Biodesign

pISSN 2288-6982 | eISSN 2288-7105

MINI REVIEW P 154-161

Next generation antibody therapeutics: bispecific antibodies and antibody-drug conjugates

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A new generation of therapeutic antibody technologies has emerged last decade, most notable among which are bispecific antibodies and antibody-drug conjugates. Traditional monoclonal antibodies recognize a single target molecule and exert their therapeutic activity by neutralizing the target and/or through the effector functions. On the other hand, bispecific antibodies of various formats are able to bind two different targets simultaneously. Two major approaches to harness their bispecific binding activity for therapeutic application are being pursued: recruitment of immune effector cells to the diseased cells, and simultaneous/synergistic neutralization of two disease-causing molecules. Antibody-drug conjugates are disease-targeting monoclonal antibodies chemically conjugated to a highly cytotoxic compound. The internalization of the conjugate by endocytosis and subsequent release of the cytotoxin result in a potent and selective cytotoxic activity against cancerous target cells. Optimization of the drug, linker, and conjugation chemistry is a major technological challenge in developing antibody-drug conjugates. Despite their relatively recent emergence and technological difficulties, a few examples of these novel therapeutic modalities have been successfully developed and commercialized, and many others are in the late stages of clinical development. In this review, the background and the current status of technological development in this field is discussed, with emphasis on the detailed molecular design of these molecules.

INTRODUCTION

Significant scientific and technological progress has been made in the field of antibody therapy during last 30 years, since the approval of the first therapeutic antibody muromonab CD3 (tradename Orthoclone OKT3) in 1985 (Smith, 1996). More than 30 therapeutic antibodies have since been approved for clinical use worldwide. The majority of these antibodies target cancer or immunological disorders, in part because the mechanism of action for most of the antibody drugs is to inhibit protein-protein interaction (PPI) between a cell surface receptor and its cognate ligand which is crucial for the pathogenesis of the diseases. For example, anti-TNF-α antibodies such as adalimumab (Humira®) or infliximab (Remicade®) inhibits TNF-α-induced inflammatory response by blocking the binding of their target to TNF receptor. Anti-EGFR antibodies cetuximab (Erbitux®) and panitumumab (Vectibix®), or anti-VEGF antibody bevacizumab (Avastin®) have similar mechanisms of action. Anti-HER2 antibody trastuzumab (Herceptin®) also interferes protein-protein interaction although HER2 has no known ligand; instead, trastuzumab blocks the homodimerization between two HER2 molecules. A noticeable exception is rituximab (Rituxan®), which targets CD20 on B-cell surface and induces cell killing by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

More recently, new approaches to antibody therapy have emerged, including bispecific antibodies (Garber, 2014), antibody-drug conjugates (Sievers and Senter, 2013), and antibody cancer immunotherapy (Kyi and Postow, 2014). Also, while not a true antibody therapy *per se*, cancer therapy by chimeric antigen receptor-T cell (CAR-T) is gaining much attention, which utilizes single-chain variable fragments (scFv) as cancer-targeting agent (Maus et al., 2014). While some of these newer therapeutic antibodies still have the blockade of PPI as their mode of action (MOA), such as PD-1/PD-L1 antibodies that act on the immune evasion mechanism of tumor, many of them have a novel MOA to kill the cancer cells or modulate immune function. These developments open new opportunities to tackle diseases refractory to currently available therapy, and hold great promise in providing better therapeutic options to the seriously ill patients. In this paper, recent developments in therapeutic antibody field is reviewed, and specifically bispecific antibody and antibody drug conjugate are extensively discussed. Along with the state of the art antibody engineering technologies that enable the generation of antibodies with highly desirable functional activity and biophysical properties, these new trends are expected to produce therapeutic antibodies that can fill unmet medical needs of many serious disorders.

BISPECIFIC ANTIBODY

Monoclonal antibodies, by definition, are ideally monospecific. The specific binding of a monoclonal antibody to its target is advantageous in most applications. When used as a therapeutic agent, the monospecificity means lack of off-target toxicity which is highly desirable. Consequently, nonspecific binding as well as binding to the molecules that are homologous to the cognate antigen need to be avoided when developing therapeutic antibodies. On the other hand, few diseases occur by just one disease-causing factor, and in general a multitude of different molecules are involved in the pathogenesis and progression of the disease. In many cases, targeting just one of these molecules to treat the disease results in insufficient therapeutic effect. This is also the case for therapeutic antibodies. Anticancer antibodies are effective for only a fraction of patients whose cancer cells express the target for the antibody, and the therapeutic efficacy is often minimal with typical survival improvement of only a few months (Baselga, 2001; Ferrara et al., 2004; Van Cutsem et al., 2011).

