Linker Strategies in Antibody-Drug Conjugates: Insights from HER2-Targeted ADCs

Huirong Su [1,*], Haoxuan Teng [2], Yu Tong [3]

[1] School of Natural Sciences, The University of Manchester, Manchester, United Kingdom

[2] Shanghai Foreign Language School Affiliated to SISU Hangzhou, Hangzhou, China

[3] College of Veterinary Medicine, Northwest A&F University, XianyangYangling, Shaanxi, China

* Corresponding Author Email: huirong.su@student.manchester.ac.uk

Abstract. In tumors with alterations of human epidermal growth factor receptor 2 (HER2), conventional monoclonal antibodies and tyrosine kinase inhibitors (TKIs) are limited by intratumoral heterogeneity and acquired resistance. Antibody-drug conjugates (ADCs) take advantage of the selectivity of monoclonal antibodies to deliver highly efficient cytotoxins and rely on linkers to achieve spatiotemporal controlled release. Representative HER2-targeted ADCs can be roughly divided into three examples. The first is trastuzumab emtansine (T-DM1), which uses a non-cleavable linker to attach the maytansinoid DM1. The second example is trastuzumab drutecan (T-DXd), which uses the Gly-Gly-Phe-Gly cleavable linker for conjugation with topoisomerase I inhibitors (DXd). Recently, SHR-A1811 introduced a payload carrying a chiral cyclopropyl group, which provided different stability. These improvements enable the drug to be released more controllably within tumor cells and expand the indications from patients with high HER2 expression to those with low HER2 expression or even HER2 mutations. Among these drugs, the linker is no longer merely a simple "bridge"; it also determines the degree of exposure to the load, the way the drug is released in the body, and even affects the toxicity that patients may face. This review summarizes the development of HER2-targeted ADCs, with a focus on the evolution of linker strategies and their impact on efficacy and safety, with the aim of providing ideas for the future design of HER2-targeted ADCs.

Keywords: HER2, ADC, linker, cyclopropyl, trastuzumab.

1. Introduction

As early as 1913, German doctor and scientist Paul Ehrlich proposed the concept of selectively delivering toxic substances to pathogenic target cells [1], and this idea was eventually realized in antibody-drug conjugates (ADCs). An ADC consists of three parts including a monoclonal antibody, a cytotoxic payload, and a linker [2]. Monoclonal antibodies recognize the specific antigens that are overexpressed on the surface of cancer cells, thereby endowing drugs with high tissue selectivity. Cytotoxic payloads include traditional anti-cancer drugs and novel compounds with enhanced efficacy and unique mechanisms of action, which can rapidly induce apoptosis of tumor cells [3]. The linker acts as a molecular bridge between the antibody and the cytotoxic payload and plays a critical role in controlling the release of the payload [4]. Linkers are essential for both the efficacy and safety of ADCs. An ideal linker should remain highly stable in the blood circulation and be specifically broken in tumor cells to ensure the precise release of the load. Such cleavage may occur under acidic conditions, in the presence of proteases, or in reducing environments [5]. These properties define the pharmacokinetics, pharmacodynamics, and therapeutic window of ADCs, enhance the efficacy and safety of adc drugs [6].

On the surface of some tumor cells, the expression level of HER2 is significantly higher than that of normal cells. This feature provides an important idea for the design and development of ADC drugs [7]. Based on this distinct tumor-specific difference, HER2 has become one of the most widely used targets in ADC development [8]. In 2013, trastuzumab emtansine (Kadcyla) was approved [9], which employed a non-cleavable succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) linker. Trastuzumab deruxtecan (Enhertu), approved in 2019 [10], and SHR-A1811, approved in 2025 [11], both utilized cleavable linkers based on the Gly-Gly-Phe-Gly tetrapeptide conjugated to

topoisomerase I inhibitors. These three ADCs employ trastuzumab as the targeting antibody against HER2, yet they rely on two distinct linker strategies, non-cleavable and cleavable, to meet different clinical indications. This review aims to take HER2-targeted ADCs as an example to systematically introduce the evolution of linker strategies from non-cutting to tumor-selective cutting systems, as well as the impact of linker design on drug-to-antibody ratio, payload release kinetics and safety, providing ideas for the development of next-generation linkers with controllable release and higher stability and clinical optimization.

2. HER2 Expression Patterns and Targeted Strategies

The HER2 gene (ERBB2) encodes the HER2 protein, a transmembrane tyrosine kinase receptor [7]. Amplification of HER2 leads to protein overexpression and persistent activation of downstream signaling pathways, thereby promoting abnormal proliferation and malignant progression of tumor cells [12]. As a key driver gene in multiple solid tumors, HER2 has become an important therapeutic target in oncology drug development [13, 14].

