Antibody-Drug Conjugates: The Forefront of Targeted Chemotherapy for Cancer Treatment

Zhisong Wang¹, Nalajam Guravaiah², Chengqing Ning¹, Yujun He¹, Lei Yao¹, Jianming Wang² and Niefang Yu¹,²*

¹Department of Molecular Design and Drug Discovery, Central South University, P. R. China
²Department of Molecular Design and Drug Discovery, Hisun Pharmaceutical, P. R. China

Abstract

Antibody-drug conjugates (ADCs) are novel targeted chemotherapeutic agents that utilize the specificity of monoclonal antibodies (mAbs) to deliver potent cell-killing agents to cancer cells that express the target antigen, thereby taking advantage of the best characteristics of both components. The experience and/or lessons learned from the first generation of conjugates have guided the development of more effective antitumor agents. Along with the development of the mAbs and cytotoxins, the design of chemical linkers to covalently bind these building blocks is making rapid progress but remains challenging. Encouragingly, the recent successes in these domains show that the next generation of antibody-drug conjugates has come of age.

ABBREVIATIONS

ADC: Antibody−Drug Conjugate; AML: Acute Myeloid Leukaemia; HL: Hodgkin's Lymphoma; NHL: Non-Hodgkin's Lymphoma; ALCL: Anaplasia Large Cell Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; RCC: Renal Cell Carcinoma; SCLC: Small Cell Lung Cancer; NSCLC: Non-Small Cell Lung Cancer; CLL: Chronic Lymphocytic Leukaemia; EGFR: Epidermal Growth Factor Receptor; GPNMB: Glycoprotein NMB; PSMA: Prostate-Specific Membrane Antigen; NA: No Available

INTRODUCTION

For cancer treatment, it is highly desirable to selectively target malignant cells instead of healthy tissues. However, cancer treatment usually remains a double-edged sword in the sense that therapeutic agents should be as aggressive as possible to kill the tumor cells, but it is precisely this aggressiveness that often causes severe side effects. It is for this reason that some promising chemotherapeutics cannot be applied systemically [1]. The therapeutic effect of most anticancer drugs in clinical use is limited by their general toxicity to proliferating cells, including some normal cells. Despite the fact that chemists constantly strive toward developing novel cytotoxic agents with unique mechanisms of action, many of these compounds still lack tumor selectivity and have not been therapeutically useful [2]. One promising approach that has been advanced through a series of preclinical and clinical studies is to combine the pharmacological potency of “small” cytotoxic drugs (0.3 to 1 kDa) and the high specificity of monoclonal antibodies (150 kDa) for tumor-associated antigen targets [3,4]. In this therapeutic strategy, different classes of cytotoxic agents are covalently linked to tumor-targeted monoclonal antibodies (mAbs) forming corresponding antibody−drug conjugates (ADCs; Figure 1).

Antibody-drug conjugates are ideal candidates for targeted prodrug therapy. These types of drugs are vital members of the next generation of antibody-based therapy by taking advantage of specific molecular differences between healthy and diseased tissues. ADCs can be viewed as sophisticated delivery systems for an “tumor cytotoxic drugs. This class of product typically requires mAbs that are internalized inside cells via receptor-mediated endocytosis. The mAb delivers drugs selectively to tumors by binding to antigens that are highly expressed on cancer cells, followed by internalization and intracellular drug release, which then unleashes its cytotoxic activity [5].

