatin F-HPA	N/A	N/A	Fleximer Polymer (Cleavable)	Fatigue, nausea, aspartate aminotransferase increase, thrombocytopenia
DNA damaging agents	Calicheamicin	Mylotarg®, Besponsa®	N/A	AcButacyl hydrazone disulfide (Cleavable)	Neutropenia, thrombocytopenia, hepatic toxicity
	PBD	Zynlonta®	N/A	Valine-Alanine (Cleavable)	Neutropenia, anemia, thrombocytopenia, serosal effusion, nephron toxicity, skin toxicity
	Duocarmycin	N/A	N/A	Valine-Citrulline (Cleavable)	Neutropenia, thrombocytopenia, serosal effusion
Topoisomerase I inhibitors	SN-38	Trodelvy®	N/A	CL2A (Cleavable)	Neutropenia, gastrointestinal toxicity
	Deruxtecan	Enhertu®, Datroway®	Patritumab deruxtecan, Ifinatamab deruxtecan, JSKN-003	GGFG (Cleavable)	ILD, Neutropenia, gastrointestinal toxicity
	Belotecan	Sacituzumab tirumotecan	N/A	CL2A (Cleavable)	Neutropenia, anemia, thrombocytopenia
	SHR9265 (Exatecan)	Aveda®	N/A	Undisclosed (Cleavable)	Neutropenia, leukopenia, anemia, thrombocytopenia

Note: For references supporting the content provided please visit https://njbio.com/antibody-drug-conjugates/

6. Clinical Aspects of Antibody-Drug Conjugates

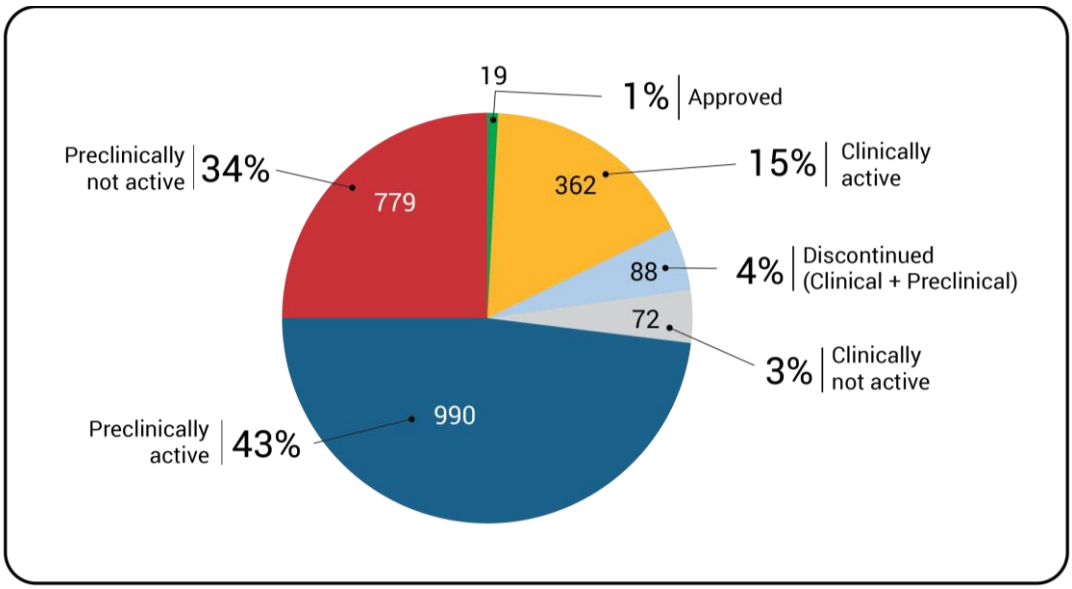


Figure 14. ADC Development Stages (December 2025)[3]

6.1 Approved Antibody-drug conjugates

The first ADC to receive market approval, Gemtuzumab ozagamicin, was introduced in 2001 by Pfizer, withdrawn in 2010, and re-introduced in 2017 along with Inotuzumab ozogamicin. Brentuximab vedotin, the second ADC launched in 2011 by SeaGen Inc. (formerly Seattle Genetics, Inc. and now Pfizer) and Millenium Pharmaceuticals (now Takeda), achieved $1.089 billion in sales in 2024.[55] Trastuzumab deruxtecan, launched by Daiichi Sankyo and Trastuzumab emtansine, launched by Roche, continue to enjoy blockbuster status with $3.754 billion[56] and $2.192 billion[57] respectively in sales, in 2024. Between 2019 and 2025, additional ADCs have received approval, bringing the total number of approved ADCs to 19, as summarized in **Table 10**.

Table 10. Approved Antibody-drug conjugates[3,58]

INN	Brand Name	Anti-body	Linker	Payload	DAR	Molecu-lar Target	Approved Disease Indication	Approval Year
Gemtuzumab ozogamicin	Mylotarg®	IgG4 κ (Human-ized)	AcButacyl Hydrazone disulfide (Acid labile hydrazone Cleavable)	Calicheami-cin	2-3	SIGLEC3	AML	2000, 2017 (Withdrawn in 2010)
Brentuximab vedotin	Adcetris®	IgG1 (Chi-meric)	Valine-Citrulline (Protease Cleavable)	MMAE	4.0	CD30	HL, sALCL	2011

INN	Brand Name	Anti-body	Linker	Payload	DAR	Molecu-lar Target	Approved Disease Indication	Approval Year
Trastuzumab emtansine	Kadcyla®	IgG1 (Human-ized)	SMCC (Non-cleavable)	DM1	3.50	HER-2	HER2+ Breast Cancer	2013
Inotuzumab ozogamicin	Besponsa®	IgG4 (Human-ized)	AcButacyl Hydrazone disulfide (Acid labile hydrazone Cleavable)	Calicheami-cin	2-3	SIGLEC2	(R/R) ALL	2017
Polatuzumab vedotin	Polivy®	IgG1 (Human-ized)	Valine-Citrulline (Protease Cleavable)	MMAE	3.5	CD79b	DLBCL	2019
Enfortumab vedotin	Padcev®	IgG1 κ (Human)	Valine-Citrulline (Protease Cleavable)	MMAE	4.0	Nectin-4	mUC	2019
Trastuzumab deruxtecan	Enhertu®	IgG1 (Human-ized)	GGFG (Protease Cleavable)	DXd	8.0 RPC	HER-2	HER2+ Breast Cancer, Gastric Cancer	2019
Sacituzumab govitecan	Trodelvy®	IgG1 (Human-ized)	CL2A (pH Sensitive - Cleavable)	SN-38	7.6	TROP-2	mTNBC, mUC	2020 (Accelerated Approval); 2021 (Full FDA Approval)
Loncastuxi-mab tesirine	Zynlonta®	IgG1 (Human-ized)	Valine-Alanine (Protease Cleavable)	PBD	2.3 ± 0.3	CD19	DLBCL	2021 (Accelerated Approval)
Tisotumab vedotin	Tivdak®	IgG1 (Human)	Valine-Citrulline (Protease Cleavable)	MMAE	4.0	Tissue factor	Cervical Cancer	2021 (Accelerated Approval); 2024 (Full FDA Approval)

INN	Brand Name	Anti-body	Linker	Payload	DAR	Molecu-lar Target	Approved Disease Indication	Approval Year
Trastuzumab emtansine	Ujvira™	IgG1 (Human-ized)	SMCC (Non-cleavable)	DM1		HER-2	HER2+ Breast Cancer	2021 (Approved for use in India)
Disitamab vedotin	Aidexi®	IgG1 (Human-ized)	Valine-Citrulline (Protease Cleavable)	MMAE	4.0	HER-2	Gastric Cancer	2021 (Approved for use in China)
Mirvetuximab soravtansine	Elahere®	IgG1 (Chi-meric)	SPDB (Glutathi-one Cleavable)	DM4	3.4	Folate Receptor Alpha	FRα+ platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	2022 (Accelerated Approval); 2024 (Full FDA Approval)
Sacituzumab tirumotecan	Jiataile®	IgG1 (Human-ized)	CL2A (pH Sensitive - Cleavable)	KL610023 (Belotecan)	8	TROP-2	Metastatic TNBC Locally Advanced TNBC	2024 (Approved for use in China)
Datopotamab deruxtecan	Datro-way®	IgG1 (Human-ized)	GGFG (Protease Cleavable)	DXd/DX8951 (MAAA-1181a) (Exatecan)	4	TROP-2	HER2- Breast Cancer, HR+ Breast Cancer	2025
Belantamab mafodotin	Blenrep	IgG1 (Human-ized)	Mc	MMAF (Auristatin)	4.0	BCMA	Myeloma/ Multiple Myeloma/ Kahler's disease/ Myelo-matosis	2020, 2022 (Withdrawn), 2025 (Re-approved)
Telisotuzumab vedotin	Emrelis™	IgG1 (Human-ized)	Valine-Citrulline	MMAE (Auristatin)	3.1	c-MET	Advance Non-Squamous Non-Small Cell Lung Cancer,	2025 (Accelerated Approval)

INN	Brand Name	Anti-body	Linker	Payload	DAR	Molecu-lar Target	Approved Disease Indication	Approval Year
Trastuzumab rezetecan	Aveda®	IgG1 (Human-ized)	Undis-closed	SHR9265 (Exatecan)	5.7	HER-2	Advanced NSCLC, Metastatic NSCLC	2025 (China)
Becotatug vedotin	Meiyouhe ng®	IgG1 (Human-ized)	Valine-Citrulline	MMAE	4	EGFR	Recur-rent/Meta-static Naso-pharyngeal Carcinoma	2025 (China)

AML: Acute Myeloid Leukemia, HL: Hodgkin's Lymphoma, sALCL: Systemic Anaplastic Large Cell Lymphoma, (R/R) ALL: relapsed or refractory acute lymphoblastic leukemia, DLBCL: Diffuse Large B-Cell Lymphoma, mUC: Metastatic urothelial cancer, mTNBC: Metastatic Triple-Negative Breast cancer

6.2 Combination Trials

ADCs are being explored in combination with chemotherapy, molecularly targeted agents, radiotherapy, immunotherapy and endocrine therapy, in preclinical and clinical studies. Combination therapies generally reduce the likelihood of drug resistance and two agents with different mechanisms of action can be used to achieve favorable treatment outcomes.[59] ADC monotherapies may be insufficient to treat certain tumor types, hence there is growing interest in exploring combination therapies. These trials appear to be primarily focused on advancing their use into earlier lines of therapy or earlier stages of disease. As per recent data, around half of the ADC trials initiated each year are combination trials (i.e. 197 out of 386 ADC trials in 2024).[3] Currently, four ADCs have had combination therapies approved by the global regulatory authorities. **Table 11** summarizes these approved ADC combination therapies.