The expression level of HER2 is determined by immunohistochemistry (IHC) and in situ hybridization (ISH) detection. The definition of high HER2 expression is: an IHC score of 3+ or a positive FISH test result. Its characteristic is the presence of strong and complete membrane staining or gene amplification in more than 10% of tumor cells [15]. An IHC score of 1+ or 2+ with a negative FISH result is classified as low expression of her2 [16].

In addition to overexpression, HER2 mutations are very common in solid tumors. Somatic alterations occurring in the ERBB2 coding region include point mutations, insertions, deletions and structural rearrangements. These alterations usually occur without gene amplification, but they can still activate downstream signal transduction and drive tumor growth [17]. In addition, tumors carrying HER2 mutations are sensitive to antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs), such as non-small cell lung cancer (NSCLC) [18].

As summarized in Table 1, currently approved HER2-targeted ADCs can be classified into two groups which are based on HER2 expression status. Kadcyla (T-DM1) represents the first-generation agent designed for HER2-high tumors [9], whereas Enhertu (T-DXd) and trastuzumab rezetecan (SHR-A1811) are effective in tumors with HER2-low expression or HER2 mutations, owing to their bystander effect. These two drugs have significantly expanded the applicable population range of HER2-targeted therapy and promoted precise stratified treatment [19]. Overall, the molecular typing of HER2 is not only an important basis for diagnosis and prognosis, but also provides guidance for the research and development of targeted drugs and clinical transformation [20].

Table 1. HER2-Targeted ADCs [9–11, 21]

ADC Name	Antibody	Linker	Cytotoxic Payload	Initial Approved Indication	Drug-to-antibody ratio (DAR)
Kadcyla (T-DM1)	Trastuzumab	Non-cleavable SMCC	DM1 (maytansinoid derivative)	Unresectable or metastatic breast cancer with HER2-positive expression (IHC 3+ or FISH positive)	3.5
Enhertu (T-DXd)	Trastuzumab	Cleavable Gly-Gly-Phe-Gly	Topoisomerase I inhibitor (exatecan derivative)	Unresectable or metastatic breast cancer with HER2-low expression (IHC 1+ or IHC 2+/ISH–)	7.8
SHR-A1811	Trastuzumab	Cleavable Gly-Gly-Phe-Gly	SHR169265 (novel topoisomerase I inhibitor)	HER2-mutant non-small cell lung cancer (NSCLC)	6

3. HER2 Targeted ADCs

3.1. Kadcyla

Kadcyla employs a non-cleavable succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) linker, which stabilizes conjugation of microtubule inhibitor DM1 to lysine residues of the antibody, can be seen in Figure 1 [22, 23].

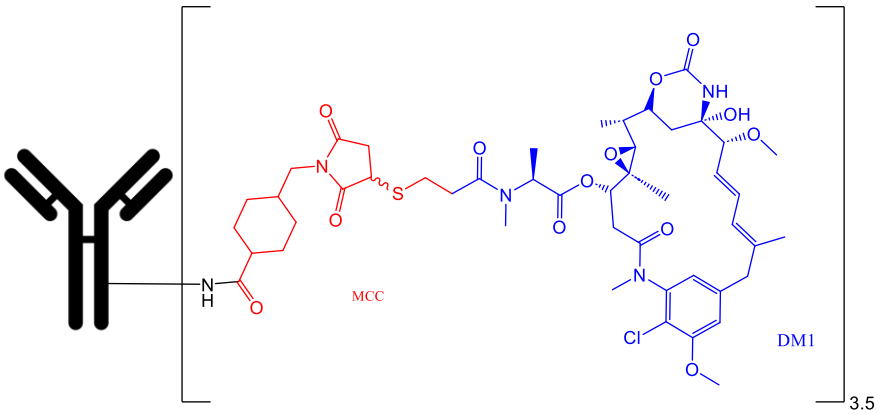

Fig. 1 Structural representation of Trastuzumab emtansine, with HER2-targeting trastuzumab monoclonal antibody in black, non-cleavable SMCC linker in red, and the microtubule inhibitor DM1 payload in blue.