Bispecific antibodies are antibodies or antibody fragments that are engineered to have a dual specificity, i.e. capable of binding two different antigens simultaneously. Bispecific antibodies as therapeutic reagents are typically developed in either of two strategies. One is to bind and neutralize two different but mechanistically related disease-causing molecules in synergistic manner, and the other is to simultaneously target a surface antigen on diseased cells and an activating surface molecule on immune effector cells, thereby recruiting the effector cells to the diseased cells and inducing cell death. The former strategy is employed in bispecific antibodies in various stages of developments. For example, anti-EGFR/c-Met (Castoldi et al., 2013) or anti-EGFR/HER3 (Schaefer et al., 2011a) antibodies target two different cell-surface receptors that promote survival and proliferation of cancer cells. Targeting just one of these receptors with a therapeutic antibody is often ineffective because of the compensating effect of other receptor signal pathways, and the simultaneous blockade of two of the major proliferative pathways can have a synergistic effect on the inhibition of cancer cell survival and proliferation. This dual-targeting strategy is also applied to immunological disorders, and bispecific antibodies targeting two different cytokines or cytokine receptors have also been reported (Fischer et al., 2015; Qi et al., 2012). The effectiveness of the latter strategy is exemplified by the approval of blinatumomab (Blincyto™), a bispecific anti-CD19/CD3 tandem scFv indicated against Philadelphia chromosome-negative, relapsed or refractory acute lymphoblastic leukemia (ALL) (Buie et al., 2015; Hoffman and Gore, 2014; Nagorsen et al., 2012). Although this and the related CAR-T therapy are currently focused on hematological cancers (Maus et al., 2014; Nelson and Paulos, 2015) because of the accessibility issue and on-target toxicity, future technological developments may enable broader application of this strategy (Frankel and Baeuerle, 2013). See Table 1 for a list of bispecific antibodies of various formats in clinical development.

Bispecific antibodies of a variety of different formats have been suggested and constructed (Garber, 2014; Kontermann, 2012) (Figure 1), each with its own advantages and shortcomings. There are scFv-based bispecific antibodies, which are small (~50 kDa) and can be recombinantly produced from *E.coli* or mammalian cells (Hayden et al., 1994; Hornig and Farber-Schwarz, 2012). These engineered antibody fragments are typically in tandem scFv format (Kontermann, 2005) in which two scFv clones are linked by an extra peptide linker, or diabody format that essentially is a heterodimer of two scFvs, each of which consists of VH of one binder clone and VL of the other (Lu et al., 2004). Unlike conventional scFv (~25 kDa) which can be relatively easily produced from *E.coli* in large amount, these dual-scFv molecules have production issues including the formation of insoluble aggregates for tandem scFv, or the homodimer formation for diabody. Several approaches have been reported to alleviate these problems. For tandem scFv, the order of the variable domains or the linker connecting two scFv moieties were manipulated to optimize the soluble expression of the bispecific antibody (Fischer et al., 2015; Korn et al., 2004). For diabodies the preferential formation of scFv heterodimer can be achieved by knob-in-hole design similar to the approach employed for the

TABLE 1 | Examples of bispecific antibodies in clinical development

Name	Targets	Indication	Development stage	Format
Blinatumomab[1]	CD19, CD3	Acute lymphoblastic leukemia (ALL)	Approved	Tandem scFv
Catumaxomab[2]	EpCAM, CD3	Malignant ascites	Approved (EMA)	IgG from quadroma
ABT-981[3]	IL-1α, IL1-β	osteoarthritis	Phase II	DVD-Ig
MM-141[4]	HER3, IGF-1R	Metastatic pancreatic cancer	Phase II	IgG-scFv
MEHD7945A[5]	EGFR, HER3	Head and neck cancer	Phase II	Two-in-one
MGD007[6]	GPA33, CD3	Colorectal cancer	Phase I	diabody
RO5520985[7]	VEGF-A, Ang-2	Advanced solid tumor	Phase II	CrossMAb

[1]Buie et al., 2015, [2]Seimetz et al., 2010, [3]Lacy et al., 2015, [4]Fitzgerald et al., 2014, [5]Li et al., 2015, [6]Hurwitz et al., 2014, [7]Garber, 2014.

