

REVIEW

Monoclonal antibodies – a proven and rapidly expanding therapeutic modality for human diseases

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ABSTRACT

The study of antibodies has been a focal point in modern biology and medicine since the early 1900s. However, progress in therapeutic antibody development was slow and intermittent until recently. The first antibody therapy, murine-derived murononab OKT3 for acute organ rejection, was approved by the US Food and Drug Administration (FDA) in 1986, more than a decade after César Milstein and Georges Köhler developed methods for the isolation of mouse monoclonal antibodies from hybridoma cells in 1975. As a result of the scientific, technological, and clinical breakthroughs in the 1980s and 1990s, the pace of therapeutic antibody discovery and development accelerated. Antibodies are becoming a major drug modality with more than two dozen therapeutic antibodies in the clinic and hundreds more in development. Despite the progress, need for improvement exists at every level. Antibody therapeutics provides fertile ground for protein scientists to fulfill the dream of personalized medicine through basic scientific discovery and technological innovation.

KEYWORDS monoclonal antibodies, personalized medicine, therapeutic antibodies

INTRODUCTION

The pioneering research by Robert Koch, Kitasato Shibasaburo, Emil von Behring, and Paul Ehrlich in late 19th and the early 20th centuries on the treatment of infectious diseases with serum from patients who had recovered from the same disease was the first use of antibodies as therapeutics. The

active components in the serum were described as “antibodies” “antitoxins” and “magic bullets” (Ehrlich, 1908; Winau et al., 2004). This crude “serum therapy” was later modified by isolating antibodies from the serum for the treatment of infectious and immune diseases, known as intravenous immune globulin (IVIG) (Stangel and Pul, 2006). Despite the early success of serum therapy and IVIG treatment, no significant progress was made in therapeutic antibody discovery and development until César Milstein and Georges Köhler developed methods for isolating mouse monoclonal antibodies (mAbs) from hybridoma cells in 1975 (Köhler and Milstein, 1975). Since then, mAbs have not only fueled breakthrough discoveries in basic research, but have also been developed as clinical diagnostics, reagents for high throughput drug screening, and more importantly, life-saving medicines. The first therapeutic mAb murononab, a murine-derived antibody for acute organ rejection, was approved by the US Food and Drug Administration (FDA) in 1986, a decade after the discovery of the mouse hybridoma technology (Thistlethwaite et al., 1987). As a result of technological breakthroughs in the 1980s and 1990s, progress in therapeutic mAbs field has been accelerated. Therapeutic antibodies have shown desirable safety profiles, high target specificity and affinity, and efficiency in disrupting protein/protein interactions. They are becoming a major drug modality with more than 25 therapeutic antibodies in clinical use and hundreds more in development (Reichert and Valge-Archer, 2007; An, 2009).

ANTIBODY STRUCTURE

An antibody of the IgG isotype is a homodimer composed of two heterodimers of one light chain and one heavy chain.

Both the heterodimers and homodimers are linked by inter chain disulphide bonds (Stanfield and Wilson, 2009) (Fig. 1A). The light and heavy chains each contain variable and constant regions. The antigen binding complementarity determining regions (CDRs) are short hypervariable amino acid sequences found in the variable domains of both light (variable light or VL) and heavy (variable heavy or VH) chains. Each VH and VL contains three pairs of non-identical CDRs (CDR1, CDR2 and CDR3). CDRs are termed hypervariable domains because the majority of the sequence variations associated with antibodies is found in the CDRs. Among the six CDRs in an IgG molecule, CDR3s have the greatest variability. The Fc-region (fragment crystallizable region) of a mAb, residing in the constant regions of the heavy chains, can recruit effector cells such as natural killer cells, macrophages or neutrophils to activate the complement system to destroy the target-associated cells. These functions are referred to as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Four additional antibody isotypes are found in humans, IgA, IgD, IgE, and IgM. All five isotypes share a common theme of a core heterodimer building unit of a heavy and light chain. In IgG, IgA and IgD antibody isotypes, the Fc region is composed of two identical protein fragments, derived from the second (CH2) and third (CH3) constant domains of the antibody's two heavy chains. The Fc regions in IgM and IgE contain three heavy chain

constant domains in each polypeptide chain. The IgG isotype is most commonly used in therapeutic applications.