Picture credit : Original

The lysine ε-amino groups on trastuzumab react randomly with sodium 1-[4-[(2,5-dioxopyrrolidin-1-yl)methyl]cyclohexanecarbonyl]oxy-2,5-dioxopyrrolidine-3-sulfonate, which incorporates the non-cleavable SMCC linker, as shown in Figure 2, resulting in the formation of a stable amide bond. Subsequently, the N-methylsuccinimide group of the SMCC linker reacts with HS-DM1, giving the final antibody–linker–payload conjugate [24]. Lysine-based conjugation strategy was used in Kadcyla. As monoclonal antibody trastuzumab contains approximately 30 accessible lysine residues lying on its surface, the average Lys-conjugation number of linkers and payload attached was recorded as DAR~3.5 [25, 26]. Compared with typical IgG1 antibodies with 2 to 3 weeks half-life, half-life of T-DM1 is only about 4 days [27]. The product release in vivo is shown in Figure 3A. The subsequent intracellular degradation of T-DM1 and the release of the DM1 payload are illustrated in Figure 4A. This indicates that the effective drug concentration in blood declines more rapidly, so slowly growing tumors may not receive sufficient exposure with T DM1. As higher exposure may be required, shortening the dosing interval could increase the treatment burden for patients.

So trastuzumab emtansine used a non-cleavable linker, which made Kadcyla showing properties of extended plasma half-life. Well documented example is the use of the non-cleavable property of SMCC linker, attached to the DM1 molecule [25]. Kadcyla became more stable in blood and circulation and reduced systemic toxicity, but simultaneously, put limitations, as the release of payloads are greatly dependent by lysosomal degradation from their antibodies. Hence, their release is not controlled or targeted, and Kadcyla has limited bystander effect, meaning that there is no diffusion into neighboring cancer cells. The combination of a non-cleavable SMCC linker with the membrane-impermeable DM1 payload contributes to insufficient efficacy in HER2-targeted tumors with low expression or heterogeneous expression.

3.2. Enhertu

Enhertu introduces cleavable GGFG linker which its peptide chain can be cleaved selectively by lysosomal proteases, for example, cathepsin B and cathepsin L, thereby enabling efficient release of exatecan *in vivo* [28-31].

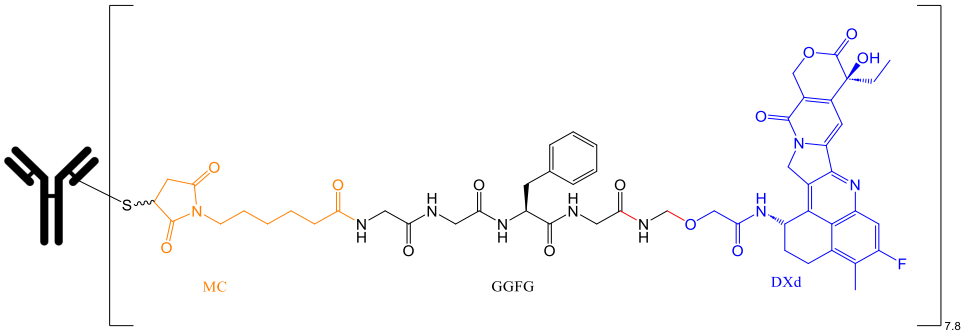

Fig. 2 Structure of trastuzumab deruxtecan, consisting of a HER2-targeting trastuzumab mAb conjugated via a maleimide–caproyl and GGFG cleavable tetrapeptide linker to DXd. Trastuzumab deruxtecan contains two major cleavage sites, which were highlighted in red.

Picture credit : Original

Trastuzumab deruxtecan employs cysteine coupling, the interchain disulfide bonds of trastuzumab were exposed and thiol groups ready for reactions. These thiols then react with cleavable GGFG linker through maleimide–thiol Michael addition, forming stable thioether bonds. This mechanism ca ne seen in Figure 3B. The protease-mediated cleavage of the GGFG linker and the liberation of DXd payload are illustrated in Figure 4B. GGFG linker can be cleaved specifically by cathepsins within tumor cells, for efficient release of payload DXd. This conjugation strategy not only maintained both targeting specificity and in vivo stability but also achieved a relatively high DAR value [32].