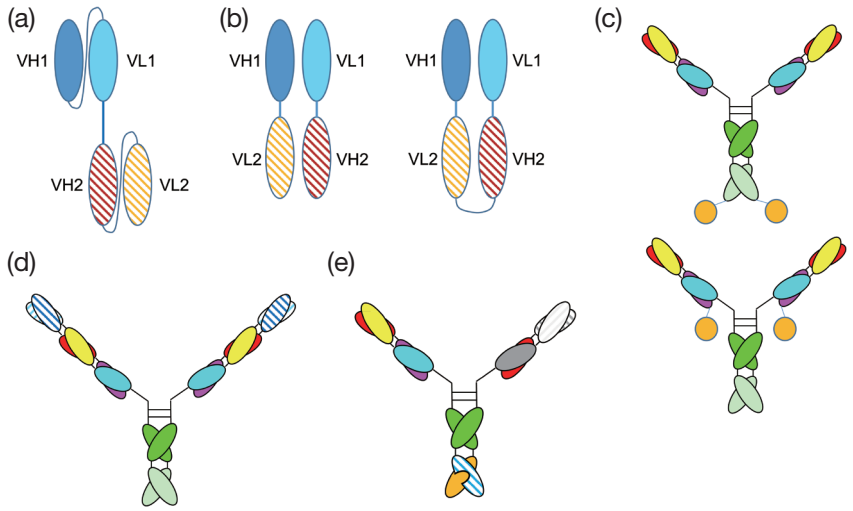

FIGURE 1 | Some of the bispecific antibody formats discussed in this review. (a) Tandem scFv has two scFvs with different specificities linked together by a peptide linker. The order of variable domains (VH-VL or VL-VH), or the linker length/sequence can be optimized to improve the expression, folding, and stability of the molecule. (b) Diabody (left) is a heterodimer of two scFvs, each of which has VH of one binder and VL of the other binder linked by a short linker that precludes the formation of intramolecular VH-VL pair. The two scFvs can be tethered by a short peptide linker to form a single-chain diabody (right). (c) IgG antibody fused to another binder (e.g. scFv) at the N- or C-termini of the heavy and/or the light chains. The orange circles denote the extra binders with the second specificity. (d) DVD-Ig (dual variable domain – immunoglobulin) has two variable domains at the N-terminus of each light and heavy chain. (e) Knobs-into-holes antibody has engineered CH3 domains that facilitates the formation of heavy chain heterodimer, and each arm of the Y-shaped IgG molecule binds to a different antigen.

generation of bispecific IgG antibodies (see below), although it involves intensive protein engineering to find optimal mutations needed for efficient heterodimer formation. Alternatively, single-chain diabodies can be constructed, which precludes the formation of inactive homodimer (Fischer et al., 2015; Kipriyanov et al., 1999).

Currently there is one tandem scFv antibody approved for clinical use. Blinatumomab (Blincyto™ developed and marketed by Amgen) is a bispecific tandem scFv antibody targeting CD19 and CD3 simultaneously, and indicated for second-line therapy for patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The anti-CD3 portion of the molecule binds to and activates T cells, while the anti-CD19 part binds to the cells of B-cell lineage including malignant B cells.

Consequently, blinatumomab ligates normal and cancerous B cells with activated cytotoxic T lymphocytes, and induces the depletion of B cells in patients (Hoffman and Gore, 2014; Schlereth et al., 2006). This approach (known as bispecific T-cell engager or BiTE®) is also pursued for other cancer targets such as carcinoembryonic antigen (CEA), which is in phase I clinical trial for a treatment in solid tumors. A similar approach using diabody, such as the dual affinity retargeting (DART™), have been reported in which CD19xCD3 or CD19xTCR bispecific diabodies were proven effective in inducing B-cell lysis in animal models (Moore et al., 2011).