ANTIBODY THERAPEUTIC HISTORY

The progress of antibody therapeutics is driven by both scientific and technological breakthroughs (Fig. 2). Therapeutic antibody development also parallels the desire of the industry to reduce immunogenicity. Immunogenicity can reduce the efficacy of therapeutic mAbs. In severe cases, immunogenicity can cause anaphylaxis and hypersensitivity reactions. Soon after the approval of the murine-derived monoclonal antibody muromonab for acute organ rejection in 1986 (Thistlethwaite et al., 1987), it was realized that murine-derived monoclonal antibodies are less than ideal therapeutics due to their high immunogenicity in humans. Several strategies to make antibodies more human, such as chimeric mAb (Morrison et al., 1984) and CDR grafting (Kettleborough et al., 1991), were devised to reduce the human anti-mouse antibody (HAMA) responses. It took a decade for the first chimeric mAb, abciximab for hemostasis, to be approved by FDA in 1994 (Faulds and Sorkin, 1994). The first humanized mAb, Zenapax for kidney transplant rejection, was approved for clinical use by FDA in 1997 (Vincenti et al., 1998). Humanization alleviated the HAMA response to various degrees, but many other drawbacks became evident. For

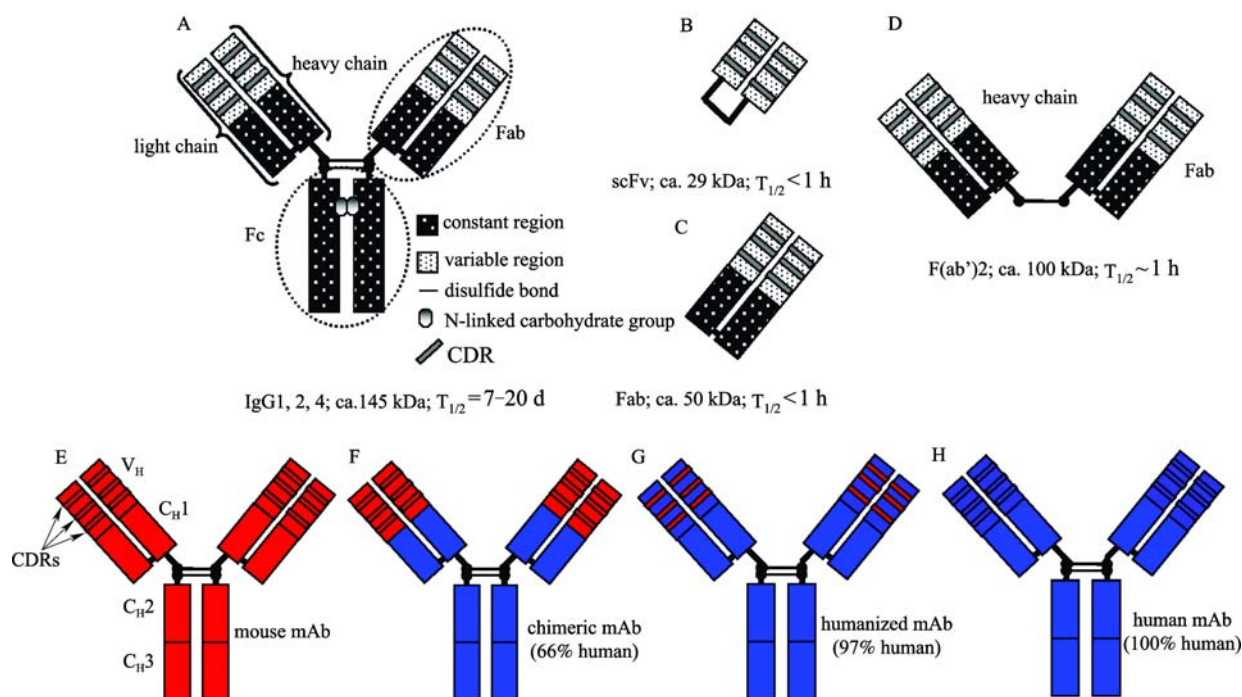


Figure 1. Diagrams of various antibody structures. (A) A generic IgG molecule. (B) A scFv fragment. (C) A Fab fragment. (D) A F(ab')₂ fragment. (E) A mouse IgG molecule. (F) A murine:human chimeric IgG molecule. (G) A humanized IgG molecule. (H) A human IgG molecule.