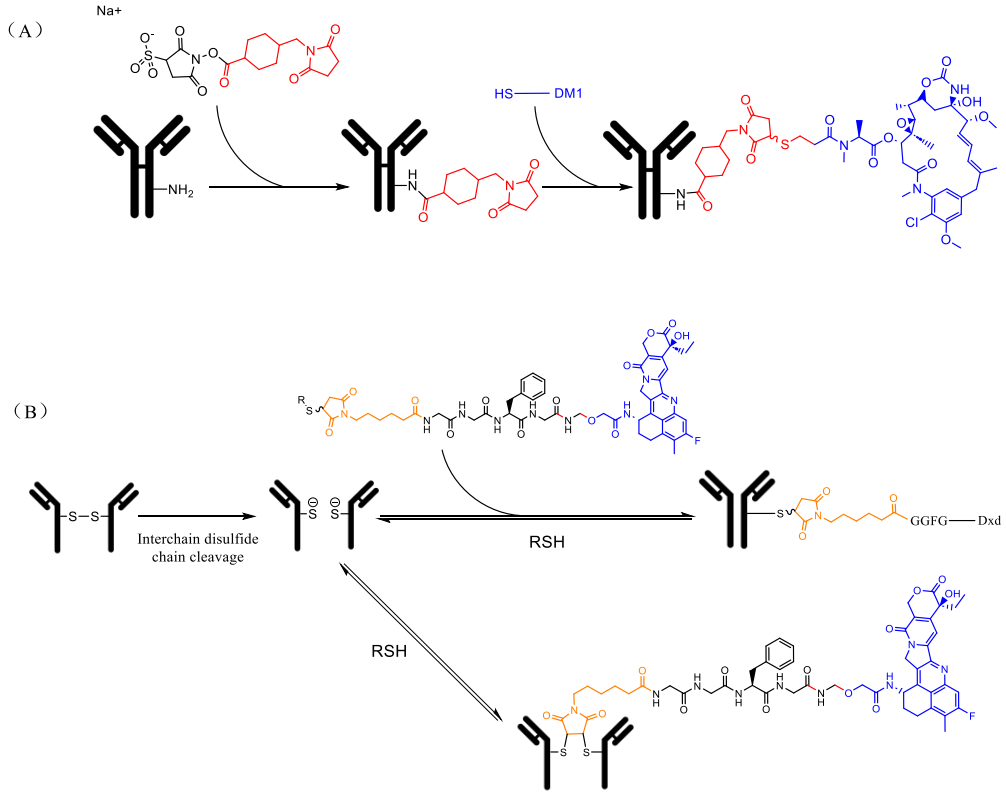

Fig. 3 Conjugation processes of HER2 targeted ADCs. (A) Lysine based conjugation process for ado trastuzumab emtansine. (B) Cysteine based conjugation process for trastuzumab deruxtecan.

Picture credit: Original

Interchain disulfide bonds within the antibody are reduced to generate free thiol groups (–SH) for cysteine-based conjugation process. Complete reaction would contain all eight reactive cysteines on mAb trastuzumab, DAR ~8 can be obtained. However, there is a special reaction where the two thiol groups in the middle connect to the same linker-payload. This results in an average DAR value being lower than the theoretical maximum of 8 [25].

In cleavable GGFG tetrapeptide linker, the peptide bond adjacent to amide group serves as the primary cleavage site. Once this peptide bond is specifically cleaved by lysosomal protease, triggering GGFG linker undergoes bond cleavage, releasing DXd payload through a self-immolation chemical process. Subsequently, the carbon–oxygen bond which is attached to the payload undergoes hydrolysis, liberating DXd payload with membrane permeability and topoisomerase I inhibitory activity [30, 31].

Enhertu has a much higher DAR value, with an average of approximately 7.8 [26], which increases payload quantity linking on trastuzumab. Moreover, the membrane-permeability of DXd molecule, leading to strong bystander effect, resulting outstanding effect to HER2-low-expressed heterogeneous tumors. However, the combination of high DAR and cleavable linkers lead to risk of systemic toxicity, especially when payload was enzymatic cleaved in non-target tissues, causing safety issues such as myelosuppression and interstitial lung diseases.