Table 11. Approved ADCs with Combination Therapies [3,58,60,61]

ADC	Payload used in ADC	Combination Drugs	Target	Approved Indication	First Approved Date	Therapy
Brentuximab vedotin	MMAE	Doxorubicin, Vinblastin, Dacarbazine (AVD)	CD30	HL	20-03-2018	Chemotherapy
Brentuximab vedotin	MMAE	Cyclophosphamide, Doxorubicin, Prednisone (CHP)	CD30	PTCL	16-11-2018	Chemotherapy
Brentuximab vedotin	MMAE	Doxorubicin, Vincristine, Etoposide, Prednisone, Cyclophosphamide	CD30	cHL	10-11-2022	Chemotherapy
Gemtuzumab ozogamicin	Calicheamicin	Daunorubicin, Cytarabine	SIGLE3	AML, APL	23-04-2018	Chemotherapy
Polatuzumab vedotin	MMAE	Bendamustine, Rituximab (BR)	CD79b	DLBCL	10-06-2019	ICM

ADC	Payload used in ADC	Combination Drugs	Target	Approved Indication	First Approved Date	Therapy
Polatuzumab vedotin	MMAE	Rituximab, Cyclophosphamide, Doxorubicin, Prednisone (R-CHP)	CD79b	BLBCL, NOS, HGBL	19-04-2023	ICM
Enfortumab vedotin	MMAE	Pembrolizumab (KEYTRUDA®)	Nectin-4	mUC	03-04-2023	ICM

6.3 ADCs in Clinical Development: Future scope

Among 2310 ADCs identified by December 2025, approximately 23% i.e. 535 ADCs are in different stages of clinical trials. Notably, a significant proportion (67%), of these clinical candidates are actively undergoing investigation in trials. There has been a significant growth in ADCs transitioning to clinical development and showing an upward trend from 2022 onwards.[3]

Table 12. Antibody-Drug Conjugates that are undergoing clinical trials[3] (Phase 2 and above)

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
AOC 1001	siRNA (small interfering RNA) (Oligonucleo-tide)	Undisclosed	DMPK; Tfr1	Central Nervous System Disease	3	Undisclosed
Arcotatug tavatecan	Exatecan and Analogues (Camptothecin Derivatives)	Valine-Alanine	CLDN18.2	Solid Tumors	3	Y
BAT8006	Exatecan and Analogues (Camptothecin Derivatives)	Undisclosed	Folate Receptor Alpha	Advanced Endometrial Cancer	3	Undisclosed
BL-M07D1	Ed-04 (Alkaloid Camptothecin)	Undisclosed	HER-2	Advanced Gastrointestinal Tumors	3	Y
Bulumtatug fuvedotin	MMAE (Auristatin)	Valine-Citrulline	Nectin-4	Adenocarci-noma; Adenosqua-mous Carcinoma	3	Y
Caxmotabart entudotin	MMAF (Auristatin)	β-Glucu-ronide	HER-2	Advanced Breast Cancer	3	Y

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
CPO-301	JS-1	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	EGFR	Adenocarcinoma	3	Undisclosed
Delpacibart braxlosiran	siDUX4.6 (siRNA (small interfering RNA))	SMCC	DUX4; Tfr1	Facioscapulohumeral muscular dystrophy (FSHD)	3	Undisclosed
DX126-262	Tub114 (Tubulysin)	Polyethylene glycol (PEG)	HER-2	Breast Cancer, Gastric Cancer	3	Undisclosed
FDA018	SN-38 (Irinotecan (CPT-11) and Analogues)	Undisclosed	TROP-2	Advanced Solid Tumors	3	Undisclosed
Fetrastobart vedotin	Vedotin (MMAE)	Valine-Citrulline (Val-Cit)	PD-L1	Cancer, Metastatic Solid Tumors	3	Undisclosed
GQ1005	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	Undisclosed	HER-2	Advanced Breast Cancer	3	Y
Ifinatamab deruxtecan	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	B7-H3	Adenocarcinoma	3	N
Izalontamab brengitecan	Ed-04 (Alkaloid Camptothecin)	Undisclosed	EGFR; HER-3	Advanced Biliary Tract Carcinoma	3	Y
JS107	MMAE (Auristatin)	Undisclosed	CLDN18.2	Gastrointestinal Malignancies/Gastrointestinal Cancer	3	Undisclosed
JSKN-003	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	HER-2	Advanced Colorectal Cancer	3	Y
JSKN033	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	GGFG	HER-2; PD-L1	Advanced Gastric Cancer	3	Y

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
LY4170156	Exatecan and Analogues (Camptothecin Derivatives)	Undisclosed	Folate Receptor Alpha	Advanced Solid Tumors	3	Undisclosed
MHB088C	Undisclosed	Undisclosed	B7-H3	Advanced Colo-rectal Cancer	3	Undisclosed
Mocertatug rezetecan	HS-9265 (Rezetecan)	GGFG (Gly-cine-Gly-cine-Phenyl-alanine-Gly-cine)	B7-H4	Advanced Breast Cancer	3	Undisclosed
MRG004	MMAE (Auristatin)	Valine-Citrulline	Tissue factor	Advanced Solid Tumors	3	Y
Notiretatug rezetecan	Rezetecan (Exatecan and Analogues)	GGFG (Gly-cine-Gly-cine-Phenyl-alanine-Glycine)	Nectin-4	Advanced Solid Tumors	3	Undisclosed
OQY-3258	SN-38 (Iri-notecan (CPT-11) and Analogues)	Valine-Citrulline	TROP-2	Advanced HER2-Negative Breast Cancer; Brain Cancer	3	Undisclosed
Patritumab Deruxtecan	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	GGFG (Gly-cine-Gly-cine-Phenyl-alanine-Glycine)	HER-3	Acral Melanoma; Breast Cancer	3	N
Puxitatug samrotecan	AZ14170132 (AZ'0132) (Samrotecan)	Valine-Alanine	B7-H4	Advanced Solid Malignancies	3	Undisclosed
Rinatabart sesutecan	Exatecan and Analogues (Camptothecin Derivatives)	Undisclosed	Folate Receptor Alpha	Advanced EGFR Mutated Non-small Cell Lung Cancer (NSCLC)	3	Undisclosed
Risvutatug rezetecan	HS-9265 (Rezetecan)	GGFG (Gly-cine-Gly-cine-Phenyl-alanine-Glycine)	B7-H3	Advanced Solid Tumors	3	Undisclosed
SHR-A1904	Undisclosed	Undisclosed	CLDN18.2	Advanced Pan-creatic Cancer	3	Undisclosed

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
SHR-A1912	Undisclosed	Undisclosed	CD79b	Advanced Breast Cancer	3	Undisclosed
SHR-A2009	Undisclosed	Undisclosed	HER-3	Advanced Non-Small Cell Lung Cancer (NSCLC)	3	Undisclosed
Sigvotatug vedotin	MMAE (Auristatin)	Valine-Citrulline	Integrin beta-6	Advanced HER2-Negative Breast Cancer	3	N
Sonesitatug vedotin	MMAE (Auristatin)	Valine-Citrulline	CLDN18.2	Adenocarci-noma of the Stomach; Ad-vanced Biliary Tract Cancer	3	Undisclosed
SYS6002	MMAE (Auristatin)	Valine-Citrulline (Val-Cit)	Nectin-4	Bladder Cancer	3	Y
Tambotatug pelitecan	YL0010014 (Pelitecan)	TMALIN	B7-H3	Non-Small Cell Lung Cancer (NSCLC)	3	Undisclosed
Tecotabart vedotin	MMAE (Auristatin)	Valine-Citrulline	CLDN18.2	Advanced Bili-ary Tract Can-cer	3	Undisclosed
Teli-sotuzumab adizutecan	Camptothecin Derivatives	Valine-Alanine	c-MET	Advanced Colorectal Cancer	3	Undisclosed
Tizetatug rezetecan	SHR9265 (Rezetecan)	Undisclosed	TROP-2	Advanced Breast Cancer	3	Undisclosed
Torvutatug samrotecan	AZ14170132 (AZ'0132) (Samrotecan)	Valine-Ala-nine (Val-Ala) (VA)	Folate Receptor Alpha	Ovarian Cancer	3	Undisclosed
TQB2102	Undisclosed	Undisclosed	HER-2	Advanced Biliary Tract Cancer	3	Undisclosed
Trastuzamab pamirtecan	P1003 (Exatecan and Analogues)	GGFG (Gly-cine-Gly-cine-Phenyl-alanine-Gly-cine)	HER-2	Advanced Breast Cancer	3	Undisclosed
Trastuzumab botidotin	Duostatin5 (MMAF)	Valine-Citrulline	HER-2	Advanced Breast Cancer	3	Y
Trastuzumab bultecan	Bultecan (Camptothecin Derivatives)	Undisclosed	HER-2	Advanced Ovarian Cancer	3	Undisclosed

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
Trastuzumab envedotin	MMAE (Auristatin)	Valine-Citrulline	HER-2	Advanced Breast Cancer	3	Y
Trastuzumab vedotin	MMAE (Auristatin)	Valine-Citrulline	HER-2	Advanced Biliary Tract Cancer	3	N
XNW27011	Undisclosed	TMALIN	CLDN18.2	Ovarian Cancer, Gastric Cancer, Esophagus Cancer	3	Undisclosed
XNW28012	Undisclosed	Undisclosed	Tissue factor	Solid Tumors, Metastatic Pancreatic Cancer	3	Undisclosed
Zilovertamab vedotin	MMAE (Auristatin)	Valine-Citrulline	ROR1	Acute Lymphocytic Leukemia	3	N
ZL-1310	YL0010014 (C24) (Pelitecan)	TMALIN (Val-Lys[Pr]2-Gly)	DLL3	Small Cell Lung Cancer (SCLC), Neuroendocrine Tumors (Solid Tumors)	3	Y
Anvatabart opadotin	Amberstatin269 (AS269) (MMAF)	Oxime	HER-2	Adenocarcinoma of the Gallbladder	2/3	Y
BL-M11D1	Ed-04 (Alkaloid Camptothecin)	Undisclosed	SIGLEC3	Acute Myeloid Leukemia	2/3	Y
Raludotatug deruxtecan	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	CDH6	Advanced Renal Cell Carcinoma	2/3	Y
Anetumab ravtansine	DM4 (Maytansine)	SPDB	Mesothelin (MSLN)	Adenocarcinoma of the Breast	2	N
BAT8008	Exatecan and Analogues (Camptothecin Derivatives)	Maleimide	TROP-2	Solid Tumors	2	Undisclosed
BB-1701	Eribulin	Valine-Citrulline	HER-2	Advanced Breast Cancer	2	Y
Camidanlumab Tesirine	SG3199 (Pyrrolobenzodiazepine (PBD))	Valine-Alanine	IL-2R Alpha	Acute Lymphoblastic Leukemia (ALL)	2	N

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
DB-1311	P1021 (Drozuntecan)	Undisclosed	B7-H3	Advanced Cervical Cancer	2	Undisclosed
Delpacibart zotadirsen	ASO (antisense oligonucleotide) (Oligonucleotide)	Undisclosed	DMD; Exon 44; Tfr1	Duchenne Muscular Dystrophy (DMD)	2	Undisclosed
DXC-008	Tubulysin	Peptide	PSMA; STEAP-1	Ewing's Sarcoma; Prostate Cancer	2	Undisclosed
Farletuzumab Ecteribulin	Eribulin	Valine-Citrulline	Folate Receptor Alpha	Adenocarcinoma of the Lung	2	N
FDA022	DXd/DX8951 (MAAA-1181a) (Exatecan and Analogues)	Cathepsin	HER-2	Advanced Breast Cancer	2	Undisclosed
FOR46	MMAE (Auristatin)	Valine-Citrulline	CD46	Adenocarcinoma	2	N
HLX43	Camptothecin Derivatives	TMALIN	PD-L1	Advanced Hepatocellular Carcinoma	2	Undisclosed
Ixotatug vedotin	MMAE (Auristatin)	Valine-Citrulline (Val-Cit)	CLDN6	Advanced Cancers	2	Undisclosed
JSKN016	Undisclosed	Undisclosed	HER-3; TROP-2	Advanced Solid Malignancies	2	Y
L-DOS47	Urease	SIAB (N-succinimidyl [4-iodoacetyl] aminobenzoate)	CEACAM6	Adenocarcinoma of the Lung	2	Undisclosed
Laventatug	MMAE (Auristatin)	Undisclosed	LIV-1	Solid tumors	2	N
Mecbotamab vedotin	MMAE (Auristatin)	Valine-Citrulline	Axl	Advanced Solid Tumors	2	N
MHB036C	Undisclosed	Undisclosed	TROP-2	Advanced Breast Cancer, Malignant Tumor, Advanced Lung Cancer	2	Undisclosed
Misitatug blivedotin	MMAE (Auristatin)	Valine-Citrulline	Mesothelin (MSLN)	Advanced Malignant Tumors	2	Undisclosed

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
MRG001	MMAE (Auristatin)	Valine-Citrulline	CD20	B-cell Non Hodgkin Lymphoma; Dermatological Disorders	2	Undisclosed
Opugotamig olatansine	DM21 (Maytansine)	L-Ala-D-Ala-L-Ala	Folate Receptor Alpha	Cervical Cancer	2	N
Ozuriftamab vedotin	MMAE (Auristatin)	Valine-Citrulline	ROR2	Advanced Non-Small Cell Lung Cancer(NSCLC)	2	N
RC108	MMAE (Auristatin)	Undisclosed	c-MET	Adenoid Cystic Carcinoma	2	Undisclosed
Sacituzumab drozuntecan	P1021 (Drozuntecan)	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	TROP-2	Cancer	2	Undisclosed
SHR-1826	Undisclosed	Undisclosed	c-MET	Advanced Hepatocellular Carcinoma	2	Undisclosed
SHR-4602	ER300 (Eribulin)	Undisclosed	HER-2	Advanced Solid Tumor Malignancy	2	Undisclosed
SHR-4849	Dxh (Exatecan and Analogues)	Undisclosed	DLL3	Advanced Malignant Solid Tumors	2	Undisclosed
SKB500	Undisclosed	Undisclosed	Undisclosed	Small Cell Lung Cancer (SCLC)	2	Undisclosed
SKB518	Undisclosed	Undisclosed	Undisclosed	Advanced Solid Tumors	2	Undisclosed
SKB571	Undisclosed	Undisclosed	Undisclosed	Lung Cancer, Gastrointestinal Tumor	2	Undisclosed
Tilatamig samrotecan	AZ14170132 (AZ'0132) (Samrotecan)	Undisclosed	c-MET; EGFR	Solid Tumors	2	Undisclosed
TRS005	MMAE (Auristatin)	Valine-Citrulline	CD20	B-cell Non Hodgkin Lymphoma	2	N
Turmetabart adizutecan	Adizutecan (Camptothecin Derivatives)	Valine-Alanine (Val-Ala) (VA)	SEZ6	Neuroendocrine Tumors (Solid Tumors)	2	Y