Other bispecific antibody formats that are based on full immunoglobulin structure have also been developed. For example, the second binding specificity can be introduced to a traditional monoclonal antibody by adding an scFv to either N- or C-terminal of the heavy or light chain of the IgG antibody. While this may be a rather straightforward approach design-wise, the actual production of bispecific antibodies in this format can pose some problems in such aspects as stability and aggregation (Schanzer et al., 2011). Non-antibody binder proteins/peptides such as Affibody™ can also be attached to IgG to produce bispecific antibodies (LaFleur et al., 2013; Yu et al., 2014). A related strategy is so-called DVD-Ig, or dual variable domain immunoglobulin, in which each of the heavy and light chains has two variable domains in tandem connected by a short linker (DiGiammarino et al., 2012), thereby pairing each of the two VHs with its respective partner VL. Some of these IgG-based bispecific antibodies are in various stages of clinical development (Garber, 2014).

Also, there are genuine bispecific IgG antibody without additional variable domains. These are asymmetric IgG molecules with each arm of the Y-shaped molecule recognizing a different antigen. They can be produced from quadromas (also known as hybrid hybridoma or tetradoma) generated by the fusion of two hybridomas. The main challenge in developing this kind of bispecific antibody is that, because the quadroma has two genes each for the heavy and the light chain, as many as ten different heavy/light chain combinations can be produced (Kontermann, 2012) and the heterotetramer with desired bispecific affinity has to be purified from the other inactive IgGs. Despite this problem, there is one approved bispecific antibody produced from quadroma. Catumaxomab (Removab™) has been approved by Eurpean Medicines Agency for the treatment of malignant ascites in patients with EpCAM-positive cancer (Seimetz et al., 2010), and binds both EpCAM on cancer cells and CD3 on T-cells. As well as recruiting T-cells to the close vicinity of cancer cells through its bispecific activity, these antibodies can also exert the effector functions through its Fc region.

In order to alleviate the problem associated with the production of quadroma bispecific antibodies, Fc region has been engineered to induce the preferential formation of heavy chain heterodimer. So-called “knobs-into-holes” approach and other similar strategies introduce structural complementarity to the

dimer interface region of CH3 that facilitates the dimerization between different heavy chains and hinders the formation of heavy chain homodimers (Ridgway et al., 1996). However, non-functional IgG molecules are still produced by the shuffling of the light chains, and additional purification/engineering steps are required to obtain functional bispecific antibodies. CrossMAb® technology, for example, swaps the light chain (VL-CL) and Fd (VH-CH1 moiety of the heavy chain) of one arm of the knobs-into-holes antibody so that the light chains preferentially pair with their cognate heavy chain (Schaefer et al., 2011b).

Another interesting strategy to generate dual specificity is 'two-in-one' antibody approach (Schaefer et al., 2011a). A two-in-one antibody is a conventional monoclonal antibody with a paratope that is capable recognizing two different antigens. Because an IgG molecule has two identical paratopes, a two-in-one antibody can bind two different antigens simultaneously.

The generation of a two-in-one antibody is not straightforward and requires a significant amount of antibody engineering, screening, and optimization work. But because they are indistinguishable from normal monoclonal antibodies and without additional fusion partner or sequence manipulation, some of the issues associated with other bispecific formats in the manufacturing and development processes may be avoided.

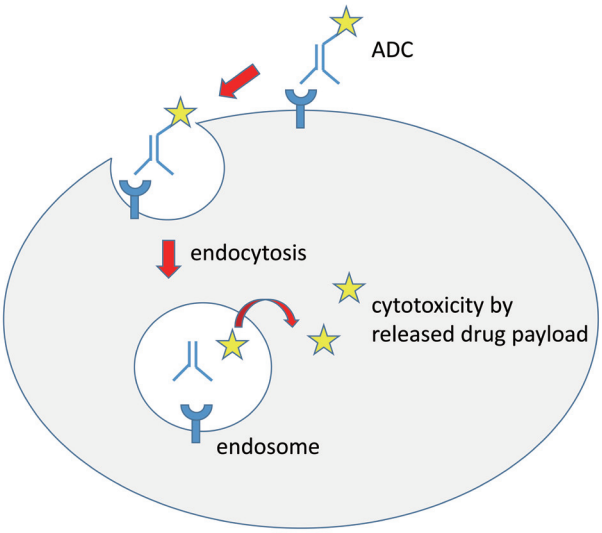

FIGURE 2 | General mechanism of action of antibody-drug conjugates. ADC binds to its target on the cell surface, and the ADC-antigen complex is internalized by endocytosis. In the endosome the payload (cytotoxic drug) is released by various mechanisms depending on the linker chemistry. The released cytotoxic payload then kills the cell, typically by the inhibition of microtubule formation or DNA alkylation.