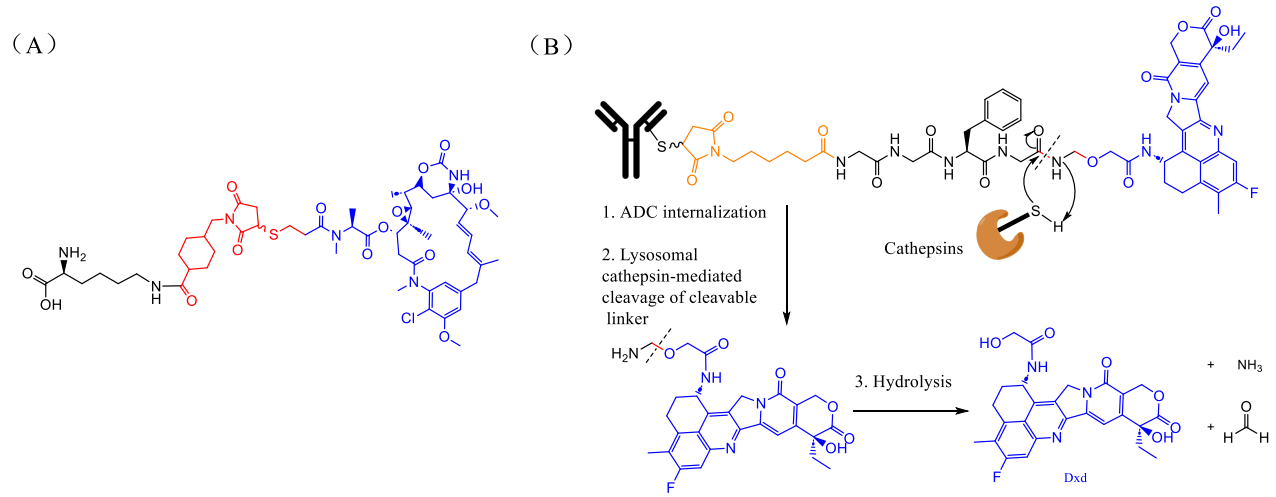

Fig. 4 Mechanisms of payload release from HER2 targeted ADCs. (A) Lysine adduct formed during lysosomal degradation of ado trastuzumab emtansine, leading to the release of the cytotoxic DM1 with potent antimitotic activity. (B) Cathepsin mediated cleavage of the GGFG linker in trastuzumab deruxtecan followed by hydrolysis, resulting in the release of the membrane permeable topoisomerase I inhibitor DXd *in vivo*.

Picture credit: Original

3.3. SHR-A1811

SHR-A1811 was approved by the National Medical Products Administration (NMPA) of China in May 2025, and consists of the novel topoisomerase I inhibitor SHR169265, coupled with trastuzumab via a cleable linker [11]. Compared with T-DM1 and T-DXd, SHR-A1811 demonstrates a unique payload design (DAR = 6), and its bystander effect helps to overcome tumor heterogeneity [33]. he overall molecular structure of SHR-A1811 is depicted in Figure 5. As shown in Table 2, SHR169265 introduces a chiral cyclopropyl group at the α-carbonyl position of the exatecan scaffold [34]. This modification increases the conformational rigidity, steric hindrance effect and lipophilicity of the drug, thereby enhancing the binding affinity with topoisomerase I, membrane permeability and in vivo stability [21], and optimizing the efficacy and safety. Importantly, the overall coupling of the linker–payload–antibody triad has been demonstrated to play a decisive role in balancing pharmacokinetics and pharmacodynamics, further improving the chemical stability of the payload as well as the overall therapeutic window [4].

Table 2. Role of the Cyclopropyl Group in SHR-A1811

Structural Feature	Pharmacological Effect	Role in SHR-A1811
Conformational rigidity (coplanarity and ring strain)	Enhances target binding affinity by reducing conformational flexibility and entropy loss	Promotes tighter binding of the payload to topoisomerase I
Metabolic stability (strong C–H bonds)	Prevents premature degradation caused by CYP450-mediated oxidation or hydrolysis	Improves *in vivo* stability
Steric hindrance	Protects labile sites and increases the stability between linker and payload	Helps protect the cleavable linker region and prevents off-target cleavage
Increased lipophilicity	Facilitates cell membrane permeability and may enhance the bystander effect	Facilitates intratumoral penetration and enhances the bystander effect of the released payload
Structural selectivity	Reduces off-target binding and toxicity	Minimizes nonspecific interactions, thereby improving safety