Drug Names	Payload	Linker	Drug Targets	Disease Indication	Highest Phase of Development	Homogeneous Conjugate
Unspecified HER2 ADC	Undisclosed	Undisclosed	HER-2	Breast Cancer	2	Undisclosed
Unspecified TROP2 ADC	Undisclosed	Undisclosed	TROP-2	Advanced Breast Cancer	2	Undisclosed
YL202	YL0014 (Camptothecin Derivatives)	TMALIN	HER-3	Advanced Breast Cancer	2	Y

6.4 Antibody-drug conjugates for non-oncological applications

While the majority of ADCs in development remain focused on oncology, the landscape is gradually expanding. Unlike in oncology, these ADCs utilize non-toxic payloads to modulate biological functions without affecting cell viability.[62] The identification of highly specific targets and development of non-toxic payloads (anti-inflammatory, anti-infective or neuroprotective) specific to the disease indication is essential to minimize off-target effects. Additionally, their usage in chronic non-oncological indications may increase the risk of immunogenicity, requiring careful design. While research for non-cancer indications is still in its early stages, ongoing preclinical and early-phase clinical trials hold promise. Applications in myotonic dystrophy, scleroderma, Duchenne muscular dystrophy, rheumatoid arthritis, amyloidosis, obesity and bacterial infections are currently being explored as summarized in **Table 13**.

Table 13. A list of some ADCs that have been tested for indications other than oncology[3]

ADC	Disease Indication	Drug Target	Payload	Linker	Highest phase of development
AOC-1001	Myotonic dystrophy type 1 (DM1)	DMPK; Tfr1	Oligonucleotide	Undisclosed	Ph 3
AOC-1020	Facioscapulohumeral muscular dystrophy (FSHD)	Dux4; Tfr1	siDUX4.6	MCC	Ph 2
Brentuximab vedotin	Acute Lymphoblastic Leukemia (ALL)	CD30	MMAE	Val-Cit	Ph 2
Belantamab mafodotin	R/R AL Amyloidosis	BCMA	MMAF	Val-Cit	Ph 2
ABBV-3373	Rheumatoid Arthritis	TNF-alpha	Steroid (Glucocorticoid)	Ala-Ala	Ph 2
AMG 133	Adiposity/ Obesity; Type 2 Diabetes Mellitus; Hypertension	GIPR; GLP-1R	BiTE	Undisclosed	Ph 3
DYNE-251	Duchenne Muscular Dystrophy (DMD)	Exon51; Tfr1	Oligonucleotide	Undisclosed	Ph 1/2

ADC	Disease Indication	Drug Target	Payload	Linker	Highest phase of development
Brentuximab vedotin	Systemic Sclerosis	CD30	MMAE	Val-Cit	Ph 1/2
DYNE-101	Myotonic dystrophy type 1 (DM1)	Undisclosed	DMPK; Oligonucleotide	Val-Cit	Ph 1/2
STI-6129	R/R Systemic AL Amyloidosis	CD38	Duostatin5.2	Undisclosed	Ph 1/2
AOC 1044	Duchenne Muscular Dystrophy (DMD)	DMD; Tfr1	Oligonucleo-tide	Undisclosed	Ph 2
DB-2304	Autoimmune disease, Systemic lupus erythematosus	CLEC4C	Glucocorticoids	Undisclosed	Ph 1
DSTA4637S	Bacteremia; Methicillin-sensitive *Staphylococcus aureus*; Methicillin-resistant *Staphylococcus aureus*	*Staphylococcus aureus*	dmDNA31 (Rifalog)	Val-Cit	Ph 1
Brentuximab vedotin	Graft vs. Host Disease (GVHD)	CD30	MMAE	Val-Cit	Ph 1

6.5. Understanding the Challenges of Discontinued ADC Programs

Although the field of ADCs has had many successes and new approvals in the last few years, there are still many discontinued programs that provide important information. The most common reasons for discontinuation of ADCs include lack of sufficient efficacy at maximum tolerated dose (MTD), low tolerability, and safety reasons. Few others have also been discontinued due to pipeline reprioritization or due to the competitive landscape. Amongst the discontinued ADCs, most have used auristatin- and maytansinoid-based payloads, and in many cases, there may have been the wrong selection of drug-linker for the indication. Some antibodies targeting HER2+ cancers have not progressed in the clinic or did not show meaningful improvements to trastuzumab emtansine, but careful selection of new drug-linkers led to trastuzumab deruxtecan, a very promising new ADC.

Table 14 displays targets and ADCs that have entered the clinic and have not proceeded. This knowledge along with careful analysis of the failures has the potential to inspire a new generation of ADCs.

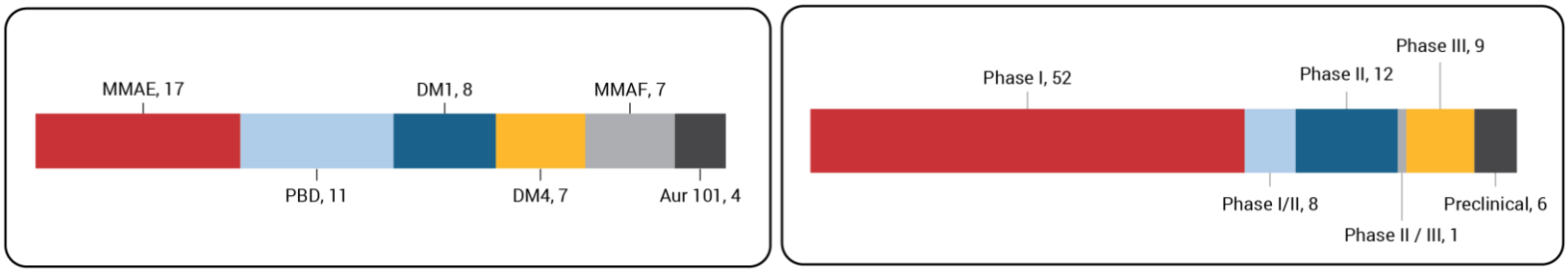


Figure 15: Top payloads used in discontinued ADCs[3](left); and discontinued ADCs according to phase[3] (right)

Table 14. List of Discontinued Antibody-Drug Conjugates.[3]

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontin-uation Year
Felmetatug vedotin	B7-H4	Adenoid Cystic Carcinoma	Valine-Citrulline	MMAE (Auristatin)	Ph I	Unlikely to achieve a meaningful im-provement over standard-of-care chemotherapy	2025
Izeltabart tapatansine	ADAM9	Advanced Solid Tumors	L-Ala-D-Ala-L-Ala	DM21 (May-tansine)	Ph I/II	Limited anti-tumor activity	2025
ORM-5029	GSPT1; HER-2	Advanced Breast Cancer	Valine-Citrulline	SMol006	Ph I	Sponsor Decision	2025
PRO1107	PTK7	Solid Tumors	Valine-Citrulline (Val-Cit)	MMAE (Auristatin)	Ph I/II	overall benefit-risk profile no longer supports continuation for treatment	2025
Vobramitamab duocarmazine	B7-H3	Advanced Solid Tumors	Valine-Citrulline	DUocar-mycin-hy-droxyBen-zamide Azaindole (DUBA) (Duocar-mycin)	Ph II/III	Based on vobra duo safety and efficacy profile and an internal resource and portfolio review	2025
Ladiratuzumab vedotin	LIV-1	Advanced Breast Cancer	Valine-Citrulline	MMAE (Auristatin)	Ph II	Undisclosed	2024

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
Mipasetamab Uzoptirine	Axl	Advanced Solid Tumors	Valine-Alanine	SG3199 (Pyrrolobenzodiazepine (PBD))	Ph I	Unable to demonstrate a favorable benefit-risk profile during the dose optimization/expansion phase	2024
Samatatug zovodotin	Tissue factor	Cervical Cancer	Valine-Citrulline	Auristatin	Ph I	Unlikely to improve upon existing TF-targeting ADCs	2024
SYSA1801	CLDN18.2	Gastric Cancer	Valine-Citrulline	MMAE (Auristatin)	Ph III	Insufficient to provide patients with a competitive benefit-risk profile	2024
Trastuzumab duocarmazine	HER-2	Breast Cancer	Valine-Citrulline (Val-Cit)	DUocarmycin-hydroxyBenzamide Azaindole (DUBA) (Duocarmycin)	Ph III	Regulators required extensive additional clinical studies	2024
Trastuzumab imbotolimod	HER-2; TLR7/8 (Payload target)	Adenocarcinoma of the Breast	Undisclosed	Undisclosed	Ph II	Determination that program will not meet its pre-defined success criter	2024
Upinitatug rilsodotin	NaPi2b	Adenocarcinoma of the Lung	Fleximer Polymer	Auristatin F-HPA (XMT-1267) (Auristatin)	Ph III	Efficacy did not-meet prespecified primary endpoint criterion in UPLIFT trial	2024
VIR-2981 ADC	Neuraminidase	Influenza A Virus Infection, Influenza B Virus Infection	Undisclosed	Undisclosed	Preclinical	Undisclosed	2024
Zanidatamab zovodotin	HER-2	HER2-positive cancers	Val-Cit	ZD02044 (Zovodotin)	Ph I	Undisclosed	2024
Adalimumab fosimdesonide	TNF-alpha	Crohn's Disease	BrAc-Gly-Glu	Steroid (Glucocorticoid receptor modulator)	Ph II	Benefit-risk profile does not sufficiently differentiate 154 from other available treatments	2023

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
Cofetuzumab pelidotin	PTK7	Advanced Non-Small Cell Lung Cancer (NSCLC)	Valine-Citrulline	PF-06380101 (Aur 101) (Auristatin)	Ph I	Undisclosed	2023
NJH395	HER-2; TLR 7 (payload target)	Adenocarcinoma of the Small Intestine	Maleimide	TLR7 agonist (TLR agonists)	Ph I	No objective responses were observed in 18 treated patients	2023
OBI-999	Globo H	Advanced Solid Tumors	Valine-Citrulline	MMAE (Auristatin)	Ph I/ II	Expected therapeutic potential not shown for the enrolled patients	2023
Opelkibart elmanitin	cKIT	Acute Myeloid Leukemia	Undisclosed	Amanitin	Ph I	Grade 5 serious adverse event	2023
SGN-ALPV	Alkaline phosphatase, placental-like 2; ALPP	Advanced Endometrial Cancer	Undisclosed	MMAE (Auristatin)	Ph I	Prioritization assessment	2023
SGN-STNV	STn	Advanced Solid Tumors	Valine-Citrulline	MMAE (Auristatin)	Ph I	Prioritization assessment	2023
Tusamitamab ravtansine	CEACAM5	Adenocarcinoma	SPDB	DM4 (Maytansine)	Ph III	Trial that did not meet the dual primary endpoint of improving progression-free survival	2023
BDC-2034	CD66	Breast Cancer	Undisclosed	TLR 7/8 agonist (TLR agonists)	Preclinical	Focus shifted to other promising programs	2022
PCA062	P-Cadherin	Esophagus Cancer	SMCC	DM1 (Maytansine)	Ph I	Limited anti-tumor activity at the maximally tolerated dose level	2022
Pertuzumab zuvotolimod	HER-2; TLR 8 (Payload target)	Advanced HER2 Positive Solid Tumor	Undisclosed	Undisclosed	Ph I/II	Limited monotherapy anti-tumor activity and cytokine-related adverse events	2022