Clay B. Siegall (Seattle Genetics president and CEO) notes that ADCs offer formidable theoretical advantages over conventional chemotherapy in that they attach specifically to tumor cells with
special target receptors while not affecting healthy cells that do not have relevant receptors. This strategy means that the cytotoxic agents delivered by ADCs can be much more potent than systemic chemotherapeutic agents, which do not discriminate between cancer cells and healthy cells. As such, intense research focused on optimization to increase the therapeutic indices of ADCs has been the spotlight of target cancer therapy. A safe and effective ADC such as brentuximab vedotin (Adcetris) should have many properties: antibody specificity, avidity and affinity for the antigens expressed on the surface of a cancer cell; antibody internalization so the ADC gets inside cancer cells; cytotoxin potency so the cancer cell is killed or stops dividing; and linker stability so the antibody and the cytotoxin stay together in the bloodstream but are cleaved inside a tumor cell to activate the drug payload (Figure 1) [6]. Each of these properties is essential, and trying to optimize one invariably means making changes to technology that has been created.

The ADC is exposed to different conditions on its journey from the blood vessels to the molecular target in the tumor tissue. The mode of action at the cellular or molecular level is complex, with each step bringing its own challenges. ADCs must behave like a naked antibody when circulating in the bloodstream. In particular, the linker must be stable in the plasma due to decomposition or decay would release the cytotoxin before it can be delivered to the target site, which will inflict damage to healthy tissue. It is also necessary that the conjugated mAb retains high immunoaffinity. Attaching the cytotoxic compound to the mAb must not disturb its binding specificity [7,8]. Moreover, a sufficient intracellular concentration of the drug must be achieved. This is challenging because antigen targets on cell surfaces are often present in limited numbers and the internalization process for antigen-antibody complexes is frequently inefficient. Once internalized, the ADC is delivered to lysosomes, although there are some exceptions, where effective drug release takes advantage of the catabolic environment found within these organelles. Following release from the lysosome, the drug either binds to its pharmacological target or leaves the cell via active or passive processes [9]. ADCs have demonstrated the intracellular accumulation of released drug in antigen-positive cells but no intracellular accumulation in antigen negative cells, highlighting the antigen specificity of drug delivery by ADCs (Figure 2). There have also been some reports that poorly internalized antigens can successfully be targeted with ADCs by potentially utilizing drug release strategies that occur in the tumor microenvironment rather than inside cells. For example, sub endothelial modified ECM components may serve as a target for ADCs, which do not require internalization for their activity [10].

Here, we will briefly discuss the low-molecular-weight cytotoxic drugs used in ADCs, the selection of tumor-specific antigens as targets, linker technologies and emerging technologies that seek to further advance this exciting area of research.

**Drug payload**

In spite of the extraordinary mode of action and potency of many cytotoxins, their development as single agent therapies has not been pursued because of delayed toxicity which limits the therapeutic dose range for treatment [11]. However, natural cytotoxins are well suited for the role of ADC payload because they often possess the potency, mechanism of action, chemical tractability, and structural properties required for effectiveness [12]. Tumor-specific antibodies have been conjugated to these cytotoxic drugs, including small molecules that alkylate DNA, disrupt microtubules or bind DNA [6,13].

On the basis of the knowledge gained from first-generation ADCs, the following parameters in the cytotoxic component of the ADC were deemed to be highly pivotal for optimal activity. (1) The cytotoxic component was less immunogenic than toxins (e.g., ricin) that may be required; [14] (2) High potency of the effector molecule in vitro toward tumor cell lines, with IC values in the range of 0.01–10 nM. The use of ADCs bearing more highly potent effectors will increase the probability of delivering a therapeutic dose to tumor cells that have low antigen expression or have poor processing; [12,13,15] (3) A suitable functional group for linkage to an antibody. If a functional group is not already present, the desired substituent should be introduced at a suitable site to retain the potency of the parent drug. The key requirement was that the nature and position of the substituent would not

![Figure 1](image-url) Key characteristics of antibody-drug conjugates.
Figure 2 Mechanisms of drug delivery mediated by ADCs.

Figure 3 New drug classes for ADCs.
diminish the potency of the parent molecule; [13] (4) The drug component of ADC should also be stable during preparation or storage and during circulation in a patient; [14] (5) Solubility and membrane permeability [16].