ANTIBODY-DRUG CONJUGATES (ADC)

Traditional therapeutic antibodies treat cancer by blocking receptor activation, and/or inducing cell killing by effector mechanisms such as ADCC and CDC. Usually the efficacy of these mechanisms of action is not strong enough to eradicate cancer cells, and the survival benefits of these antibodies are often marginal. Antibody-drug conjugates (ADC) consist of a disease-targeting antibody molecule chemically conjugated to varying numbers of highly cytotoxic chemical compounds ("payloads") via a linker part. Each of these parts (antibody/target, payload, linker, and the conjugation chemistry) needs to be optimized in the context of the others to develop an ADC. The general mechanism of action of ADC is shown in Figure 2.

The delivery of the ADC payload relies on the clathrin-dependent, receptor-mediated endocytosis that is triggered by the specific binding of the antibody to the cell surface target antigen (Ritchie et al., 2013), therefore the ADC target needs to exist in sufficient quantity on the cell surface and have an internalization rate sufficiently rapid for effective cell killing by ADC. Also, the target antigen should not be expressed, or expressed at very low levels, on normal cells because the ADC payload is extremely cytotoxic (see below). These requirements may restrict the choice of target antigen even narrower than traditional therapeutic antibodies (which can only target cell-surface or secreted molecules). However, the function of the target antigen itself is not a major concern when developing ADC, and molecules that had been considered unsuitable as targets of traditional therapeutic antibody because of the lack of functional role in disease occurrence and progression may be targeted by ADC. Currently there are two ADCs approved for clinical use, trastuzumab-DM1 (Kadcyla™) targeting HER2 and brentuximab vedotin (Adcetris™) targeting CD30, with many others in various stages of clinical development (Table 2).

The ADC payload needs to be highly toxic, considering the number of ADC molecules that are internalized per cell (a few thousand molecules, equivalent to the concentration in picomolar range) (Lapusan et al., 2012). This rules out most of the chemotherapeutic agents as the payloads. The most commonly employed class of payload molecules is microtubule inhibitors such as the derivatives of auristatin or maytansine (Chari et al., 2014). These compounds typically have sub-nanomolar IC_{50} values which are > 10-times more powerful than chemotherapeutic microtubule inhibitors such as paclitaxel or docetaxel (Liebmann et al., 1993; Morse et al., 2005). Other classes of cytotoxic chemicals such as DNA alkylating agents (Chari et al., 2014) are also being developed. Once endocytosed, the payload molecules are cleaved from the ADC in the endosome and released to cytosol, where they exert the cytotoxic activity. Therefore the linker that connects the payload to the antibody needs to be labile in the endosome. On the other hand, because the payload is very toxic, the cleavage of the linker should be minimized in blood. This apparent contradiction can be resolved by employing linkers that are normally stable but become selectively labile in the endosome or lysosome (Jain et al., 2015). One such linker, employed in brentuximab vedotin, contains a valine-citrulline dipeptide moiety that is a substrate for cathepsin B, a lysosomal protease. After internalization of the ADC, the endosome matures and fuses

TABLE 2 | Examples of antibody-drug conjugates in clinical development

Name	Target	Conjugation residue	Linker cleavage	Payload	Indication[a]	Development stage
Brentuximab vedotin[1]	CD30	Cysteine	Val-Cit	Auristatin	HL, ALCL	approved
Trastuzumab emtansine[2]	HER2	Lysine	Non-cleavable	DM1 (maytansinoid)	Metastatic breast cancer	approved
Inotuzumab ozogamicin[3]	CD22	Lysine	Acid-labile (hydrazone)	Calicheamicin	NHL, ALL	Phase III
BT062[4]	CD138	Lysine	disulfide	DM4 (maytansinoid)	MM	Phase II
SAR3419[5]	CD19	Lysine	disulfide	DM4 (maytansinoid)	DLBCL, ALL	Phase II
MDX-1203[6]	CD70	Cysteine	Val-Cit	Duocarmycin	NHL, RCC	Phase I
BAY79-4620[7]	CA9	Cysteine	Val-Cit	Auristatin	Solid tumors	Phase I