example, the humanization process is technically demanding and the process may result in reduced antigen binding affinity and decreased efficacy. To avoid the human immune response to murine-derived mAbs and to overcome the technical challenges associated with humanizing murine mAbs, two major approaches were developed for generating fully human mAbs. The first approach was to express human antibody fragments on bacteriophage surfaces. The resulting libraries contain billions of unique human antibody fragments which can be screened for leads (Vaughan et al., 1996). Humira, the first fully human mAb derived from a bacteriophage displayed antibody library, was approved by the FDA in 2003 for the treatment of rheumatoid arthritis (Weinblatt et al., 2003). The second approach was to use transgenic mice to produce fully human antibodies (Russell et al., 2000; Lonberg, 2005). This is achieved by replacing the mouse native antibody genes with their human counterparts. Vectibix, an anti-EGFR antibody approved for colorectal cancer therapy in 2006, was the first fully human antibody therapeutic derived from a transgenic mice system (Chua and Cunningham, 2006). The industry trend is to develop more human like antibodies for clinical use. However, immunogenicity is a complex biological

process and it cannot be predicted solely on human content of an antibody. For example, Humira, a fully human antibody, has a relatively high incidence of immunogenicity (Bender et al., 2007). Surprisingly, there is little difference in immunogenicity (anti-antibody response) between humanized and chimeric mAbs in clinical use today (Table 1). Clearly more basic and clinical research is needed to develop reliable parameters to predict immunogenicity of therapeutic antibodies prior to their reaching the clinic.

SOURCES OF THERAPEUTICS ANTIBODIES

Accessing diversified antibody sources are paramount to the success in the discovery and development of antibody therapies. Most therapeutic antibodies in the clinic today are of murine origin largely due to the early availability of the mouse hybridoma technology; however, entirely mouse antibodies have poor pharmacokinetics in humans due to human anti-mouse antibody immune responses (Fig. 1E). To reduce immunogenicity, murine antibodies are commonly modified to murine/human chimeric antibodies or humanized antibodies for therapeutic applications (Carter, 2006; Reichert