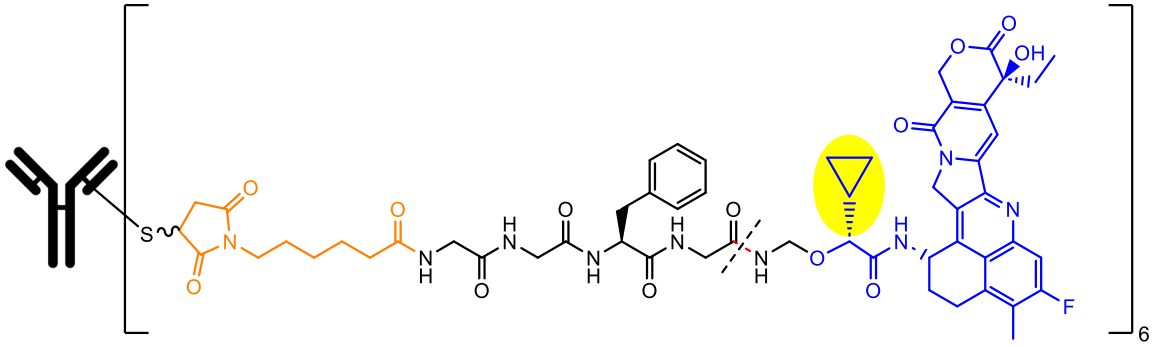

Fig. 5 Structure of SHR-A1811. This structure was highly similar to trastuzumab deruxtecan. The only difference was the payload, carrying a topoisomerase I inhibitor exatecan derivative, where the cyclopropyl moiety was highlighted in yellow.

Picture credit : Original

3.4. Pharmacological Value of Cyclopropyl Modification Across Therapeutic Areas

The cyclopropyl group exhibits a unique structural optimization effect in drug molecules in different therapeutic fields and has been well validated [35]. As shown in Table 3, representative drugs include ciprofloxacin, efavirenz, and ticagrelor. For example, in the anti-HIV agent efavirenz, the incorporation of a cyclopropyl moiety not only helps to cross the blood–brain barrier (BBB) but also improves target-binding selectivity, thereby enhancing clinical efficacy [36].

Table 3. Representative Drugs with Cyclopropyl Modifications

Drug	Role of Cyclopropyl Group	Clinical Use	Primary Biological Target
Ciprofloxacin	Enhances membrane permeability and binding affinity to enzymes	Antibacterial (broad-spectrum)	DNA gyrase and topoisomerase IV
Efavirenz	Improves blood–brain barrier (BBB) penetration and binding selectivity	Antiviral (HIV)	HIV-1 reverse transcriptase (RT)
Ticagrelor	Increases metabolic stability and oral bioavailability	Antiplatelet agent (cardiovascular)	$P2Y_{12}$ ADP receptor

Overall, the introduction of a cyclopropyl group improves physicochemical properties [37], while also enhancing pharmacokinetic profiles in multiple disease areas [38]. This cross-domain structural modification strategy has also obtained reliable pharmacological evidence in drug development in different disease areas such as cardiovascular diseases and tumor treatment. Therefore, the introduction of cyclopropyl in the chemical structure of drugs has become an important tool for modern drug design and optimization [34].

4. Evolution of Linker Strategies

The linker–payload–antibody triad has been continuously optimized to achieve more efficient, controllable, and safer ADC products [2, 3]. Currently, ADCs have emerged as one of the major classes of biologics in oncology, with nine FDA-approved agents and more than 60 in clinical trials [6]. By combining the tumor selectivity of monoclonal antibodies with the potent cytotoxicity of small-molecule toxins, ADCs achieve a broadened therapeutic window. The linker is the key to ADCs. It determines whether the drug release is "punctual and accurate", thereby affecting the effectiveness and safety of the entire treatment [5]. An ideal linker must remain highly stable in the bloodstream, improve the water solubility of cytotoxic payloads, and ensure rapid release within target cells [4].

Linker design has evolved from non-cleavable to cleavable systems. Early non-cleavable linkers, such as SMCC, provided superior circulatory stability to compensate for the short half-life of cytotoxic payloads. However, this type of ADC depends on whether the antibody main chain can be completely degraded in lysosomes, so the drug release efficiency will be limited [9]. Subsequently, cleavable peptide-based linkers such as MC-GGFG were developed. These structures can be specifically cleaved by lysosomal proteases such as cathepsin B, triggering payload release and producing a bystander effect [4, 39]. By high-DAR designs, hydrophilic shielding moieties (such as PEGylation or glycosylation), and site-specific conjugation strategies, these innovations have markedly broadened the cytotoxic coverage within the tumor microenvironment [2, 40]. Notably, compared with the commonly used classical topoisomerase I inhibitors in clinical practice, Exatecan demonstrates a stronger TOP1 capture ability and can cause a higher level of DNA damage [8,10]. Unlike early non-cleavable systems that depended on complete lysosomal degradation, enzyme-cleavable linkers ensure high plasma stability while enabling selective intracellular release [4,41].