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
PYX-202	DLK-1	SCLC	β-glucuronidase (BG) linker	MMAE (Auristatin)	Preclinical	Undisclosed	2022
SBT6290	Nectin-4; TLR 8 (Payload target)	Breast Cancer	Undisclosed	TLR8 agonist (TLR agonists)	Ph I/ II	Similar clinical profile	2022
SYD1875	5T4	Solid tumors	Valine-Citrulline	DUocarmycin-hydroxyBenzamide Azaindole (DUBA) (Duocarmycin)	Ph I	Lack of significant benefit or progress, or potential patient safety concerns	2022
XMT-1592	NaPi2b	Adenocarcinoma	Undisclosed	Auristatin F-HPA (XMT-1267) (Auristatin)	Ph I	Increasingly competitive nature of non-small cell lung cancer indication	2022
BAT8001	HER-2	Breast Cancer	3AA	Maytansinoid (Maytansine)	Ph III	Did not achieve phase 3 clinical end points	2021
BAT8003	TROP-2	Solid tumors	3AA	Maytansine	Ph I	Considered development risk of drugs	2021
DS-6157	GPR20	Gastrointestinal Tumor	GGFG (Glycine-Glycine-Phenylalanine-Glycine)	DXd/DX8951 (MAAA-1181a) (Topoisomerase I inhibitor)	Ph I	No clear response in patients	2021
PF-06804103	HER-2	Advanced Solid Tumors	Valine-Citrulline	PF-06380101 (Aur 101) (Auristatin)	Ph I	AEs (44/93, 47.3%) and progressive disease (35/93, 37.6%)	2021
TAK-500	CCR2; STING	Gastric Cancer	Undisclosed	TAK-676	Ph I/II	Clinical futility was met.	2021
AGS62P1	FLT3	Acute Myeloid Leukemia	Oxime	MMAF (Auristatin)	Ph I	Lack of efficacy	2020

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
BioAtla-Pfizer ADC	Undisclosed	Cancer Indications	Undisclosed	Undisclosed	Preclinical	License and option agreement with Pfizer was terminated	2020
Enapotamab vedotin	Axl	Solid tumors	Valine-Citrulline	MMAE (Auristatin)	Ph I/ II	Undisclosed	2020
MEDI7247	ASCT2	Acute Myelogenous/Myeloid Leukemia (AML)	Valine-Alanine	Pyrrolobenzodiazepine (PBD)	Ph I	Undisclosed	2020
SC-004	CLDN6; CLDN9	Endometrial Cancer	Valine-Alanine	SG3199 (Pyrrolobenzodiazepine (PBD))	Ph I	Low tolerability	2020
TAA013	HER-2	Breast Cancer	SMCC	DM1 (Maytansine)	Ph III	Undisclosed	2020
AGS16F	ENPP3	RCC	mc	MMAF (Auristatin)	Ph II	Did not meet its primary end point	2019
Depatuxizumab mafodotin	EGFR	AML	mc	MMAF (Auristatin)	Ph III	Lack of survival benefit	2019
DHES0815A	HER-2	Breast Cancer	Undisclosed	Pyrrolobenzodiazepine (PBD)	Ph I	Undisclosed	2019
IMGN779	CD33	AML	Sulfo-SPDB	DGN462 (Indolino-benzodiazepine dimer (IGN))	Ph I	Portfolio prioritization and restructuring initiatives	2019
NN-ATAC	CD37	Leukemia	Undisclosed	Amanitin	Preclinical	Undisclosed	2019
PF-06647263	EFNA4	Solid tumors	AcBut acyl hydrazone-disulfide	Calicheamicin	Ph I	Change in sponsor prioritization	2019
PF-06688992	GD3	Melanoma	Undisclosed	Undisclosed	Ph I	Undisclosed	2019
RG6109	CLL-1	AML	Undisclosed	Pyrrolobenzodiazepine (PBD)	Ph I	Unfavourable benefit-risk profile	2019
Rovalpituzumab tesirine	DLL3	SCLC	Valine-Alanine	SG3199 (Pyrrolobenzodiazepine (PBD))	Ph III	Lack of survival benefit	2019

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
SGN-CD48A	CD48	Myeloma	β-glucuronidase (BG) linker	MMAE (Auristatin)	Ph I	Portfolio prioritization and restructuring initiatives	2019
XMT-1522	HER-2	Adenocarcinoma of the Breast	Fleximer Polymer	Auristatin F-HPA (Auristatin)	Ph I	Discontinued as per strategic evaluation	2019
ADCT-502	HER-2	Solid tumors	Valine-Alanine	SG3199 (Pyrrolobenzodiazepine (PBD))	Ph I	Lacks sufficient efficacy at the maximally tolerated dose level	2018
AGS67E	CD37	AML	Valine-Citrulline	MMAE (Auristatin)	Ph I	Undisclosed	2018
AMG 595	EGFRviii	Glioma	SMCC	DM1 (Maytansine)	Ph I	Undisclosed	2018
CDX-014	TIM-1	RCC	Valine-Citrulline	MMAE (Auristatin)	Ph I	Costly to develop	2018
Denintuzumab mafodotin	CD19	ALL	mc	MMAF (Auristatin)	Ph II	Portfolio prioritization and restructuring initiatives	2018
Glembatumumab vedotin	gpNMB	Breast Cancer	Valine-Citrulline	MMAE (Auristatin)	Ph II	Did not meet its primary end point	2018
Indusatumab vedotin	GCC	ALL, AML	Valine-Citrulline	MMAE (Auristatin)	Ph II	Lack of efficacy	2018
Losatuxizumab vedotin	EGFR	Advanced Solid Tumors	Valine-Citrulline	MMAE (Auristatin)	Ph I	Safety reasons	2018
MEDI4276	HER-2	Breast Cancer	mc-lysine	AZ13599185 (Tubulysin)	Ph I	Safety/ Efficacy reason	2018
Pfizer-CytomX ADC	EGFR	Cancer Indications	Undisclosed	Undisclosed	Preclinical	Received notification of Pfizer's intent to terminate the companies' research collaboration, option and license agreement	2018
SAR428926	LAMP-1	Solid tumors	SPDB	DM4 (Maytansine)	Ph I	Undisclosed	2018
SAR566658	CA6	Advanced TNBC	SPDB	DM4 (Maytansine)	Ph II	Undisclosed	2018
SGN-CD123A	CD123	AML	Valine-Alanine	SGD-1882 (Pyrrolobenzodiazepine (PBD))	Ph I	Portfolio prioritization and restructuring initiatives	2018

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
SGN-CD19B	CD19	B-Cell Lymphoma	Valine-Alanine	SGD-1882 (Pyrrolobenzodiazepine (PBD))	Ph I	Portfolio prioritization and restructuring initiatives	2018
SGN-CD352A	CD352	Myeloma	Valine-Alanine	SGD-1882 (Pyrrolobenzodiazepine (PBD))	Ph I	Portfolio prioritization and restructuring initiatives	2018
Vadastuximab talirine	CD33	AML	Valine-Alanine	SGD-1882 (Pyrrolobenzodiazepine (PBD))	Ph III	Portfolio prioritization and restructuring initiatives	2018
Aprutumab ixadotin	FGFR2	Advanced Solid Tumors	Caproyl	Auristatin W analog (Auristatin)	Ph I	Dose-limiting toxicities	2017
AMG 172	CD70	RCC	MCC	DM1 (Maytansine)	Ph I	Undisclosed	2016
CMB-401	MUC-1	Ovarian Cancer	AcBut acyl hydrazone-disulfide	Calicheamicin	Ph II	Dose-limiting toxicities	2016
LOP628	cKIT	AML	SMCC	DM1 (Maytansine)	Ph I	Undisclosed	2016
PF-06650808	NOTCH3	Solid tumors	Valine-Citrulline	PF-06380101 (Aur 101) (Auristatin)	Ph I	Undisclosed	2016
PF-06664178	TROP-2	Solid tumors	Valine-Citrulline	PF-06380101 (Aur 101) (Auristatin)	Ph I	Business-related decision	2016
SGN-CD70A	CD70	B-Cell Lymphoma	Valine-Alanine	SGD-1882 (Pyrrolobenzodiazepine (PBD))	Ph I	Portfolio prioritization and restructuring initiatives	2016
PF-06263507	5T4	Solid tumors	mc	MMAF (Auristatin)	Ph I	Portfolio prioritization and restructuring initiatives	2015
CMD-193	Lewis Y antigen	Adenocarcinoma of the Lung	AcBut acyl hydrazone-disulfide	Calicheamicin	Ph I	Undisclosed	2014
ASG-5ME	SLC44A4	Prostate Cancer	Valine-Citrulline	MMAE (Auristatin)	Ph I	Undisclosed	2013

Name	Target	Indication	Drug-Linker	Payload	Last Phase	Reasons for Discontinuation	Discontinuation Year
Lorvotuzumab Mertansine	CD56	ALL	SPP	DM1 (Maytansine)	Ph II	Lack of efficacy signal and safety concerns	2013
Vorsetuzumab mafodotin	CD70	Lymphoma	mc	MMAF (Auristatin)	Ph I	Undisclosed	2013
MEDI-547	EphA2	Bladder-Cancer	mc	MMAF (Auristatin)	Ph I	Drug-related adverse events	2012
BAY79-4620	carbonic anhydrase IX (CAIX)	Solid tumors	Valine-Citrulline	MMAE (Auristatin)	Ph I	Safety reasons	2011
BIIB015	Cripto	Solid tumors	SPDB	DM4 (Maytansine)	Ph I	Undisclosed	2011
IMGN388	CD51	NSCLC	SPDB	DM4 (Maytansine)	Ph I	Focus shifted to other resources	2011
AVE9633	SIGLEC3	AML	SPDB	DM4 (Maytansine)	Ph I	Absence of evidence of clinical activity up to toxic doses	2009
Cantuzumab ravtansine	CanAg	Advanced Gastric Cancer	SPDB	DM4 (Maytansine)	Ph II	Slow pace of progress	2009
MLN2704	PSMA	Adenocarcinoma of the Prostate	SPP	DM1 (Maytansine)	Ph I/ II	Dose-limiting adverse effects	2006
Bivatuzumab Mertansine	CD44v6	Squamous Cell Carcinoma	SPP	DM1 (Maytansine)	Ph I	Skin toxicity	2005
SGN-15	Lewis Y antigen	NSCLC	Hydrazone	Doxorubicin (Anthracycline)	Ph II	Focus on advancing its other pipeline programs	2005

INN = International Nonproprietary Name; RCC = Renal Cell Carcinoma; AML = Acute Myeloid Lymphoma; ALL = Acute Lymphocytic Leukemia; NSCLC = Non-Small Cell Lung Cancer; TNBC = Triple Negative Breast Cancer

7. Business Landscape of Antibody-Drug Conjugates

A flurry of deal-making activity is occurring in the ADC space, with these modalities re-emerging as a leading field of interest. With blockbuster deals from Abbvie's $10.1 billion acquisition of ImmunoGen to Pfizer's acquisition of Seagen for $43 billion in 2023, and multiple licensing agreements and strategic collaborations, ADC deals range from early to late-stage/ marketed products and include a variety of oncology targets and indications. The integration of early pioneering ADC companies with large pharmaceutical firms highlights the increasing therapeutic potential of ADC programs for various disease indications.

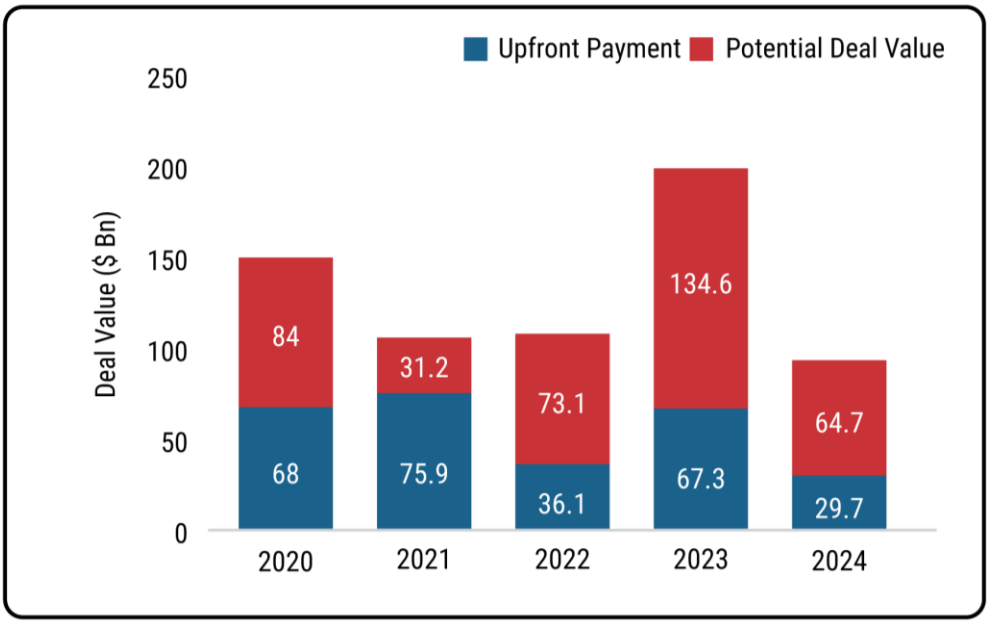


Figure 16. Total value of deals in the past 5 years[3]

The tables below summarize recent partnership deals, venture capital funding events, and successful IPOs. **Table 15** lists key licensing deals, mergers, and acquisitions (M&As) in the ADC space from January 2020. **Table 16** lists key venture capital funding events and IPOs in the ADC space since January 2020.