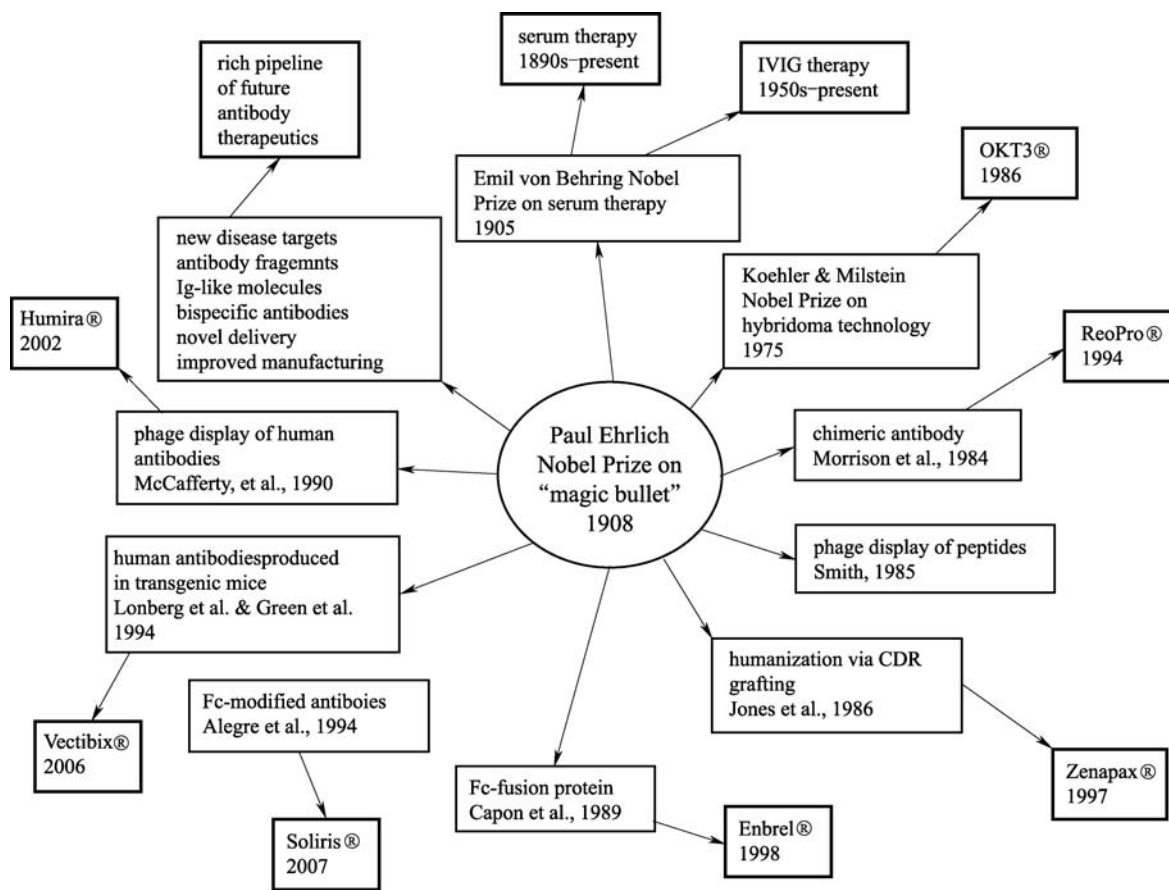


Figure 2. History of antibody therapeutics. Green boxes represent scientific and technology milestones. Blue boxes are antibody therapeutics developed as a result of the scientific and technology breakthroughs.

Table 1 Monoclonal antibody therapeutics approved for clinical use

generic name trade name manufacturer	launch date	therapy area	major indication	target	protein form/isotype	delivery	reference
Muromonab Orthoclone/OKT3 Johnson & Johnson	1986	AIID	transplant rejection	CD3	murine IgG2a	IV	Cohen et al., 1989
Abciximab ReoPro Eli Lilly	1995	CV	cardiovascular disease	CD41	chimeric Fab	IV	Faulds and Sorkin, 1994
Rituximab Rituxan/MabThera Genentech/Roche	1997	oncology	Non-Hodgkin's lym- phoma	CD20	chimeric IgG1	IV	Maloney et al., 1997
Daclizumab Zenapax Roche	1997	AIID	transplant rejection	CD25	humanized IgG1	IV	Vincenti et al., 1998
Basiliximab Simulect Novartis	1998	AIID	transplant rejection	CD25	chimeric IgG1	IV	Nashan et al., 1997
Infliximab Remicade Centocor	1998	AIID	rheumatoid arthritis	TNF alpha	chimeric IgG1	IV	Onrust and Lamb, 1998
Palivizumab Synagis Medimmune	1998	ID	respiratory syncytial virus	RSV F-protein	chimeric IgG1	IM	Storch, 1998
Trastuzumab Herceptin Genentech	1998	oncology	breast cancer	Her2	humanized IgG1	IV	Albanell and Baselga, 1999
Gemtuzumab/ozogami- cin Mylotarg Wyeth	2000	oncology	acute myelogenous leukemia	CD33	humanized IgG4 conju- gated with ozogamicin	IV	Sorokin, 2000
Alemtuzumab Campath Bayer-Schering	2001	oncology	chronic lymphocytic leukemia	CD52	humanized IgG1	IV	Ferrajoli et al., 2001