Promising data have been reported for ADCs composed of highly potent drugs such as calicheamicins, doxorubicin, maytansinoids, auristatins, and camptothecin. With much effort, important advances have been made on exploiting new drug types used in ADCs. For instance, pyrrolobenzodiazepine-pine (PBD) dimer, α-Amanitin, duocarmycin analogs, Tubulysin B, cryptophycin analogs and soon have been explored as potent payloads for antibody-drug conjugates (Figure 3) [17-19].

**Tumor-associated antigen selection**

The goal of targeted therapy with mAb-drug conjugates is to achieve high degrees of therapeutic activity while sparing normal tissues from chemotherapeutic damage. Toward this end, the choice of the appropriate target antigen for ADCs is a critical parameter that affects the efficacy, therapeutic window, and toxicity profile of ADCs [20]. Ideally, the target antigens should be abundant and accessible. They should be expressed homogeneously, consistently and exclusively on the surface of cancer cells [21]. It is crucial that antigens should have high tumor cell selectivity to limit toxicity and off-target effects [4]. Data from clinical trials of bivatuzumab mertansine suggested that tumor selectivity of the antibody is even more important than antigen density [22]. In addition, antigen secretion should be minimal, as secreted antigens can bind the antibody in the circulation and prevent sufficient antibody from binding to the tumor [23]. These desirable properties of antigens can lead to greater ADC potency, but they are rarely achieved [24].

Although homogenous tumor expression is preferred, it is likely not an absolute requirement owing to the cell-lethal ability of some ADCs to induce bystander killing [25,26] or by combining an ADC with another therapeutic modality, such as cytotoxic chemotherapy [27]. Especially on solid tumors with heterogeneous antigen expression, the bystander effect is one of the major mechanisms of action, as demonstrated by HuC242-DM1 in vivo xenograft studies with a heterogeneously expressed antigen, Can Ag [28]. Certainly, antigen expression on normal tissue can lead to on-target toxicity with ADCs in patients, but inefficient ADC localization to antigen-positive normal tissue is presumed to lower the risk of on-target toxicity [24,29]. Interestingly, the expression of antigen in some normal tissues does not necessarily preclude the development of an ADC. Prostate-specific membrane antigen (PSMA) is, for example, expressed on normal prostate and on prostate cancer cells, but it still has been applied in several ADC programs [25,30]. This is the case when the normal tissue is either non-essential or insensitive to the action of the drug [31].

Another major and critical property of ADC targets is their ability to be internalized, which can be an intrinsic feature of the antigen by itself or it can be induced by the binding of the antibody to its antigen. 4 Indeed, ADC internalization is crucial to reduce the side effect associated with the extracellular delivery of the drug payload. HER2 (target of T-DM1), for example, is internalized fairly quickly, which is also important, and it is not down regulated. Thus, once bound to the ADC antibody, HER2 does not disappear from the cell but keeps being produced. This factor is of prime interest to ensure specific drug internalization in cancer cells. To date, HER2 has been chosen as the target for the currently most clinically advanced ADCs in HER2-positive patients who are refractory to trastuzumab [4,32,33].

**Conjugation technologies**

It was recognized early on that conjugation technology is a critical aspect in generating effective ADCs, and optimization strategies can vary with the drug payload, the linker selected, and the antibody used, as conjugation methods significantly affect the potency, selectivity and the pharmacokinetics of the resulting conjugate [34]. Traditionally, the cytotoxic agent is attached to the monoclonal antibody by a chemosynthetic linker. The linker should be sufficiently stable while in circulation to allow delivery of the intact ADC to the tumor sites, but, conversely, it should be sufficiently labile to allow release of the cytotoxic agent from the ADC once inside the targeted tumor cells [35]. The development of stable linkers together with the identification of relevant biomarkers has been a key to the success of a series of ADCs approved or in clinical trials [36].