At the same time, several frontier strategies are further expanding the boundaries of linker design and demonstrating promising clinical potential. A novel ADC design approach is the use of “dual-mechanism linkers,” which enable two different types of complementary payloads with distinct mechanisms of action to be conjugated to the same antibody. For example, a topoisomerase I inhibitor (which disrupts DNA replication) and a microtubule inhibitor (which interferes with cell division) can be simultaneously conjugated, thereby exerting stronger and broader cytotoxic effects on tumor cells [40]. Another strategy focuses on degradable polymer linkers. For example, the polyacetal-based systems such as Dolaflexin/Fleximer, undergo programmed kinetic degradation to release payloads. These constructs not only balance circulatory stability with controlled release but also exploit the hydrophilic shielding of the polymer backbone to improve pharmacokinetics and biodistribution, enhancing delivery in complex tumor microenvironments [41]. In addition, researchers are actively exploring smart-release and microenvironment-responsive linkers that integrate multiple triggers (such as pH, proteases, redox conditions, or oxidative stress) with self-immolative modules. Such designs provide high sensitivity to tumor-specific conditions while minimizing systemic leakage, thereby broadening the applicability of ADCs to heterogeneous solid tumors [39].

5. Conclusion

This review analyzes the application of linker in HER2-targeted ADCs, from the early non-cleavable types toward cleavable types. The linker is often regarded as a simple connector, yet in practice it functions in concert with the antibody and the payload, influencing stability in circulation,

the timing of intracellular release, and the overall balance between therapeutic efficacy and adverse effects. Comparing examples such as T-DM1, T-DXd, and SHR-A1811 shows that the early versions left some clear limitations, while later approaches, through changes in chemistry and linker structure, managed to overcome part of these issues. Nowadays, ADC design is being explored along multiple fronts, including site-specific conjugation, multi-trigger and self-immolative linkers, degradable polymers, and dual-mechanism linkers, as well as fine-tuning of DAR and hydrophobicity. These strategies aim to deliver more precise, effective, and safer therapies to patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

References

[1] Ehrlich P. Address in pathology, on chemotherapy: delivered before the seventeenth international congress of medicine. British Medical Journal, 1913, 2 (2746): 353-359.

[2] Beck A, Goetsch L, Dumontet C, et al. Strategies and challenges for the next generation of antibody–drug conjugates. Nature Reviews Drug Discovery, 2017, 16 (5): 315-337.

[3] Chari R V J, Miller M L, Widdison W C, et al. Antibody–drug conjugates: an emerging concept in cancer therapy. Angewandte Chemie International Edition, 2014, 53 (15): 3796-3827.

[4] Bargh J D, Isidro-Llobet A, Parker J S, et al. Cleavable linkers in antibody–drug conjugates. Chemical Society Reviews, 2019, 48 (16): 4361-4374.

[5] Tsuchikama K, An Z. Antibody–drug conjugates: recent advances in conjugation and linker chemistries. Protein & Cell, 2018, 9 (1): 33-46.

[6] Chau C H, Steeg P S, Figg W D, et al. Antibody–drug conjugates for cancer. The Lancet, 2019, 394 (10200): 793-804.

[7] Moasser M M. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene, 2007, 26 (45): 6469-6487.

[8] Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clinical Cancer Research, 2016, 22 (20): 5097-5108.

[9] Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. New England Journal of Medicine, 2012, 367 (19): 1783-1791.

[10] Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. New England Journal of Medicine, 2020, 382 (7): 610-621.

[11] NMPA approves Hengrui Pharma's trastuzumab rezetecan for HER2-mutant NSCLC. Precision Medicine Online, 2025-05-29. Accessed 2025-08-27.

[12] Yarden Y, Sliwkowski M X. Untangling the ErbB signalling network. Nature Reviews Molecular Cell Biology, 2001, 2 (2): 127-137.

[13] Arteaga C L, Engelman J A. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell, 2014, 25 (3): 282-303.

[14] Slamon D J, Clark G M, Wong S G, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science, 1987, 235 (4785): 177-182.

[15] Wolff A C, Hammond M E H, Allison K H, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Journal of Clinical Oncology, 2018, 36 (20): 2105-2122.

[16] Tarantino P, Hamilton E, Tolaney S M, et al. HER2-low breast cancer: pathological and clinical landscape. Journal of Clinical Oncology, 2020, 38 (17): 1951-1962.

[17] Li B T, Ross D S, Aisner D L, et al. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. Journal of Thoracic Oncology, 2016, 11 (3): 414-419.

[18] Robichaux J P, Elamin Y Y, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer. Nature Medicine, 2018, 24 (5): 638-646.

[19] Tarantino P, Morganti S, Curigliano G, et al. Targeting HER2 in breast cancer: new drugs and paradigms on the horizon. Exploration of Targeted Anti-tumor Therapy, 2021-03-23.