Table 15. Antibody-Drug Conjugate Licensing and Merger and Acquisition (M&A) Deals

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Crescent Biopharma & Kelun-Biotech	SKB105	ITGB6	Strategic Partnership	Dec-2025	Phase I/II	Upfront payment of $80 million and additional milestone payments of $1.25 billion plus tiered middle single-digit to low double-digit royalties on net sales

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Takeda Pharmaceuticals and Innovent Biologics	IBI343	Claudin 18.2 protein	Global Strategic Partnership	Oct-2025	Phase III	Upfront payment of $1.2 billion including equity investments of $100 million, potential milestones and royalty payments
Glenmark Pharmaceuticals Ltd. and Hengrui Pharma	Trastuzumab Rezetecan (SHR-A1811)	HER-2	License and Collaboration Agreement	Sep-2025	Marketed in China	Upfront payment of $18 million, plus regulatory and commercial milestone payments of up to $1.093 billion, plus corresponding royalties based on net sales
Novatim Immune Therapeutics & Radiance Biopharma, Inc	RB-601	c-MET; EGFR	Licensing Agreement	Aug-2025	Phase I/II	$ 15 million upfront payment, upto $150 million in potential development and regulatory milestone payments, $1 billion in commerical milestone payments & tiered royalties
Simcere Pharmaceutical Group & NextCure, Inc	SIM 0505	CDH6	Partnership & Collaboration, Licensing Agreement	Jun-2025	Phase I	$12 million upfront cash payment, upto $732 million in milestone payments, $1 million equity payment + tiered royalties
Astellas & Evopoint	XNW27011	CLDN18.2	Licensing Agreement	May-2025	Phase I/II	$130 million upfront payment, $1.34 billion milestone payments and royalties on net sales
Qilu & Minghui	MHB088C	B7-H3	Partnership & Collaboration, Licensing Agreement	May-2025	Phase III	$38 M upfront payment and upto $ 150 M in milestone payments

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Radiance & CSPC	RB-164	ROR1	Licensing Agreement	Feb-2025	Phase I	$15 million upfront payment, up to $150 million in potential development and regulatory milestone payments, over $1 Billion in potential commercial milestone payments, potential tiered royalties
Roche & Innovent Biologics	IBI3009	DLL3	Licensing Agreement	Jan-2025	Phase I	$80 million upfront payment ; $1 billion in milestone payments with tiered royalties on net sales
Aadi Bioscience & WuXi Biologics and HANGZHOU DAC	biSEZ6-CPT113, mMUC16-CPT113, PTK7-CPT113	PTK7, MCU16, SEZ6	Licensing Agreement, Partnership & Collaboration	Dec-2024	Preclinical	$849 million + tiered royalties
Gilead Sciences & Tubulis	Tubulis-Gilead ADC	Undisclosed	Licensing Agreement	Dec-2024	Preclinical	$465 million + tiered royalties
BioNTech & Biotheus	Undisclosed	Undisclosed	Acquisition	Nov-2024	N/A	$800 million and $150 million in Potential Milestone payments
IDEAYA Biosciences & Biocytogen	BCG034	B7-H3, PTK7	Option and License Agreement	Nov-2024	Preclinical	$400 million upfront, option exercise fee & milestone payment; including up to $100 million in development & regulatory milestone payments.

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Ono Pharmaceutical Co. Ltd & Ligachem Biosciences	LCB97	L1CAM	Licensing Agreement	Oct-2024	Preclinical	$700 million + tiered royalties
JMT-BioTechnology Co., Ltd. & Jiangsu Alphamab Biopharmaceuticals Co., Ltd.	JSKN-003	HER-2	Licensing Agreement	Sep-2024	Clinical	$439.2 million + royalties
Adcendo ApS & Multitude Therapeutics	ADCE-T02	Tissue Factor	Licensing Agreement	Aug-2024	Preclinical	$1 billion; single-digit to low double-digit tiered royalties
Vertex Pharmaceuticals & Orum Therapeutics	Vertex-Orum therapeutics Degrader-Antibody Conjugate	Undisclosed	Licensing Agreement	Jul-2024	Preclinical	$15 million upfront payment and up to $310 million in potential option fees and milestone payments per target plus tiered royalties
SOTIO Biotech & Biocytogen Pharmaceuticals Co. Ltd	SOTIO-Biocytogen Bispecific ADC	Undisclosed	Option & License Agreement	Jul-2024	Preclinical	$325.5 million upfront payment and potential development milestone payments
Ipsen Biopharmaceuticals & Foreseen Biotechnology	FS001	Undisclosed	Licensing Agreement	Jul-2024	Preclinical	$1.03 billion Comprising upfront, development, regulatory & commercial milestone payments & tiered royalties
Day One & MabCare Therapeutics	DAY-301 (MTX-13)	PTK7	Exclusive Licensing Rights	Jun-2024	Phase I	$55 M upfront; $1.15 B in milestone payments & royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
ArriVent & Alphamab	Proprietary Linker-Payload Platform, Glycan Conjugation Technology	N/A	Collaboration Agreement	Jun-2024	Discovery	$615.5 million
Merck KGaA & Biolojic Design	Clinically Validated AI Platform	N/A	Multi-target drug Discovery Collaboration	Jun-2024	Discovery	Upfront payment + up to €346 million in milestone payments
BioNtech & MediLink Therapeutics	YL202	HER-3	License Agreement	May-2024	N/A	$25 million upfront payment; $1.8 billion for additional development, regulatory and sales milestone payments, as well as tiered royalties
Merck & Abceutics	Undisclosed	Undisclosed	Acquisition	Apr-2024	N/A	$208 million
Merck KGaA & Caris Life Sciences	Undisclosed	Undisclosed	Multi-Year Collaboration	Apr-2024	Preclinical	$1.4 billion
Genmab & ProfoundBio	Clinical & Preclinical ADC candidates in-cluding Rina-S; ADC Technology Platforms	Rina-S: FRα	Acquisition	Apr-2024	Phase I/II	$ 1.8 billion cash
Ipsen & Sutro Biopharma	STRO-003	ROR1	Licensing Agreement	Apr-2024	Preclinical	$900 million potential upfront and milestone payments; ~$90m in near-term payments; equity investment; tiered royalties
Astrazeneca & Fusion Pharmaceuti-cals	FPI-2265	mCRPC	Acquisition	Mar-2024	Phase II	$2 billion upfront

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Immunome & Zentalis Pharmaceuti-cals	ZPC-21	ROR1	Exclusive License Agreement	Jan-2024	Preclinical	$35 million upfront; $275 million in milestone payments; mid-to-high single-digit royalties
Johnson & Johnson & Ambrx	ARX517, ARX788, ARX305	PSMA, HER-2, CD-70	Acquisition	Jan-2024	Phase I/II, Phase III, Phase I	$ 1.9 billion
Roche & MediLink	YL211	c-Met	Licensing Agreement	Jan-2024	Preclinical	~ $ 1 billion + royalties
Janssen & LegoChem	LCB84	Trop2	Licensing Agreement	Dec-2023	Phase I/II	$ 100 million upfront; $ 200 M option exercise payment; milestone payment royalties
GSK & Hansoh Pharma	HS-20089	B7-H4	Licensing Agreement	Dec-2023	Phase I	$ 85 million upfront
Pfizer & Nona Biosciences	HBM9033	MSLN	Licensing Agreement	Dec-2023	Preclinical	$53 million upfront & near term payments; up to $1.05 billion in milestone payment; royalties
Merck & C4 Therapeutics	Undisclosed	Undisclosed	License and Collaboration Agreement	Dec-2023	N/A	$10 million upfront; $600 million in milestone payments; tiered royalties
BMS & SystImmune	BL-B01D1	EGFR X HER3	Strategic Collaboration Agreement	Dec-2023	Phase III	$800 million upfront; $500 million in contingent near term payments; $1.7 billion milestone payments

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
AbbVie & ImmunoGen	ELAHERE®	FRα	Acquisition	Nov-2023	Marketed	$ 10.1 billion
Merck & Jiangsu Hengrui Pharmaceuti-cals	SHR-A1904	Claudin 18.2	Strategic Collaboration	Oct-2023	Phase II	€160 million upfront; up to € 1.4 billion in potential payments
GSK & Jiangsu Hansoh Pharmaceuti-cals	HS-20089	B7-H4	Exclusive License Agreement	Oct-2023	Phase I	$ 85 million upfront; up to $ 1.485 billion in milestone payments; royalties
Merck & Daiichi Sankyo	Patritumab deruxtecan, ifinatamab deruxtecan, raludotatug deruxtecan	B7H3; HER3; CDH6	Global Development and Commercial Collaboration	Oct-2023	Phase II	$ 4 billion upfront; $ 1.5 billion continuation payment; up to $16.5 billion milestone payments
Endeavour Biomedicines & Humming-bird Bioscience	Undisclosed	HER3	Licensing Agreement	Oct-2023	Preclinical	$ 430 million + royalties
SOTIO & Synnafix	Technology Platforms: GlycoConnect, HydraSpace, toxSYN linker-payloads	Undisclosed	Licensing Agreement	Oct-2023	Undisclosed	$ 740 million
BioNTech & MediLink	Undisclosed	HER3	Strategic Collaboration & License Agreement	Oct-2023	Undisclosed	$ 70 million upfront; over $ 1 billion in milestone payments
Takeda & ImmunoGen	ELAHERE®	Folate R1	Exclusive Collaboration	Aug-2023	Marketed	$ 34 million upfront + milestone payments and royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Gilead Sciences & Everest Medicines	TRODELVY®	Trop 2	Clinical Development and Commer-cialization Agreement	Aug-2023	Marketed	$280 million upfront; $175 million milestone payments
GSK & Mersana	XMT-2056	HER2	Option Agreement	Aug-2023	Preclinical	$100 million upfront; up to $1.36 billion in milestone payments
BeiGene & DualityBio	Investigational, Preclinical ADCs for select solid tumors	N/A	License Agreement	Jul-2023	Preclinical	$1.3 billion plus tiered royalties
Eli Lilly & Emergence Therapeutics	N/A	N/A	Merger & Acquisition	Jun-2023	N/A	$ 12 million
AstraZeneca & La Nova Medicines	LM-305	G protein-coupled receptor	License Deal	May-2023	Preclinical	$55 million upfront and near-payments; $545 million in milestone payments
FibroGen & Fortis Therapeutics	FOR46	Epitope on CD46	Licensing Agreement	May-2023	Phase I	Upto $80 million and total $200 million based on regulatory approvals
Eisai Co., Ltd. & Bliss Biopharma-ceuticals	BB-1701	HER2	Joint Development Agreement	May-2023	Phase I/II	$2 billion
Bristol Myers Squibb & Tubulis	Tubutecan payloads in combination with proprietary P5 conjugation platform	Topoisomer-ase-1	License Agreement	Apr-2023	N/A	$22.75 million upfront, $1 billion milestone payment
Pfizer & Seagen	N/A	N/A	Acquisition	Apr-2023	N/A	$43 billion