Cytotoxic drugs are most often linked to the antibody via lysine or cysteine residues on the antibody by chemical linkers. In the case of lysine attachment, the linkage of effector molecules to the antibody could theoretically occur through the ε-amino group of lysine residues present on an antibody. In the case of cysteine attachment, the effector can be linked to reactive cysteine residues, activated by the reduction of internal hinge region cysteine disulfide bonds of the antibody or cysteine disulfides in the light chains to linking the heavy chains of the antibody [37-40]. The common methods for conjugating mAbs include alkylation of reduced interchain disulfides, acylation of lysines, and alkylation of genetically engineered cysteines. Stability of the drug-linker in circulation is important because it determines the long circulating half-life of the ADCs. Linkers differ in terms of plasma stability and in the mechanism of release [41]. Based on these differences, there are currently four different classes of linkers used in the ADCs approved or in clinical trial that broadly fall under two categories—cleavable and noncleavable linkers [42]. Moreover, some novel linkers, such as traceless linkers, are being exploited and evaluated [10].

After ADC internalization into the target cell, an intracellular release mechanism should cleave the linker to release the active drug. For cleavable linkers, the payload is released when the linker is cleaved by lysosomal enzymes or by the chemical environment of the intracellular compartment. Cleavable linkers usually release free drug or a simple derivative by hydrolytic or proteolytic means [2,43,44]. For non-cleavable linkers, the ADC is catabolized by proteases. Once in the lysosome, the antibody is fully catabolized while the linker remains intact, resulting in a released species that consists of the payload-linker bound to the remaining conjugated amino acid residue [43,44].

Traditionally, the drug is conjugated non-selectively to solvent-accessible cysteine or lysine residues in the antibody [45]. The procedure can generate a heterogeneous mixture of up to 10^6 species with different molar ratios of drug to...
antibody ranging between 0 and 9 for the loading of warhead molecules, linked at different sites, each with distinct in vivo pharmacokinetic, efficacy and safety profiles [46-48]. These factors made the optimization of the biological, physical, and pharmacological properties of an ADC challenging. On the one hand, coupling at many different sites will lead to a heterogeneous mixture of ADCs, the components of which likely have distinct properties [49]. On the other hand, there is limited stoichiometric control because of the large number of disulfide bonds and lysine residues in antibody molecules, which leads to a typical distribution of zero to eight toxins per antibody [47,50]. To assess the impact of drug stoichiometry on therapeutic potential, the investigation of cAC10-MMAE conjugates (anti-CD30 ADCs) with varied drug/antibody ratios was carried out by Seattle Genetics, Inc [51]. The experimental design involved coupling MMAE to the cysteines that comprise the interchain disulfides of cAC10, creating an antibody-drug conjugate population, which was purified using hydrophobic interaction chromatography to yield antibody-drug conjugates with two, four, and eight drugs per antibody (E2, E4, and E8). The potency, maximum-tolerated dose and pharmacokinetic profiles of the distinct antibody-drug conjugates were then compared. Although antibody-drug conjugate potency in vitro was directly dependent on drug loading (IC50 values E8<E4<E2), the in vivo antitumor activity of E4 was comparable with E8 at equal mAb doses, although the E4 contained half the amount of MMAE per mAb. The maximum-tolerated dose of E2 in mice was at least double that of E4, which in turn was twice that of E8 [51]. These results showed that the maximum-tolerated dose increased inversely with respect to drug loading. The study also demonstrated that MMAE loading affects plasma clearance, as E8 cleared 3-fold faster than E4 and 5-fold faster than E2. As we know, slower clearance resulted in a greater pharmacokinetic area under the curve. The study results provided reliable guidance that moderate drug loading is a key design parameter for antibody-drug conjugates, as evidenced by the 2-fold increase in therapeutic index by reducing the loading from 8 to 4 drugs/antibody.