(Continued)

generic name trade name manufacturer	launch date	therapy area	major indication	target	protein form/isotype	delivery	reference
Ibritumomab tiuxetan Zevalin Biogen/Idec	2002	oncology	Non-Hodgkin's lymphoma	CD20	murine IgG1 conjugated with Yttrium 90	IV	Krasner and Joyce, 2001
Omalizumab Xolair Genentech/Novartis	2003	respiratory	asthma	IgE	humanized IgG1	SC	Davis, 2004
Efalizumab Raptiva Genentech	2003	AIID	psoriasis	CD11A	humanized IgG1	SC	Gauvreau et al., 2003
Tositumomab Bexxar GSK	2003	oncology	Non-Hodgkin's lymphoma	CD20	murine IgG2a conjugated with iodine-131	IV	Davies, 2004
Adalimumab Humira Abbott	2003	AIID	rheumatoid arthritis	TNF alpha	human IgG1	SC	Weinblatt et al., 2003
Cetuximab Erbix ImClone/BMS	2003	oncology	colorectal cancer	EGFR	chimeric IgG1	IV	Kies and Harari, 2002
I-131 ch-TNT Shanghai Medipharm Biotech Co.	2003	oncology	advanced lung cancer	intracellular DNA in tumors	chimeric IgG1 conjugated with iodine-131	IV	Chen et al., 2005
Bevacizumab Avastin Genentech	2004	oncology	colorectal and non-small cell lung cancer	VEGF	humanized IgG1	IV	Kerr, 2004
Natalizumab Tysabri Biogen IDEC/Elan	2004	CNS/AIID	multiple sclerosis	VLA4	humanized IgG1	IV	Rudick and Sandrock, 2004
Tocilizumab Actemra Roche/Chugai	2005	AIID	Castleman's disease	IL-6R	humanized IgG1	IV	Paul-Pletzer, 2006

(Continued)

generic name trade name manufacturer	launch date	therapy area	major indication	target	protein form/isotype	delivery	reference
Ranibizumab Lucentis Genentech/Novartis	2006	ophthalmology	wet age-related macular degeneration	VEGF	humanized mab fragment of Avastin	injection into the eye	Kenneth and Kertes, 2006
Panitumumab Vectibix Amgen	2006	oncology	colorectal cancer	EGFR	human IgG2	IV	Cohenuram and Saif, 2007
Certolizumab pegol Cimzia UCB-Schwarz	2007	AiID	rheumatoid arthritis	TNF alpha	PEGylated fragment	SC	Rutgeerts et al., 2007
Eculizumab Soliris Alexion	2007	hematology	PNH (chronic hemolysis)	C5a	humanized IgG2/IgG4 hybrid	IV	Rother et al., 2007
Ofatumumab Arzerra GSK	2009	oncology	chronic lymphocytic leukemia	CD20	human IgG1	IV	Keating et al., 2010
Golimimumab Simponi Johnson & Johnson	2009	AiID	rheumatoid arthritis	TNF alpha	human IgG1	SC	Pappas et al., 2009

AiID, arthritis, immune and inflammatory disorders; CNS, central nervous system; CV, cardiovascular; ID, infectious disease; IM, intramuscular; IV, intravenous; SC, subcutaneous

and Valge-Archer, 2007) (Fig. 1F–G). Later, transgenic mice and *in vitro* phage display were employed to generate fully human therapeutic antibodies to circumvent the immunogenicity issue associated with murine sequences (Fig. 1H) (Hoogenboom, 2005; Lonberg, 2005; Jakobovits et al., 2007; Lee et al., 2007). In addition to phage display, antibody fragments can also be displayed on yeast (Feldhaus et al., 2003), bacteria (Harvey et al., 2004), mammalian cells (Smith and Zauderer, 2009) and other *in vitro* systems such as ribosomes (Hanes et al., 1998). The pros and cons of the various antibody platforms have been broadly reviewed recently (An, 2009). The ever increasing demand for improved tools for antibody drug discovery will lead to new platforms and technologies. For example, humanized rabbit mAbs are being developed as therapeutics (News, 2010; Yu et al., 2010).