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Lonza & Synaffix	Proprietary Synaffix technology platform and R&D capabilities, including payload and site-specific linker technology	N/A	Acquisition	Apr-2023	N/A	$107 million cash; up to $64 million in performance-based consideration
Bristol Myers Squibb & Tubulis	P5 conjugation and Tubutecan platform	N/A	Licensing Agreement	Apr-2023	N/A	$22.75 million upfront; over $1 billion in milestone payments + royalty payments
Gene Quantumm Healthcare & Pyramid Biosciences	GQ1010	Trop 2	Exclusive License Agreement	Apr-2023	Preclinical	$ 20 million upfront; up to $ 1 billion in milestone payments + royalties
BioNTech & DualityBio	DB-1303; DB-1311	HER2	License Agreement	Apr-2023	Phase II	$ 170 million upfront; $ 1.5 billion milestone payments; royalties
Genmab & Synaffix	GlycoConnect, HydraSpace, toxSYN linker payloads	Undisclosed	License Agreement	Mar-2023	Preclinical	$ 415 million + royalties
MacroGenics & Synaffix	GlycoConnect, HydraSpace, toxSYN linker payloads	Undisclosed	Expansion of License Agreement	Mar-2023	Clinical	$ 2.2 billion
Takeda & Innate Pharma	R&D of ADCs focused on treating Celiac disease	Undisclosed	License Agreement	Mar-2023	Discovery	$5 million upfront; $410 million in milestone payments; tiered royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Vertex & ImmunoGen	Next generation ADCs	N/A	License and Option Agreement	Mar-2023	N/A	$15 million upfront payment; up to $337 million in option fees & milestone payments; tiered royalties
AstraZeneca & KYM Biosciences	CMG901	Claudin 18.2	Licensing Agreement	Feb-2023	Phase I	$63 million upfront; up to $1.1 billion in milestone payments; royalties
Corbus Pharmaceuticals & CSPC Megalith Biopharmaceutical	CRB-701 (SYS6002)	Nectin-4	Licensing Agreement	Feb-2023	Phase I	$7.5 million upfront; up to $130 million in development & regulatory milestone payments; $555 million in commercial milestone payments
Hummingbird Bioscience & Synaffix	Glyco-Connect™, Hydra Space™, select to xSYN™ linker-payloads	N/A	Licensing Agreement	Jan-2023	N/A	$150 million
Amgen & Synaffix	Glyco-Connect™, Hydra Space™, select to xSYN™ linker-payloads	N/A	Licensing Agreement	Jan-2023	N/A	$2 billion
Merck & Mersana	Immunosynthen STING-agonist ADC platform	2 Undisclosed Targets	License Agreement	Dec-2022	N/A	$30 million upfront; $80 million in milestone payments
Merck & Kelun-Biotech	7 ADCs	N/A	Licensing Agreement	Dec-2022	Discovery	$175 million upfront; Up to $9.3 billion in milestone payments; tiered royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Amgen & LegoChem Biosciences	ConjuAll ADC Technology	N/A	Licensing Agreement	Dec-2022	Discovery	$1.25 billion upfront; milestone payments & royalties
Exelixis & Iconic Therapeutics	XB002	Tissue factor	Licensing Agreement	Dec-2022	Phase I	$1.25 billion
Exelixis & Catalent	Three target programs with Ab and/or ADC candidates	Undisclosed	License Agreement	Nov-2022	Undisclosed	$ 30 million
Celltrion & Pinot Bio	PINOT-ADC Technology	15 separate cancer Targets	Licensing Agreement	Oct-2022	Discovery	$1 billion
Zai Lab & Seagen	TIVDAK®	CD142	Strategic Collaboration and License Agreement	Sep-2022	Marketed	$ 30 million upfront + milestone payments and royalties
GSK & SpringWorks	BLENREP®	BCMA	Non-exclusive License and Collaboration Agreement	Sep-2022	Marketed	$ 75 million equity investment; up to $ 550 million milestone payments
Emergence Therapeutics & Synaffix	ADC platform (GlycoConnect, HydraSpace); SYNtecan E linker payload	Undisclosed	Licensing Agreement	Sep-2022	Undisclosed	$ 360 million + royalties
Elevation Oncology & CSPC Megalith Biopharma-ceutical	EO-3021	Claudin18.2	Exclusive Agreement	Jul-2022	Phase I	$ 27 million upfront; up to $ 148 million in development & regulatory milestone payments; up to $ 1.0 billion in commercial milestone payments & royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Chiome Bioscience & Heidelberg Pharma	Amanitin toxin-linker platform technology	Undisclosed	Research and Option Agreement	Jul-2022	Discovery	€ 105 million
Swedish Orphan Biovitrum AB (Sobi) & ADC Therapeutics	ZYNLONTA®	CD19	Exclusive License Agreement	Jul-2022	Marketed	$ 55 million upfront; $ 50 million of first EC approval; up to $ 330 million in milestone payments
Astellas & Sutro	Novel iADCs	N/A	Licensing Agreement	Jun-2022	Discovery	$90 million upfront; up to $422.5 million in milestone payments; royalties
Turning Point Therapeutics & LaNova Medicines	LM-302	Claudin18.2	Exclusive License Agreement	May-2022	Phase I	$ 25 million upfront; $ 195 million milestone payments; royalties
Huadong Medicine & Heidelberg Pharma	HDP-101, HDP-103	BCMA; PSMA	Strategic Partnership Agreement	Feb-2022	pre-IND	$ 20 million upfront; up to $ 449 million in milestone payments; royalties
MacroGenics & Synaffix	GlycoConnect, HydraSpace, toxSYN linker payloads	Undisclosed	License Agreement	Feb-2022	Clinical	$ 586 million + royalties
Eli Lilly & ImmunoGen	Camptothecin ADC platform	Type I Topo-isomerase	Licensing Agreement	Feb-2022	Discovery	$13 million upfront; $32.5 million additional targets; $1.7 billion milestone payments; tiered royalties

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Janssen & Mersana	Dolasynthen platform	Multiple	Licensing Agreement	Feb-2022	Discovery	$ 40 million upfront payment; up to $1 billion in potential milestone payments, percent royalties
Odeon & OBI Pharma	OBI-999. OBI-833	Globo H	Licensing Agreement	Feb-2022	Phase I/II	Fully paid equity equivalent to $12 million; up to $188 million milestone payments; royalties on net sales
Mitsubishi Tanabe & ADC Therapeutics	ZYNLONTA®	CD19	Commercialization Agreement	Feb-2022	Accelerated US approval (Apr 2022)	$30 million upfront payment; Up to $205 million in milestone payments
Iksuda Therapeutics & LegoChem Biosciences	LCB14	HER 2	Co-development and Technology Transfer Agreement	Dec-2021	N/A	$50 million up-front payment; up to $950 million in milestones
SOTIO & LegoChem Biosciences	Conjugation technology ConjuAll™ and potent linker-payload Platform	Undisclosed	Exclusive Collaboration & License Agreement	Nov-2021	Discovery	Up to $ 1027.5 upfront and milestone payments + royalties
Mersana & Synaffix	GlycoConnect™	N/A	Licensing Agreement	Nov-2021	N/A	$1 billion+ royalties
Seagen and RemeGen	Disitamab Vedotin	HER2	License and Co-Development Agreement	Sep-2021	Marketed	Upfront $200 million; $2.4 billion in potential developmental and regulatory milestones
HealthCare Royalty & ADC Therapeutics	ZYNLONTA® and Cami	CD19	Financing Agreement	Aug-2021	ZYNLONTA™ : Marketed; Cami : Phase II	$325 million

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Bristol Myers Squibb & Eisai	MORAb-202	FRα	Strategic Collaboration	Jun-2021	Phase 1/ 2	$ 650 million upfront; up to $ 2.45 billion in milestone payments; royalties
Boehringer Ingelheim & NBE-Therapeutics	NBE-002 + immune stimulatory iADC™ platform	ROR1	Acquisition	Dec-2020	Phase I	$1.5 billion (€1.2 billion) includes contingent clinical and regulatory milestones
Merck & VelosBio	VLS-101	ROR1	Acquisition	Nov-2020	Phase II	$2.75 billion
CStone Pharmaceuti-cals & LegoChem Biosciences	LCB71	ROR1	Licensing	Oct-2020	Pre-clinical	$10 million upfront; up to $353.5 million in milestone payments, plus tiered royalties
Gilead & Immuno medics	Trodelvy (Sacituzumab govitecan)	TROP2	Acquisition	Sep-2020	Accelerated US approval (Apr 2020)	~$21 billion
Merck & SeaGen	Ladiratuzumab vedotin	LIV-1	Strategic Collaboration	Sep-2020	Phase II	$600 million upfront; $1 billion equity investment; up to $2.6 billion in milestone payments
AstraZeneca & Daiichi Sankyo	DS-1062	TROP2	Strategic Collaboration	Jul-2020	Phase I	$1 billion upfront (staged); up to $1 billion in regulatory milestones; up to $4 billion in sales milestones
SeaGen & Five Prime	Multi-product	N/A	Licensing	Feb-2020	N/A	$5 million upfront; up to $525 million in future milestone payments

Partners	Asset(s)	Target	Deal Type	Date	Phase of Lead Asset at Time of Deal	Deal Value
Shanghai Miracogen & Synaffix	GlycoConnect™ and HydraSpace™	N/A	License Agreement	Apr-2019	N/A	$125 million
AstraZeneca & Daiichi Sankyo	Trastuzumab deruxtecan (DS-8201)	HER2	Strategic Collaboration	Mar-2019	Development	Upfront payment of $1.35 billion; contingent payments of up to $5.55 billion

Note: For references supporting the content provided please visit https://njbio.com/antibody-drug-conjugates/

Table 16. List of Antibody-Drug Conjugate Venture Capital Funding Events and IPOs

Company	Asset (s)	Target	Funding Event	Date	Phase of Lead Asset at Time of Deal	Deal Value
NEOK Bio, Inc.	NEOK001 & NEOK002	ROR1 and B7-H3; EGFR and MUC1	Series A	Nov-2025	N/A	$75 million
Adcytherix	ADCX-020	N/A	Series A	Oct-2025	N/A	$122 million
Tubulis GmbH	TUB-040 & TUB-030	NaPi2b	Series C	Oct-2025	Preclinical	$401 million
TORL BioTherapeutics	TORL-1-23	CLDN6+	Series C	Oct-2025	Phase II	$96 million
Avenzo Therapeutics	small molecules and antibody-drug conjugates (ADCs)	N/A	Series B	Sep-2025	N/A	$60 million
Callio Therapeutics	Advance Multi-Payload Antibody-Drug Conjugate Platform	N/A	Series A	Mar-2025	N/A	$187.0 million

Company	Asset (s)	Target	Funding Event	Date	Phase of Lead Asset at Time of Deal	Deal Value
Alentis Therapeutics	ALE.P02 & ALE.P03	CLDN1	Series D	Nov-2024	Phase I/II	$181.4 million
Allink Biotherapeutics	N/A	N/A	Series A	Nov-2024	Phase I/II	$42 million
Adcendo	ADCE-T02 & A0401	Tissue factor & Undis-closed	Series B	Nov-2024	Preclinical	$135 million
LaNova Medicines	LM-302 & LM-108	N/A	Series C1	Oct-2024	N/A	~$41 million (300 million yuan)
Kivu Bioscience	Synaffix site-specific linker-payload Technology	N/A	Series A	Oct-2024	N/A	$92 million
Myricx Bio	NMTi-ADC platform	N/A	Series A	Jul-2024	N/A	$114 Million
Indupro	N/A	N/A	Series A	Jun-2024	N/A	$85 million
Pheon Therapeutics	N/A	N/A	Series B	May-2024	Preclinical	$120 million
Endeavor BioMedicines	ENV-101; ENV-501	Hedge-hog (Hh); HER-3	Series C	Apr-2024	Phase II	$ 132.5 million
TORL BioTherapeutics	TORL-1-23; TORL-2-307; TORL-3-600; TORL-4-500	Claudin 6; Claudin 18.2; CDH17; DLK1	Series B-2	Apr-2024	Phase I	$158 million

Company	Asset (s)	Target	Funding Event	Date	Phase of Lead Asset at Time of Deal	Deal Value
ProfoundBio	Clinical and Preclinical ADC programs	N/A	Series B	Feb-2024	N/A	$112 million
Firefly Bio	Degrader Antibody Conjugate	N/A	Series A	Feb-2024	Fast-track designation	$94 million
OnCusp Therapeutics	CUSP06	CDH6	Series A	Jan-2024	Phase I	$100 million
Mbrace Therapeutics	ADCs for oncology Targets	N/A	Series B	Nov-2023	Preclinical	$85 million
Tagworks Pharmaceuticals	Unique Click-to-Release platform	TAG72	Series A	Jun-2023	Preclinical	$65 million
Adcentrx	ADRX-0706	N/A	Series A+	Apr-2023	Preclinical	$38 million
Adcendo	Lead candidate uPARAP-ADC	uPARAP	Series A	Apr-2023	Preclinical	€31 million
Solve Therapeutics	Novel mAbs, ADCs incorporating next-generation linker and payload constructs, and bispecific antibodies	N/A	Series A	Dec-2022	N/A	$126 million
Dantari	T-HDC (Targeted High-capacity Drug Conjugate) platform	N/A	Series A	Dec-2022	N/A	$47 million
Mablink	Patented hydrophilic drug-linker technology	N/A	Series A	Oct-2022	Preclinical	€31 million