Although, it was discovered that conventional conjugation strategies was liable to yield heterogeneous conjugates with relatively narrow therapeutic indexes [40]. The good news is that linker technology is also rapidly improving. To limit these potential liabilities associated with traditional conjugation methods, intense efforts are being devoted to the development of methods for site-specific drug conjugation that will enable the production of homogeneous ADCs with defined sites and stoichiometries of drug attachment and with improved performance and batch-to-batch reproducibility [34,40-41]. The available schemes to generate such homogeneous ADCs includes site-specific conjugation using cysteine/unnatural amino acids [52,53-55], metabolic engineering of antibody carbohydrates for site-specific conjugation [56,57-58], enzymatic site-specific conjugation [59,60-64] and site-specific conjugation via native disulfide bond bridging [65].

**Representative ADCs at different stages of clinical development**

With approximately 40 antibody-drug conjugates in clinical trials and two FDA-approved drugs, it is clear that ADCs have demonstrated remarkable pre-clinical and clinical efficacy and may at some point obviate the need for systemic chemotherapy [37]. At least 30 ADCs were entered in to clinical trials from different organization in the recent past (2011-2014), it is about 4 folds higher than the drugs entered into clinical trials the in the years of 2008-2010 [66]. Table 1 lists the ADCs that are currently approved and most ADCs in clinical development. Updated information on the clinical research on this topic can be acquired via the Thomson Pharma database and clinical trials.gov (http://clinicaltrials.gov/). After its approval, annual sales of brentuximab vedotin (Figure 3) in the United States were US$136 million (October 2011 to September 2012) in a relatively small patient population.

**CONCLUSION AND PERSPECTIVE**

Despite complexities in designing ADCs, the promise of this therapeutic class has generated intense interest in recent years. With so many companies seeking access to ADC technology and strengthening cooperation, the field looks poised to take-off. Evolving clinical data will continue to drive technological

---

Yu et al. (2015)  
Email: nfy_group@126.com
Table 1: Antibody-Drug Conjugates currently in approval or in clinical trials.