Another important source of antibodies is the human antibody B cell repertoire. The isolation of human mAbs has been a labor-intensive endeavor, either through EBV immortalization or hybridoma fusion, or by constructing phage-displayed antibody libraries (Vaughan et al., 1996; Traggiai et al., 2004; Li et al., 2006b; Rothe et al., 2007). Significant technological breakthroughs in B lymphocyte culture and cloning were reported recently including the analysis of HIV and flu mAbs in naturally infected or vaccinated humans (Wrammert et al., 2008; Jin et al., 2009; Ogunniyi et al., 2009; Scheid et al., 2009; Walker et al., 2009; Kwakkenbos et al., 2010). It is now possible to isolate human memory B cells (CD27⁺, sIgG⁺, IgD⁻) from peripheral blood mononuclear cells (PBMC), and more importantly, culture them where they proliferate and differentiate to IgG secreting cells (ISC) (Smith et al., 2009; Walker et al., 2009). Single cell culturing vessels have been engineered, thus enabling for high-throughput screening of functional mAbs (Jin et al., 2009; Ogunniyi et al., 2009). New methods of B cell immortalization other than EBV infection or hybridoma, such as Bcl-6/Bcl-xL, or hTERT, have been reported (Kwakkenbos et al., 2010). In addition, methods for cloning of IgG encoding genes from single B cells have been optimized (Wrammert et al., 2008; Jin et al., 2009; Ogunniyi et al., 2009; Scheid et al., 2009; Walker et al., 2009; Kwakkenbos et al., 2010). These technical and engineering accomplishments make it feasible to isolate human mAbs with broad coverage of therapeutic targets.

FORMATS OF ANTIBODY THERAPEUTICS

Most therapeutic antibodies are full length IgG molecules and IgG1 is the most commonly used sub-isotype (Table 1). This is because IgG1 molecules possess several favorable characteristics: they are structurally stable; they have a long *in vivo* half life; and IgG1 confer Fc-mediated biological effects. In designing antibody therapeutics, it is sometimes desirable to diminish or abolish the ADCC and CDC functions while retaining its pharmacokinetic profile, in the case of a “benign

blocker” antibody. For this purpose, both IgG2 and IgG4 have been used in antibody therapeutics (Table 1). Protein engineering has been applied to create Fc with altered properties. For example, IgG2m4, a novel engineered IgG isotype with reduced Fc functionality was recently reported (An et al., 2009). The engineered IgG2m4 is based on the IgG2 isotype with four key amino acid residue changes derived from IgG4 (H268Q, V309L, A330S and P331S). An IgG2m4 antibody has an overall reduction in complement and Fc γ receptor binding in *in vitro* binding analyses while maintaining the normal *in vivo* serum half-life in rhesus monkeys.

In addition to IgG molecules, antibody fragments (e.g., Fab) have also been developed as therapeutics (Sandborn et al., 2007). Relative to IgG molecules, antibody fragments have more extensive penetration of tissues (particularly of solid tumors) due to their smaller size. The smaller size of antibody fragments has the advantage of accessing therapeutically important epitopes that may be sterically hindered. In addition, antibody fragments may be manufactured more cost effectively in a microbial fermentation system. The shorter half life of antibody fragments can be extended by modifying the molecules such as through PEGylation. The absence of the Fc region in an antibody fragment may lessen side effects caused by the interaction between Fc and the immune system. ReoPro, an anti-GPIIb/IIIa chimeric Fab for the prevention of blood clots in angioplasty, was the first antibody fragment approved for clinic use in the US (Faulds and Sorokin, 1994). Lucentis, a Fab fragment of Avastin, is used for the treatment of wet age-related macular degeneration (Kenneth and Kertes, 2006). More recently, Certolizumab pegol (Cimzia), a PEGylated antibody fragment, was approved for the treatment of rheumatoid arthritis in Europe (Rutgeerts et al., 2007). Currently, about 19 antibody fragment based therapeutics are in active clinical development (Nelson and Reichert, 2009).

Other antibody formats such as domain antibodies and single chain antibodies are also being explored for diagnostic and therapeutic applications (Holt et al., 2003; Holliger and Hudson, 2005; Enever et al., 2009). A PEGylated human anti-IL-1R domain antibody is in clinical testing for the treatment of rheumatoid arthritis (Vk or VH dABs) (Enever et al., 2009). A llama nanoantibody targeting the von Willebrand factor is being developed for the treatment of thrombosis (Van Bockstaele et al., 2009).