[a]HL, Hodgkin's lymphoma; ALCL, anaplastic large cell lymphoma; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; RCC, renal cell carcinoma. [1]Younes et al., 2010, [2]Verma et al., 2012, [3]Kantarjian et al., 2013, [4]Lutz and Whiteman, 2009, [5]Blanc et al., 2011, [6]Owonikoko et al., 2015, [7]Petrul et al., 2012.

with lysosome where the linker gets cleaved by cathepsin B and the free drug molecules are released. There are other types of cleavable linkers, such as acid-labile linkers that utilizes the pH difference between serum (pH = 7.4) and endosome/lysosome (pH ~ 5), or disulfide-containing linkers that becomes reduced by the higher intracellular glutathione concentration. Unlike these cleavable linkers, non-cleavable linkers are chemically inert in both extracellular and intracellular environments, and the release of the cytotoxic payload of the ADC with a non-cleavable linker relies on the complete endolysosomal degradation of the antibody. Trastuzumab-DM1 contains a non-cleavable linker, and the actual chemical species that kills the cell after internalization is the cytotoxic agent (DM1) with the linker moiety still attached, plus a single amino acid (lysine in this case) from trastuzumab (Jain et al., 2015). The efficiency of endolysosomal escape by diffusion after linker degradation depends on the chemistry of the linker and the payload (Jain et al., 2015; Maass and Wittrup, 2015). The linker structures and the cleavage chemistry of brentuximab vedotin and trastuzumab-DM1 (trastuzumab emtansine) are shown in Figure 3.

The chemistry of the conjugation reaction is also important in developing and producing ADCs. In most cases, the linker-payload moieties are conjugated to the antibody through covalent attachment to the side chains of either lysine or cysteine

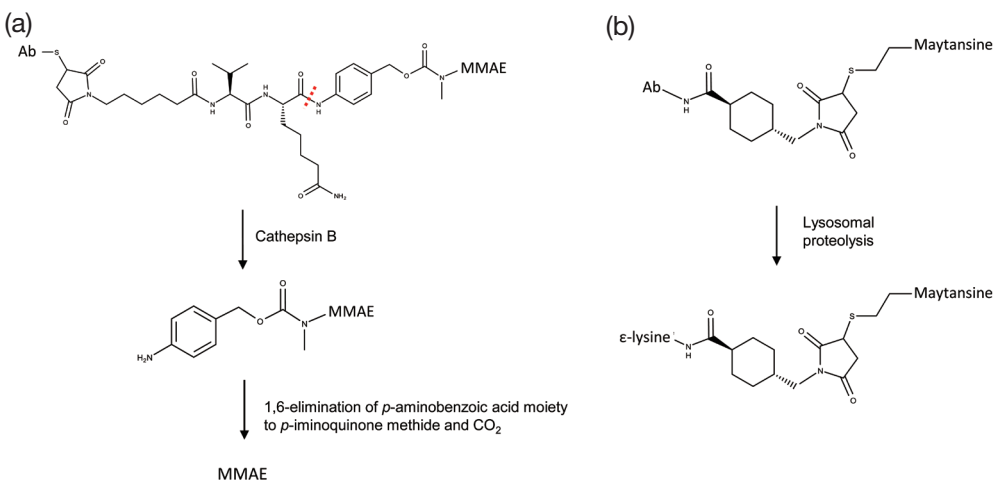

FIGURE 3 | Chemical structures and cleavage mechanisms for brentuximab vedotin (Adcetris) with a cleavable valine-citrulline linker (a), and trastuzumab emtansine (Kadcyla) with a non-cleavable linker (b). (a) After cleavage of the valine-citrulline linker by cathepsin B, self-immolative 1,6-elimination of *p*-aminobenzoic acid results in the release of free monomethylauristatin E (MMAE). (b) The maleimidomethyl cyclohexane-1-carboxylate (MCC) linker of Kadcyla is non-cleavable, and after the complete degradation of the antibody part in the lysosome, the drug (a maytansine derivative DM1) with the MCC linker attached to a lysine via ε-amino group is released.