<table>
<thead>
<tr>
<th>INN</th>
<th>Drug Linker</th>
<th>Target</th>
<th>Indication</th>
<th>Sponsor</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mylotarg</td>
<td>Calicheamycin Ac-But linker</td>
<td>CD33</td>
<td>AML</td>
<td>Pfizer</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>SGN-35</td>
<td>MMAE Val-Git</td>
<td>CD30</td>
<td>HL/ALCL</td>
<td>Seattle Genetics</td>
<td>Approved</td>
</tr>
<tr>
<td>CMC-544</td>
<td>Calicheamycin Ac-But linker</td>
<td>CD22</td>
<td>NHL</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>Kadcyla</td>
<td>DM1 SMCC</td>
<td>HER2</td>
<td>Breast cancer</td>
<td>Genentech</td>
<td>Approved</td>
</tr>
<tr>
<td>IMGN901</td>
<td>DM1 SPP</td>
<td>CD56</td>
<td>SCLC</td>
<td>physician-sponsored IND</td>
<td></td>
</tr>
<tr>
<td>IMGN-388</td>
<td>DM4 SPDB</td>
<td>αv-integrin</td>
<td>Solid tumors</td>
<td>Cebitocor</td>
<td>I / II</td>
</tr>
<tr>
<td>SAR3419</td>
<td>DM4 SPDB</td>
<td>CD19</td>
<td>DLBCL</td>
<td>Sanofi-Aventis</td>
<td>II</td>
</tr>
<tr>
<td>BIIB015</td>
<td>DM4 NA</td>
<td>CD37</td>
<td>Multiple myeloma</td>
<td>Biotest</td>
<td></td>
</tr>
<tr>
<td>BT-062</td>
<td>DM4 SPDB</td>
<td>CD138</td>
<td>Multiple myeloma</td>
<td>Biotest</td>
<td></td>
</tr>
<tr>
<td>CDX-011</td>
<td>MMAE Val-Git</td>
<td>GPNMB</td>
<td>Breast cancer Melanoma</td>
<td>Cellfex</td>
<td>II</td>
</tr>
<tr>
<td>SGN-75</td>
<td>MMAE MalC linker</td>
<td>CD70</td>
<td>NHL / RCC</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>PSMA ADC</td>
<td>MMAE Val-Git</td>
<td>PSMA</td>
<td>Prostate cancer</td>
<td>Progenics</td>
<td></td>
</tr>
<tr>
<td>MED1-547</td>
<td>MMAE MalC linker</td>
<td>Epha2</td>
<td>Solid cancer</td>
<td>Progenics</td>
<td></td>
</tr>
<tr>
<td>ASG-5ME</td>
<td>MMAE Val-Git</td>
<td>SLC44A4</td>
<td>Pancreatic cancer</td>
<td>Agensys</td>
<td></td>
</tr>
<tr>
<td>ASG-15ME</td>
<td>MMAE Val-Git</td>
<td>SLITRK6</td>
<td>Lung cancer</td>
<td>Agensys</td>
<td></td>
</tr>
<tr>
<td>ASG-22ME</td>
<td>MMAE Val-Git</td>
<td>Nectin-4</td>
<td>Solid tumors</td>
<td>Agensys</td>
<td></td>
</tr>
<tr>
<td>MDX-1203</td>
<td>Duocarmycin Val-Git-PABC</td>
<td>CD70</td>
<td>NHL / RCC</td>
<td>Medarex</td>
<td></td>
</tr>
<tr>
<td>BAY-94-9343</td>
<td>DM4 SPDB</td>
<td>Mesothelin</td>
<td>Mesotheliomas Ovarian tumor</td>
<td>Bayer</td>
<td>I</td>
</tr>
<tr>
<td>MLN-0264</td>
<td>MMAE NA</td>
<td>Guanylyl cyclase</td>
<td>Gastrointestinal tumour</td>
<td>Millennium</td>
<td>I / II</td>
</tr>
<tr>
<td>MLN-2704</td>
<td>DM1 NA</td>
<td>PSMA</td>
<td>Prostate cancer</td>
<td>Millennium</td>
<td>I / II</td>
</tr>
<tr>
<td>SGN-75</td>
<td>MMAF Maleimidocaproyl</td>
<td>CD70</td>
<td>RCC</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>ART-414</td>
<td>NA</td>
<td>NA</td>
<td>Ovarian tumour</td>
<td>Genentech</td>
<td>II</td>
</tr>
<tr>
<td>AMG-595</td>
<td>DM1 SMCC</td>
<td>EGFRvIII</td>
<td>Glioma</td>
<td>AbbVie</td>
<td>I / II</td>
</tr>
<tr>
<td>AMG-172</td>
<td>DM1 SMCC</td>
<td>CD70</td>
<td>RCC</td>
<td>Amgen</td>
<td></td>
</tr>
<tr>
<td>RG-7596</td>
<td>MMAE Val-Git</td>
<td>CD79b</td>
<td>NHL</td>
<td>Genentech</td>
<td>II</td>
</tr>
<tr>
<td>RG-7600</td>
<td>NA</td>
<td>NA</td>
<td>Ovarian tumour</td>
<td>Genentech</td>
<td></td>
</tr>
<tr>
<td>SGN-CD19A</td>
<td>MMAE Maleimidocaproyl</td>
<td>CD19</td>
<td>AML / NHL</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>SGN-CD33A</td>
<td>PBD dimer MalC linker</td>
<td>CD33</td>