Antibodies can also be used as carrier agents of small molecule toxins or radiolabeled isotopes, guiding drugs to specific disease sites and limiting undesired effects on healthy cells. This application is most commonly employed in oncology. At least two radiolabeled antibodies, Zevalin and Bexxar, are approved for clinical use (Table 1). These drugs are difficult to administer because a radiologist and an oncologist are needed to oversee the administration. Mylotarg, a humanized anti-CD33 IgG4 antibody conjugated to

calicheamicin, is an example of antibody used to carry a cytotoxic payload (Table 1). Many challenges still exist in designing antibody:drug conjugates such as choice of linker, stoichiometry, and conjugation chemistry. Recent advances have resulted in linkers having increased stability in the bloodstream while allowing efficient payload release within the tumor cell (Ducry and Stump, 2010). Increasing evidence suggests that conjugated antibodies remain an effective alternative to mAb, small molecule or radiolabeled isotope monotherapies.

It is interesting to note that the early antibody therapeutics started as crude polyclonals (serum therapy and IVIG) and the majority of today's antibody therapeutics is target-specific monoclonals. Progress is being made in developing recombinant polyclonal antibodies (rpAb) for the treatment or prophylaxis of human diseases (Pedersen et al., 2010). The difference is between IVIG and rpAbs is that rpAbs are mixtures of carefully selected monoclonal antibodies. Recombinant polyclonal antibodies (rpAb) mimic the natural human immune response in which the human body produces different types of antibodies targeting different epitopes of an antigen. This polyclonal response may have a better chance to neutralize the disease target than a single antibody does. One of the major challenges facing this approach is to manufacture the antibody cocktail consistently in both quantity and quality.

Today's monoclonal antibody therapeutics functions on a single disease target. It is advantageous if one antibody molecule can bind to two or more different targets since many complex diseases are the result of multiple mediators. Multispecificity has shown in naturally isolated antibodies, for example, the monoclonal IgE antibody SPE7 binds not only to its intended antigen 2,4-dinitrophenyl (DNP) hapten, but it also binds to several unrelated compounds with a broad range of affinities (James et al., 2003). More recently, antibodies that binds to both HER2 and VEGF were reported (Bostrom et al., 2009). In these cases, the multispecificity is conferred by a single binding pocket (James et al., 2003; Bostrom et al., 2009). Multispecificity antibodies are not common in nature, but they can be constructed by recombinant DNA methods (Kufer et al., 2004; Wu et al., 2007). Design of bispecific antibodies is an active research area and the anti-IL-12/IL-18 dual-variable-domain immunoglobulin DVD-Ig molecule is an example of the many designs of bispecific antibodies (Wu et al., 2007).

IMPACT OF POST-TRANSLATIONAL MODIFICATION ON THE PHYSICAL AND BIOLOGICAL PROPERTIES OF THERAPEUTIC ANTIBODIES

Antibodies are large proteins which are subjected to extensive and complex posttranslational modifications, such as deamidation, glycosylation, N-terminal pyroglutamation, C-terminal lysine truncation, and methionine oxidation; and

these posttranslational modifications profoundly impact the physical, chemical, and pharmacological properties of therapeutic antibodies (Wang et al., 2009). Oxidation of methionine residues is one of the most common protein degradation pathways including antibodies. In addition, methionine oxidation of recombinant monoclonal antibodies can alter their interaction with protein A and protein G resulting in a decrease in binding affinity (Gaza-Bulseco et al., 2008). The spontaneous nonenzymatic deamidation of glutaminyl and asparaginyl residues can alter the structure and function of therapeutic antibodies, potentially resulting in decreased bioactivity, as well as alterations in pharmacokinetics and antigenicity of antibody therapeutics (Huang et al., 2005). Among the various posttranslational processes, glycosylation has the broadest effect on biologic activity, protein conformation, stability, solubility, secretion, pharmacokinetics and immunogenicity of therapeutic antibodies (Arnold et al., 2007). For example, differential IgG sialylation may provide a switch from innate anti-inflammatory activity in the steady-state to generating adaptive pro-inflammatory effects upon antigenic challenge (Kaneko et al., 2006). Low fucose levels on antibodies enhance neutrophil- and mononuclear cell-mediated ADCC (Peipp et al., 2008). Antibody glycoengineering is one of most active areas of research in therapeutic antibody discovery and development today (Mimura et al., 2009).