Company	Asset (s)	Target	Funding Event	Date	Phase of Lead Asset at Time of Deal	Deal Value
Araris	Proprietary Linker Technology	N/A	Series A	Oct-2022	N/A	$24 million
Tubulis	Advance proprietary pipeline of ADCs towards clinical evaluation	N/A	Series B	May-2022	N/A	$63 million
Medlink Therapeutics	Proprietary technology platform	N/A	Series B	Mar-2022	N/A	$70 million
Pheon Therapeutics	Next generation ADCs	N/A	Series A	Mar-2022	N/A	$68 million
ProfoundBio	Novel technology platforms for ADCs and IO therapeutics	N/A	Series A	Jul-2021	N/A	$55 million
Suzhou Medilink Therapeutics	Next generation ADCs	N/A	Series A	Mar-2021	N/A	$50 million
Silverback Therapeutics	ImmunoTAC™ technology platform	HER2	IPO	Dec-2020	Phase I	$278 million
Silverback Therapeutics	SBT6050 (anti-HER2 antibody conjugated to a potent TLR8 agonist), pipeline of ImmunoTAC™ Programs	HER2	Series C	Sep-2020	Phase I	$85 million

Company	Asset (s)	Target	Funding Event	Date	Phase of Lead Asset at Time of Deal	Deal Value
Bolt Therapeutics	Immune Stimulating Antibody Conjugate (ISAC) platform, BDC-1001	HER2	Series C	Jul-2020	Phase I/II	$93.5 million
VelosBio	VLS-101 and other ROR1-directed ADCs	ROR1	Series B	Jul-2020	Phase II	$137 million
Tubulis	Tub-tag™platform, TUB-010, TUB-020	N/A	Series A	Jul-2020	Preclinical	€10.7 million
Avidity	Antibody Oligonucleotide Conjugates™, including AOC 1001	TfR1	IPO	Jun-2020	Preclinical	$298 million
ADC Therapeutics	Loncastuximab tesirine, Camidanlumab tesirine and others	CD19, CD25	IPO	May-2020	Phase II	$268 million
Silverback Therapeutics	SBT6050 (anti-HER2 antibody conjugated to a potent TLR8 agonist), pipeline of ImmunoTAC™ Programs	HER2	Series B	Mar-2020	Preclinical	$78.5 million
NBE Therapeutics	NBE-002	ROR1	Series C	Jan-2020	Preclinical	$22 million

8. Conclusions

In summary, ADCs have emerged as an important therapeutic class of agents that can lead to new opportunities in the treatment of various cancers. Recent significant scientific and clinical advances in the field of ADCs have highlighted it as an important space for continued research and investment.

Acquiring insights into the novel strategies, understanding the efficacy and safety profiles of ADCs, identifying patterns of success and failure, and optimizing R&D strategies are crucial steps to streamline the development process and increase the likelihood of regulatory approval. Antibody engineering and site-specific conjugation technologies have also shown potential to enhance the therapeutic index in preclinical studies. An integrated approach, combining careful target selection with optimization of the antibody, linker, and payload components of the ADC tailored to specific disease indications, holds promise for future ADC approvals.

Major pharmaceutical companies, biotechnology firms, and academic institutions are actively engaged in the development of ADCs through strategic partnerships and collaborations. This collaborative approach not only accelerates the pace of innovation but also mitigates the inherent risks associated with drug development, making ADCs an attractive investment opportunity.

Overall, ongoing advancements in ADC technology, alongside refinements in clinical processes and combination therapies, offer scope of enhanced treatment outcomes.

References

[1] AstraZeneca. (**2024**, June 02). ENHERTU® (fam-trastuzumab deruxtecan-nxki) demonstrated a median progression-free survival of 13.2 months in HR-positive, HER2-low and HER2-ultralow metastatic breast cancer following one or more lines of endocrine therapy [Press Release] https://www.astrazeneca-us.com/media/press-releases/2024/enhertu-fam-trastuzumab-deruxtecan-nxki-demonstrated-a-median-progression-free-survival-of-13-2-months-in-hr-positive-her2-low-and-her2-ultralow-metastatic-breast-cancer-following-one-or-more-lines-of-endocrine-therapy.html#:~:text=PFS%20results%20by%20BICR%20in,0.75%3B%20p%3C0.0001).

[2] Gilead Sciences. (**2022**, June 06). Final data from phase 3 ASCENT study demonstrates Trodelvy extends overall survival over chemotherapy in second-line metastatic TNBC. [Press Release] https://www.gilead.com/news-and-press/press-room/press-releases/2022/6/final-data-from-phase-3-ascent-study-demonstrates-trodelvy-extends-overall-survival-over-chemotherapy-in-second-line-metastatic-tnbc

[3] Beacon ADC. Available https://beacon-intelligence.com/.

[4] Antibody-drug conjugate market (**2023**) MarketsandMarkets. [Report] https://www.marketsandmarkets.com/Market-Reports/antibody-drug-conjugates-market-122857391.html

[5] U.S. Food and Drug Administration. (**2013**). Approval letter for Kadcyla (ado-trastuzumab emtansine). U.S. Department of Health and Human Services. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf

[6] Saura, C., Modi, S., Krop, I., Park, Y.H., Kim, S.B., Tamura, K., Iwata, H., Tsurutani, J., Sohn, J., Mathias, E. and Liu, Y., (**2024**). Trastuzumab Deruxtecan in previously treated patients with HER2-positive metastatic breast cancer: updated survival results from a phase II trial (DESTINY-Breast01). Annals of Oncology, 35(3), 302-307. https://doi.org/10.1016/j.annonc.2023.12.001

[7] Fu, Z., Li, S., Han, S., Shi, C., & Zhang, Y. (**2022**). Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal transduction and targeted therapy, 7(1), 93. https://doi.org/10.1038/s41392-022-00947-7

[8] Jain, N.; Smith, S. W.; Ghone, S.; Tomczuk, B. (**2015**) Current ADC Linker Chemistry. Pharmaceutical Research 32, 3526–3540. https://doi.org/10.1007/s11095-015-1657-7

[9] Lu, R. M., Hwang, Y. C., Liu, I. J., Lee, C. C., Tsai, H. Z., Li, H. J., & Wu, H. C. (**2020**). Development of therapeutic antibodies for the treatment of diseases. Journal of biomedical science, 27, 1-30. https://doi.org/10.1186/s12929-019-0592-z

[10] Drachman, J. G., & Senter, P. D. (**2013**). Antibody-drug conjugates: the chemistry behind empowering antibodies to fight cancer. Hematology 2013, the American Society of Hematology Education Program Book, 2013(1), 306-310. https://doi.org/10.1182/asheducation-2013.1.306

[11] Pettinato, M. C. (**2021**). Introduction to antibody-drug conjugates. Antibodies, 10(4), 42. https://doi.org/10.3390/antib10040042

[12] Timeline: charting the choppy history of 'magic bullet' antibody-drug conjugates (**2021**) Pharmaceutical Technology. https://www.pharmaceutical-technology.com/features/antibody-drug-conjugates-timeline/?cf-view

[13] Shastry, M., Gupta, A., Chandarlapaty, S., Young, M., Powles, T., & Hamilton, E. (**2023**). Rise of antibody-drug conjugates: the present and future. American Society of Clinical Oncology Educational Book, 43, e390094. https://doi.org/10.1200/EDBK_390094

[14] Amiri-Kordestani, Laleh, Gideon M. Blumenthal, Qiang Casey Xu, Lijun Zhang, Shenghui W. Tang, Linan Ha, Wendy C. Weinberg et al. (**2014**). FDA approval: ado-trastuzumab emtansine for the treatment of patients with HER2-positive metastatic breast cancer. Clinical cancer research, 20(17), 4436-4441. https://doi.org/10.1158/1078-0432.CCR-14-0012

[15] Wyeth Pharmaceuticals, Inc.; Withdrawal of Approval of a New Drug Application for MYLOTARG. (**2011**) A Notice by the Food and Drug Administration. https://www.federalregister.gov/documents/2011/11/28/2011-30473/wyeth-pharmaceuticals-inc-withdrawal-of-approval-of-a-new-drug-application-for-mylotarg

[16] FDA approves Mylotarg for treatment of acute myeloid leukemia (**2017**) FDA News Release. https://www.fda.gov/news-events/press-announcements/fda-approves-mylotarg-treatment-acute-myeloid-leukemia

[17] Su, Z., Xiao, D., Xie, F., Liu, L., Wang, Y., Fan, S., Zhou, X. and Li, S., (**2021**). Antibody–drug conjugates: recent advances in linker chemistry. Acta Pharmaceutica Sinica B, 11(12), 3889-3907. https://doi.org/10.1016/j.apsb.2021.03.042

[18] Bargh, J. D., Walsh, S. J., Ashman, N., Isidro-Llobet, A., Carroll, J. S., & Spring, D. R. (**2021**). A dual-enzyme cleavable linker for antibody–drug conjugates. Chemical Communications, 57(28), 3457-3460. https://doi.org/10.1039/D1CC00957E

[19] Kostova, V., Désos, P., Starck, J. B., & Kotschy, A. (**2021**). The chemistry behind ADCs. Pharmaceuticals, 14(5), 442. https://doi.org/10.3390/ph14050442

[20] Antibody-drug conjugates. (**2012**). Therapeutic Antibody Engineering, 345–95. https://doi.org/10.1533/9781908818096.345

[21] Bo̎hnke, N., Berger, M., Griebenow, N., Rottmann, A., Erkelenz, M., Hammer, S., Berndt, S., Gu̎nther, J., Wengner, A.M., Stelte-Ludwig, B. and Mahlert, C., (**2022**). A novel NAMPT inhibitor-based antibody–drug conjugate payload class for cancer therapy. Bioconjugate Chemistry, 33(6), pp.1210-1221. https://doi.org/10.1021/acs.bioconjchem.2c00178

[22] Wang, Z., Li, H., Gou, L., Li, W., & Wang, Y. (**2023**). Antibody–drug conjugates: Recent advances in payloads. Acta Pharmaceutica Sinica B. https://doi.org/10.1016/j.apsb.2023.06.015

[23] Sun, L., Zhang, Y., Li, W., Zhang, J., & Zhang, Y. (**2023**). Mucin glycans: A target for cancer therapy. Molecules, 28(20), 7033. https://doi.org/10.3390/molecules28207033

[24] Ho, W. L., Hsu, W. M., Huang, M. C., Kadomatsu, K., & Nakagawara, A. (**2016**). Protein glycosylation in cancers and its potential therapeutic applications in neuroblastoma. Journal of hematology & oncology, 9, 1-15.

[25] Diamantis, N., & Banerji, U. (**2016**). Antibody-drug conjugates—an emerging class of cancer treatment. British journal of cancer, 114(4), 362-367. https://doi.org/ 10.1186/s13045-016-0334-6

[26] Vidarsson, G., Dekkers, G. and Rispens, T., (**2014**). IgG subclasses and allotypes: from structure to effector functions. Frontiers in immunology, 5, p.520. https://doi.org/10.3389/fimmu.2014.00520

[27] Walsh, S.J., Bargh, J.D., Dannheim, F.M., Hanby, A.R., Seki, H., Counsell, A.J., Ou, X., Fowler, E., Ashman, N., Takada, Y. and Isidro-Llobet, A., (**2021**). Site-selective modification strategies in antibody–drug conjugates. Chemical Society Reviews, 50(2), 1305-1353. https://doi.org/10.1039/D0CS00310G

[28] Hoffmann, R.M., Coumbe, B.G., Josephs, D.H., Mele, S., Ilieva, K.M., Cheung, A., Tutt, A.N., Spicer, J.F., Thurston, D.E., Crescioli, S. and Karagiannis, S.N., (**2018**). Antibody structure and engineering considerations for the design and function of Antibody Drug Conjugates (ADCs). Oncoimmunology, 7(3), e1395127. https://doi.org/10.1080/2162402X.2017.1395127

[29] Deonarain, M. P., & Xue, Q. (2020). Tackling solid tumour therapy with small-format drug conjugates. Antibody Therapeutics, 3(4), 237-245. https://doi.org/10.1093/abt/tbaa024

[30] Deonarain, M.P., Yahioglu, G., Stamati, I., Pomowski, A., Clarke, J., Edwards, B.M., Diez-Posada, S. and Stewart, A.C., (**2018**). Small-format drug conjugates: a viable alternative to ADCs for solid tumours? Antibodies, 7(2), 16. https://doi.org/10.3390/antib7020016

[31] Alley, S. C.; Okeley, N. M.; Senter, P. D. (**2010**). Antibody–Drug Conjugates: Targeted Drug Delivery for Cancer. Current Opinion in Chemical Biology, 14 (4), 529–537. https://doi.org/10.1016/j.cbpa.2010.06.170

[32] Doronina, S. O.; Toki, B. E.; Torgov, M. Y.; Mendelsohn, B. A.; Cerveny, C. G.; Chace, D. F.; Deblanc, R. L.; Gearing, R. P.; Bovee, T. D.; Siegall, C. B.; Francisco, J. A.; Wahl, A. F.; Meyer, D. L.; Senter, P. D.; Zhang, L.; Miles, M. F.; Aldape, K. D. (**2003**). Development of Potent Monoclonal Antibody Auristatin Conjugates for Cancer Therapy Corrigendum : A Model of Molecular Interactions on Short Oligonucleotide Microarrays. Nat. Biotech. 21 (8), 2003.