<td>drug-resistant AML</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>SGN-CD70A</td>
<td>PBD dimer NA</td>
<td>CD70</td>
<td>NHL / RCC</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>IMMU-110</td>
<td>Doxorubicin Ac-But linker</td>
<td>CD74</td>
<td>Multiple myeloma</td>
<td>Immunomedics</td>
<td>I / II</td>
</tr>
<tr>
<td>IMMU-115</td>
<td>Doxorubicin Ac-But linker</td>
<td>CD74</td>
<td>NHL / CLL</td>
<td>Immunomedics</td>
<td>I / II</td>
</tr>
<tr>
<td>IMMU-132</td>
<td>SN38 Phenylalanine-lysine</td>
<td>TACSTD2</td>
<td>Solid tumors</td>
<td>Immunomedics</td>
<td></td>
</tr>
<tr>
<td>IMMU-130</td>
<td>SN38 Phenylalanine-lysine</td>
<td>CEACAM5</td>
<td>Colorectal tumor</td>
<td>Immunomedics</td>
<td></td>
</tr>
<tr>
<td>IMGN-529</td>
<td>DM1 SPP</td>
<td>CD37</td>
<td>Hematologic tumors</td>
<td>Immunogen</td>
<td></td>
</tr>
<tr>
<td>IMGN-289</td>
<td>DM1 SPP</td>
<td>EGFR</td>
<td>Solid tumors</td>
<td>Immunogen</td>
<td></td>
</tr>
<tr>
<td>SAR-5666S8</td>
<td>DM4 SPDB</td>
<td>DS6</td>
<td>Solid tumors</td>
<td>Sanofi</td>
<td></td>
</tr>
<tr>
<td>SNT985</td>
<td>Duocarmycin NA</td>
<td>HER2</td>
<td>Solid tumors</td>
<td>Synthon</td>
<td></td>
</tr>
<tr>
<td>ACS67E</td>
<td>MMAE Val-Git-PABC</td>
<td>CD37</td>
<td>CLL / AML</td>
<td>Agensys</td>
<td></td>
</tr>
<tr>
<td>AGS-16AM8F</td>
<td>MMAF MalC linker</td>
<td>ENPP3</td>
<td>Renal cancer</td>
<td>Agensys</td>
<td></td>
</tr>
<tr>
<td>SC16LD6.5</td>
<td>D6.5 NA</td>
<td>Fyn3</td>
<td>SCLC</td>
<td>Stem CentRx</td>
<td>I / II</td>
</tr>
<tr>
<td>DNB6000A</td>
<td>MMAE Val-Git</td>
<td>NaP2b</td>
<td>NSCLC</td>
<td>Roche Group</td>
<td></td>
</tr>
<tr>
<td>IMGN853</td>
<td>DM4 sulfop-SPDB</td>
<td>FRα</td>
<td>ovarian cancer</td>
<td>Immunomedics</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AML: Acute Myeloid Leukaemia; HL: Hodgkin’s Lymphoma; NHL: Non-Hodgkin’s Lymphoma; ALCL: Anaplasia Large Cell Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; RCC: Renal Cell Carcinoma; SCLC: Small Cell Lung Cancer; NSCLC: Non-Small Cell Lung Cancer; CL: Chronic Lymphocytic Leukaemia; EGFR: Epidermal Growth Factor Receptor; GPNMB: glycoprotein NMB; PSMA: Prostate-Specific Membrane Antigen; NA: No Available
advancements in the field, and further insight into the optimal design characteristics of effective ADCs will be best gained from these clinical data. Progress in site-specific conjugation approaches, optimization of linkers with balanced stability, identification of novel targets, application of new cytotoxic agents and monitoring ADCs by dual radiolabelling [69] may pave the way for greater insight into the contribution of these various factors to ADC efficacy, safety and PK properties. Much work is underway to incorporate unnatural amino acids into the antibodies, which will allow novel connection chemistry to impact the nature of the ADCs and to investigate novel targets against solid tumors, such as antigens expressed selectively on the tumor vasculature. In the future, both the development of new ADCs and the exploration of combination treatments involving ADCs and other antineoplastic agents will continue and grow. Of course, the question whether the ADC technology can be applied beyond oncology to broader indications, such as immune disease, should be expounded.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (81172927) and Hisun Pharmaceutical, China.

REFERENCES

16. Kingston DG, Snyder JP. The quest for a simple bioactive analog of...