MANUFACTURING

Manufacturing of mAbs is expensive. A large scale facility can take multiple years and hundreds millions of dollars to build. Mammalian cell culture is the dominant production platform for mAb therapeutics. About half of the current marketed mAbs are expressed in Chinese hamster ovary (CHO) cell lines. Recombinant myelomas or hybridomas are still being used for antibody production, but their utility as a production platform is limited due to the low expression titer and instability of the cell lines. To reduce the cost of antibody production, other methods of antibody expression, such as bacteria, plants, transgenic animals (milk), eggs, and yeast, are being developed. Certolizumab pegol is an example of mAb (fragment) therapeutic made in a bacteria (Rutgeerts et al., 2007). However, antibodies produced in *E. coli* are not glycosylated and this severely limits its use as a manufacturing platform. Antibodies with specific human N-glycan structures have been expressed in glycoengineered lines of the yeast *Pichia pastoris* and its utility as a general platform for producing recombinant antibodies with human N-glycosylation is being developed (Li et al., 2006a; Lin et al., 2010). Antibody has been expressed in engineered chicken eggs and in plants (Zhu et al., 2005; Cox et al., 2006). Despite significant effort, cost saving alternative antibody manufacturing platforms is still lacking. This is in part due to the effect of the various expression hosts on antibody posttranslational

modifications and the low production titers. There is a clear need for innovation and technology breakthroughs in reducing the manufacturing cost of therapeutic antibodies. This is not limited to the choice of expression hosts. Purification, formulation, storage, and other steps in the entire manufacturing process need to be improved to bring antibody therapeutics in a more cost competitive position against small molecule drugs.

ANTIBODY THERAPEUTIC TARGETS

Antibodies can engage a wide range of extracellular drug targets such as membrane bound proteins or circulating ligands and cytokines (Table 1). Even though antibodies do not readily cross cell membranes or the brain blood barrier (BBB), about 80% of the current druggable targets are accessible to antibodies (Strohl, 2009). Extracellular signaling (ECS) drug targets generally are not modulated by small molecules as ECS targets typically function through protein-protein interactions. ECS proteins have been successfully targeted by antibodies. The therapeutic areas in which antibodies have the strongest presence, in terms of marketed products and developmental research, are oncology and Arthritis, immune and inflammatory disorders (AIID). Of the more than 200 monoclonal antibodies in clinical use and development today, about half are being developed for oncology. The second largest therapeutic category is in the AIID area, and infectious disease is fast becoming a major disease area for antibody therapeutics. While the emphasis on oncology and AIID therapeutic areas will continue, antibody therapeutics are being developed in almost all disease areas such as central nervous system, cardiovascular, women's health, diabetes/endocrinology, hematology, ophthalmology, and respiratory diseases (Strohl, 2009).

SUMMARY

Antibody therapeutics represent a major breakthrough in combating human diseases and the improvement of human health. This is reflected by the recent trend in drug discovery and development. In 2000, nine of the top 10 medicines were small molecules while only one was a recombinant protein but by 2008, a short eight years later, half of the top 10 medicines are recombinant proteins and antibodies. This trend will continue as about 50% of the new drugs in various stages of clinical development are antibodies. Despite the remarkable progress, many scientific, technological, and clinical challenges remain in the area of therapeutic antibody discovery and development. Opportunities for innovation exist at every level: accessing difficult antibody targets (such as G protein-coupled receptors), novel antibody sources and formats, crossing the BBB and cell membranes, modified effector functions, improved formulation and delivery methods, and lower cost manufacturing, to name a few.

ABBREVIATIONS

AIID, arthritis, immune and inflammatory disorders; ADCC, antibody-dependent cellular cytotoxicity; BBB, brain blood barrier; CDC, complement-dependent cytotoxicity; CDRs, complementarity determining regions; DNP, 2,4-dinitrophenyl; ECS, extracellular signaling; FDA, Food and Drug Administration; HAMA, human anti-mouse antibody; IM, intramuscular; ISC, IgG secreting cells; IV, intravenous; IVIG, intravenous immune globulin; mAbs, mouse monoclonal antibodies; PBMC, peripheral blood mononuclear cells; rpAb, recombinant polyclonal antibodies; SC, subcutaneous; VL, variable light; VH, variable heavy

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