[20] Swain S M, Shastry M, Hamilton E, et al. Targeting HER2-positive breast cancer: advances and future directions. Nature Reviews Drug Discovery, 2023, 22 (2): 101-126.

[21] Zhang T, Xu J, Yin J, et al. SHR-A1811, a novel anti-HER2 antibody–drug conjugate with optimal drug-to-antibody ratio, efficient tumor killing potency, and favorable safety profiles. PLOS ONE, 2025, 20 (6): e0326691.

[22] Chia C S B. A patent review on FDA-approved antibody-drug conjugates, their linkers and drug payloads. ChemMedChem, 2022, 17 (11): e202200032.

[23] Chen L, Wang L, Shion H, et al. In-depth structural characterization of Kadcyla (ado-trastuzumab emtansine) and its biosimilar candidate. mAbs, 2016, 8 (7): 1210-1223.

[24] Ou J, Si Y, Goh K, et al. Bioprocess development of antibody-drug conjugate production for cancer treatment. PLOS ONE, 2018, 13 (10): e0206246.

[25] Jain N, Smith S W, Ghone S, et al. Current ADC linker chemistry. Pharmaceutical Research, 2015, 32 (11): 3526-3540.

[26] Wang R, Hu B, Pan Z, et al. Antibody–drug conjugates (ADCs): current and future biopharmaceuticals. Journal of Hematology & Oncology, 2025, 18 (1): 51.

[27] Lu D, Girish S, Gao Y, et al. Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody–drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates. Cancer Chemotherapy and Pharmacology, 2014, 74 (2): 399-410.

[28] Tan X, Fang P, Li K, et al. A HER2-targeted antibody-novel DNA topoisomerase I inhibitor conjugate induces durable adaptive antitumor immunity by activating dendritic cells. mAbs, 2023, 15 (1): 2220466.

[29] Jang J Y, Kim D, Lee N K, et al. Antibody–drug conjugates powered by deruxtecan: innovations and challenges in oncology. International Journal of Molecular Sciences, 2025, 26 (13): 6523.

[30] Miller J T, Tumey L N. ADC linkers strategies for the release of alcohol-containing payloads. In: Van Delft F, Lambert J M, eds. Chemical Linkers in Antibody–Drug Conjugates (ADCs). The Royal Society of Chemistry, 2021, 7: 232-262.

[31] Balamkundu S, Liu C F, et al. Lysosomal cleavable peptide linkers in antibody–drug conjugates. Biomedicines, 2023, 11 (11): 3080.

[32] Walsh S J, Bargh J D, Dannheim F M, et al. Site-selective modification strategies in antibody–drug conjugates. Chemical Society Reviews, 2021, 50 (2): 1305-1353.

[33] SHR-A1811 maintains efficacy, safety in pretreated HER2-expressing or mutated breast cancer and other solid tumors. OncLive, 2025-01-22. Accessed 2025-08-27.

[34] Sun M R, Li H L, Ba M Y, et al. Cyclopropyl scaffold: a generalist for marketed drugs. Mini-Reviews in Medicinal Chemistry, 2021, 21 (2): 150-170.

[35] Meanwell N A. Improving drug candidates by design: a focus on physicochemical properties as a means of improving compound disposition and safety. Chemical Research in Toxicology, 2011, 24 (9): 1420-1456.

[36] Rakhmanina N Y, Van Den Anker J N. Efavirenz in the therapy of HIV infection. Expert Opinion on Drug Metabolism & Toxicology, 2010, 6 (1): 95-103.

[37] Lovering F, Bikker J, Humblet C, et al. Escape from flatland: increasing saturation as an approach to improving clinical success. Journal of Medicinal Chemistry, 2009, 52 (21): 6752-6756.

[38] Wermuth C G, Aldous D, Raboisson P, et al. The Practice of Medicinal Chemistry: Index, 2015.

[39] Cazzamalli S, Dal Corso A, Neri D, et al. Linker stability influences the anti-tumor activity of acetazolamide-drug conjugates for the therapy of renal cell carcinoma. Journal of Controlled Release, 2017, 246: 39-45.

[40] Trail P A, Dubowchik G M, Lowinger T B, et al. Antibody drug conjugates for treatment of breast cancer: novel targets and diverse approaches in ADC design. Pharmacology & Therapeutics, 2018, 181: 126-142.

[41] Thomas A, Teicher B A, Hassan R, et al. Antibody–drug conjugates for cancer therapy. The Lancet Oncology, 2016, 17 (6): e254-e262.