residues. Immunoglobulin molecules contain multiple interchain disulfide bonds, which can be reduced to expose free sulfhydryl groups. For example, the human IgG1 subtype has two disulfides between the heavy chain hinge regions and one disulfide bond each between heavy and light chains. Thus, full reduction of an IgG1 molecule results in eight free reactive sulfhydryl groups available for drug conjugation. Linkers containing maleimide moiety readily reacts with cysteines, and as many as eight drug molecules can be conjugated to an antibody molecule. However the drug-antibody ratio (DAR) is generally lower than 8, and brentuximab vedotin which utilizes the cysteine linkage method has a mean DAR of 4 (Lhospice et al., 2014). Higher DAR would make the ADC more potent, but other DAR-associated problems such as solubility and structural stability may arise. One potential problem to the cysteine conjugation is that the maleimide adduct is chemically unstable in plasma, and the drug can be cleaved by retro-Michael reaction before ADC binds to the target cells and internalized (Jain et al., 2015), and a recently reported linker design reduces this problem by introducing self-hydrolyzing functionality (Lyon et al., 2014). Drugs can be conjugated via lysine residues. A typical IgG molecule has ~80 lysine residues and many are exposed on surface. The ε-amino group of these lysines can be conjugated to the linker by acylation. Because there are greater number of lysines than cysteines in an antibody molecule and at various positions, the lysine conjugation method generally yields more heterogeneous conjugation patterns than the cysteine conjugation method. Through the optimization of the manufacturing process, a reproducibly consistent drug conjugation to lysine residues can be achieved, and trastuzumab-DM1 is reported to have a mean DAR of 3.5 (Kim et al., 2014) by using this method.

The above-described conventional conjugation methods produce significant heterogeneity in ADC pattern, in which the site of conjugation and DAR differ in each species and hence the therapeutic efficacy and *in vivo* pharmacokinetic profiles may vary. Lot-to-lot consistence is also a problem, which makes the production and purification process more complicated and expensive. The new generation of ADCs in development employ more elaborate conjugation methods, and site-specific ADCs with more homogeneous drug conjugation patterns and DAR distribution can be produced with these methods (Panowksi et al., 2014). The antibody can be engineered to include functional chemical groups that can be selectively conjugated to the linker. For example, cysteine residues can be introduced by site-directed mutagenesis (Junutula et al., 2010; Junutula et al., 2008b). While this is conceptually straightforward, in practice there are multiple challenges to overcome to successfully produce site-specific ADC by this method. The introduced cysteine residue may form disulfide bond with other proteins during or after ER-golgi secretion, or they may form intramolecular disulfide bonds which may interfere with proper folding and functioning of the antibody. Therefore it is important to select suitable site for cysteine introduction that minimize these unwanted disulfide formations (Junutula et al., 2008a). Linkers can be conjugated in a site-specific manner by enzymatic reaction, for example by using enzymes such as formylglycine generating enzyme (FGE) (Rabuka et al., 2012), transglutaminase (Dennler et al., 2014), or glycotransferase (Boeggeman et al., 2009). Some of these methods require the engineering of the antibody for the enzymatic transfer of the linker moiety (e.g. prenyl transferase or FGE) while unengineered antibody can be used for others (e.g. glycotransferase). Another approach for site-specific drug conjugation utilizes selenocysteine (Hofer et al., 2009) or unnatural amino acids (Axup et al., 2012; Hallam and Smider, 2014) which can be modified by chemical reactions to which the conventional amino acid side chains are not sensitive. While this is a highly precise strategy to produce site-specific ADC, the production of a large amount of antibody with unnatural amino acids or selenocysteine pose a significant hurdle to the commercial development of this technology.

CONCLUDING REMARKS

Since the invention of hybrodima technology by Köhler and Milstein in 1975 and the approval of the first therapeutic antibody in 1985, the field has developed and expanded rapidly. Because of their ability to inhibit protein-protein interaction, long half lives, high affinity and specificity, these biological agents are able to modulate many disease-causing mechanisms that are considered undruggable for conventional small molecule drugs. The new antibody engineering technologies enhance the therapeutic efficacy of antibody drugs even further, and provide greater target-neutralizing or cytotoxic activity than conventional therapeutic antibodies. With antibody engineering and production technologies rapidly evolving, these and other next-generation antibody platforms are expected to offer novel opportunities for better treatment of many serious disorders.

ACKNOWLEDGEMENT

This work was supported by the National Research Foundation of Korea (NRF) grant for Medical Bioconvergence Research Center (NRF-2013M3A6A4044991) and the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (NRF-2015M3A9B6029138).

AUTHOR INFORMATION

The Authors declare no potential conflicts of interest.

Original Submission: Nov 25, 2015
Revised Version Received: Dec 12, 2015
Accepted: Dec 14, 2015

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