[33] Jeffrey, S. C.; de Brabander, J.; Miyamoto, J.; Senter, P. D. (**2010**). Expanded Utility of the β-Glucuronide Linker: ADCs That Deliver Phenolic Cytotoxic Agents. ACS Medicinal Chemistry Letters, 1 (6), 277–280. https://doi.org/10.1021/ml100039h

[34] Lyon, R. P.; Bovee, T. D.; Doronina, S. O.; Burke, P. J.; Hunter, J. H.; Neff-Laford, H. D.; Jonas, M.; Anderson, M. E.; Setter, J. R.; Senter, P. D. (**2015**) Reducing Hydrophobicity of Homogeneous Antibody-Drug Conjugates Improves Pharmacokinetics and Therapeutic Index. Nature Biotechnology, 33 (7), 733–735. https://doi.org/10.1038/nbt.3212

[35] Lewis Phillips, G. D.; Li, G.; Dugger, D. L.; Crocker, L. M.; Parsons, K. L.; Mai, E.; Blättler, W. A.; Lambert, J. M.; Chari, R. V. J.; Lutz, R. J.; Wong, W. L. T.; Jacobson, F. S.; Koeppen, H.; Schwall, R. H.; Kenkare-Mitra, S. R.; Spencer, S. D.; Sliwkowski, M. X. (**2008**). Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody-Cytotoxic Drug Conjugate. Cancer Research, 68 (22), 9280–9290. https://doi.org/10.1158/0008-5472.CAN-08-1776

[36] Su, D., & Zhang, D. (**2021**). Linker design impacts antibody-drug conjugate pharmacokinetics and efficacy via modulating the stability and payload release efficiency. Frontiers in pharmacology, 12, 687926.

[37] Matsuda, Y.; Robles, V.; Malinao, M. C.; Song, J.; Mendelsohn, B. A. (**2019**). Comparison of Analytical Methods for Antibody-Drug Conjugates Produced by Chemical Site-Specific Conjugation: First-Generation AJICAP. Analytical Chemistry, 91 (20), 12724–12732. https://doi.org/10.1021/acs.analchem.9b02192

[38] Sarrut, M.; Fekete, S.; Janin-Bussat, M.-C.; Colas, O.; Guillarme, D.; Beck, A.; Heinisch, S. (**2016**). Analysis of Antibody-Drug Conjugates by Comprehensive on-Line Two-Dimensional Hydrophobic Interaction Chromatography x Reversed Phase Liquid Chromatography Hyphenated to High Resolution Mass Spectrometry. II- Identification of Sub-Units for the Characterization of even and odd load drug species. Journal of chromatography. B, Analytical technologies in the biomedical and life sciences, 1032, 91–102. https://doi.org/10.1016/j.jchromb.2016.06.049

[39] Beck, A.; Goetsch, L.; Dumontet, C.; Corvaïa, N. (**2017**). Strategies and Challenges for the next Generation of Antibody-Drug Conjugates. Nature Reviews Drug Discovery, 16 (5), 315–337. https://doi.org/10.1038/nrd.2016.268

[40] McCombs, J. R., & Owen, S. C. (**2015**). Antibody drug conjugates: design and selection of linker, payload and conjugation chemistry. The AAPS journal, 17, 339-351. https://doi.org/ 10.1208/s12248-014-9710-8

[41] Shinmi, D., Taguchi, E., Iwano, J., Yamaguchi, T., Masuda, K., Enokizono, J., & Shiraishi, Y. (**2016**). One-step conjugation method for site-specific antibody–drug conjugates through reactive cysteine-engineered antibodies. Bioconjugate Chemistry, 27(5), 1324-1331. https://doi.org/10.1021/acs.bioconjchem.6b00133

[42] Sun, X., Ponte, J.F., Yoder, N.C., Laleau, R., Coccia, J., Lanieri, L., Qiu, Q., Wu, R., Hong, E., Bogalhas, M. and Wang, L., (**2017**). Effects of drug–antibody ratio on pharmacokinetics, biodistribution, efficacy, and tolerability of antibody–maytansinoid conjugates. Bioconjugate Chemistry, 28(5), 1371-1381. https://doi.org/10.1021/acs.bioconjchem.7b00062

[43] Sadiki, A., Vaidya, S.R., Abdollahi, M., Bhardwaj, G., Dolan, M.E., Turna, H., Arora, V., Sanjeev, A., Robinson, T.D., Koid, A. and Amin, A. (**2020**). Site-specific conjugation of native antibody. Antibody therapeutics, 3(4), 271-284. https://doi.org/10.1093/abt/tbaa027

[44] History of ADC Payloads and its Pharmocokinetic Profiles (**2023**) Boc Sciences

[45] Tong, J. T., Harris, P. W., Brimble, M. A., & Kavianinia, I. (**2021**). An insight into FDA approved antibody-drug conjugates for cancer therapy. Molecules, 26(19), 5847.

[46] Fu, C., Tong, W., Yu, L., Miao, Y., Wei, Q., Yu, Z., Chen, B. and Wei, M., (2024). When will the Immune-Stimulating Antibody Conjugates (ISACs) be transferred from bench to bedside? Pharmacological Research, 107160.

[47] Dragovich, P. S. (**2022**). Degrader-antibody conjugates. Chemical Society Reviews, 51(10), 3886-3897.

[48] Palacino, J., Lee, P., Jeong, H., Kim, Y., Song, Y., Permpoon, U., Wong, W., Bai, C., Fishkin, N., Takouri, K. and Yu, E., (**2023**). ORM-6151: a first-in-class CD33-antibody enabled GSPT1 degrader for AML. Cancer Research, 83(7_Supplement), 2700-2700.

[49] Yamazaki, C.M., Yamaguchi, A., Anami, Y., Xiong, W., Otani, Y., Lee, J., Ueno, N.T., Zhang, N., An, Z. and Tsuchikama, K., (**2021**). Antibody-drug conjugates with dual payloads for combating breast tumor heterogeneity and drug resistance. Nature communications, 12(1), 3528.

[50] Yang, Y., Wang, S., Ma, P., Jiang, Y., Cheng, K., Yu, Y., Jiang, N., Miao, H., Tang, Q., Liu, F. and Zha, Y., (**2023**). Drug conjugate-based anticancer therapy-Current status and perspectives. Cancer Letters, 552, 21596

[51] Chari, R. V. (**2008**). Targeted cancer therapy: conferring specificity to cytotoxic drugs. Accounts of chemical research, 41(1), 98-107. https://doi.org/10.1021/ar700108g

[52] Nguyen, T. D., Bordeau, B. M., & Balthasar, J. P. (**2023**). Mechanisms of ADC toxicity and strategies to increase ADC tolerability. Cancers, 15 (3), 713. https://doi.org/10.3390/cancers15030713

[53] Staudacher, A. H., & Brown, M. P. (**2017**). Antibody drug conjugates and bystander killing: is antigen dependent internalisation required? British journal of cancer, 117(12), 1736-1742. https://doi.org/10.1038/bjc.2017.367

[54] Hinrichs, M. J. M., & Dixit, R. (**2015**). Antibody drug conjugates: nonclinical safety considerations. The AAPS journal, 17, 1055-1064. https://doi.org/10.1208/s12248-015-9790-0

[55] Pfizer (**2025**) Financial results for fourth quarter and full-year 2024, [Report] https://s28.q4cdn.com/781576035/files/doc_financials/2024/q4/Q4-2024-PFE-Earnings-Release-Final.pdf

[56] AstraZeneca (**2025**) FY and Q4 2024 results. [Announcement] https://www.astrazeneca.com/content/dam/az/PDF/2024/fy/Full-year-and-Q4-2024-results-announcement.pdf

[57] Roche (**2025**) Finance Report 2024 [Report] https://assets.roche.com/f/176343/x/38d96ed8ec/fb24e.pdf

[58] U.S. Food and Drug Administration. https://www.fda.gov/

[59] Wei, Q., Li, P., Yang, T., Zhu, J., Sun, L., Zhang, Z., Wang, L., Tian, X., Chen, J., Hu, C. and Xue, J., (**2024**). The promise and challenges of combination therapies with antibody-drug conjugates in solid tumors. Journal of Hematology & Oncology, 17(1), 1. https://doi.org/10.1186/s13045-023-01509-2

[60] U.S. Food and Drug Administration. https://www.fda.gov/

[61] Pfizer. https://www.pfizer.com/

[62] Liu, R., Wang, R. E., & Wang, F. (**2016**). Antibody-drug conjugates for non-oncological indications. Expert opinion on biological therapy, 16(5), 591-593. https://doi.org/10.1517/14712598.2016.1161753

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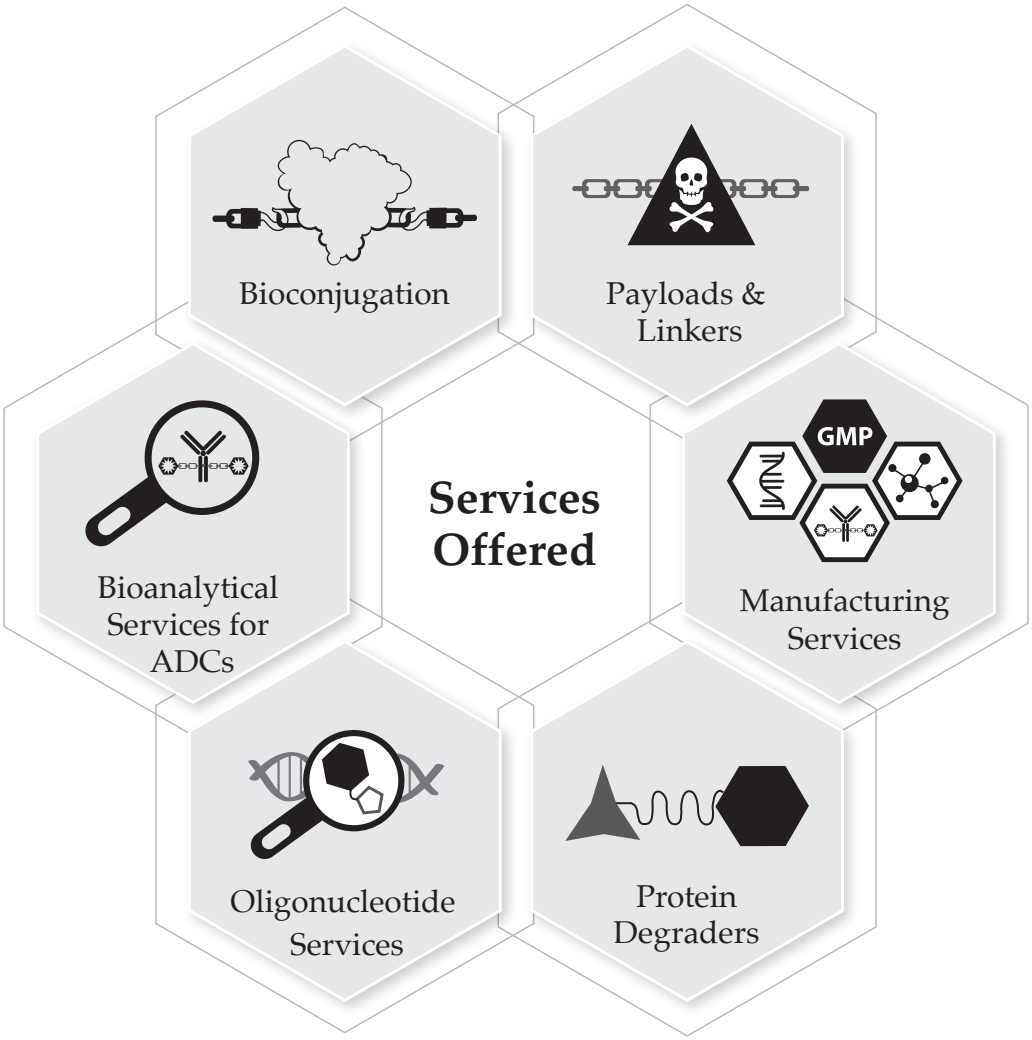

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