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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 crystalizable 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 murononab 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

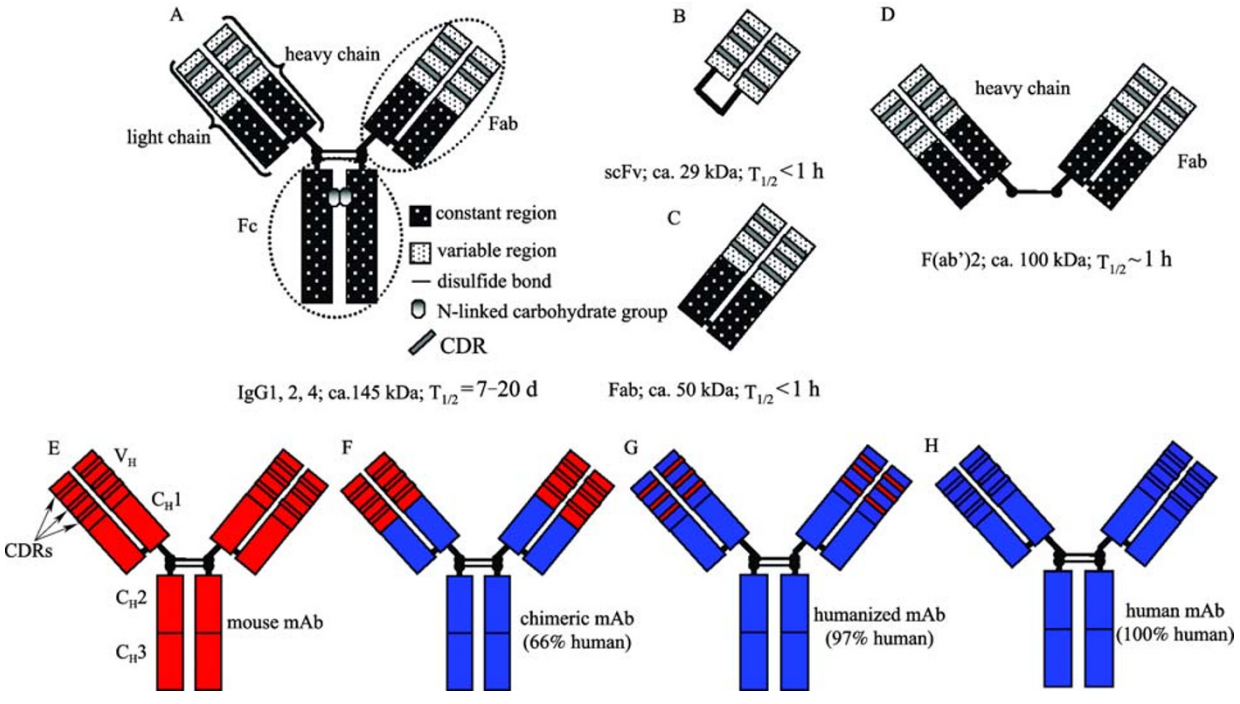

Figure 1. Diagrams of various antibody structures. (A) A generic IgG molecule. (B) A scFv fragment. (C) A Fab fragment. (D) A F(ab')2 fragment. (E) A mouse IgG molecule. (F) A murine:human chimeric IgG molecule. (G) A humanized IgG molecule. (H) A human IgG molecule.

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

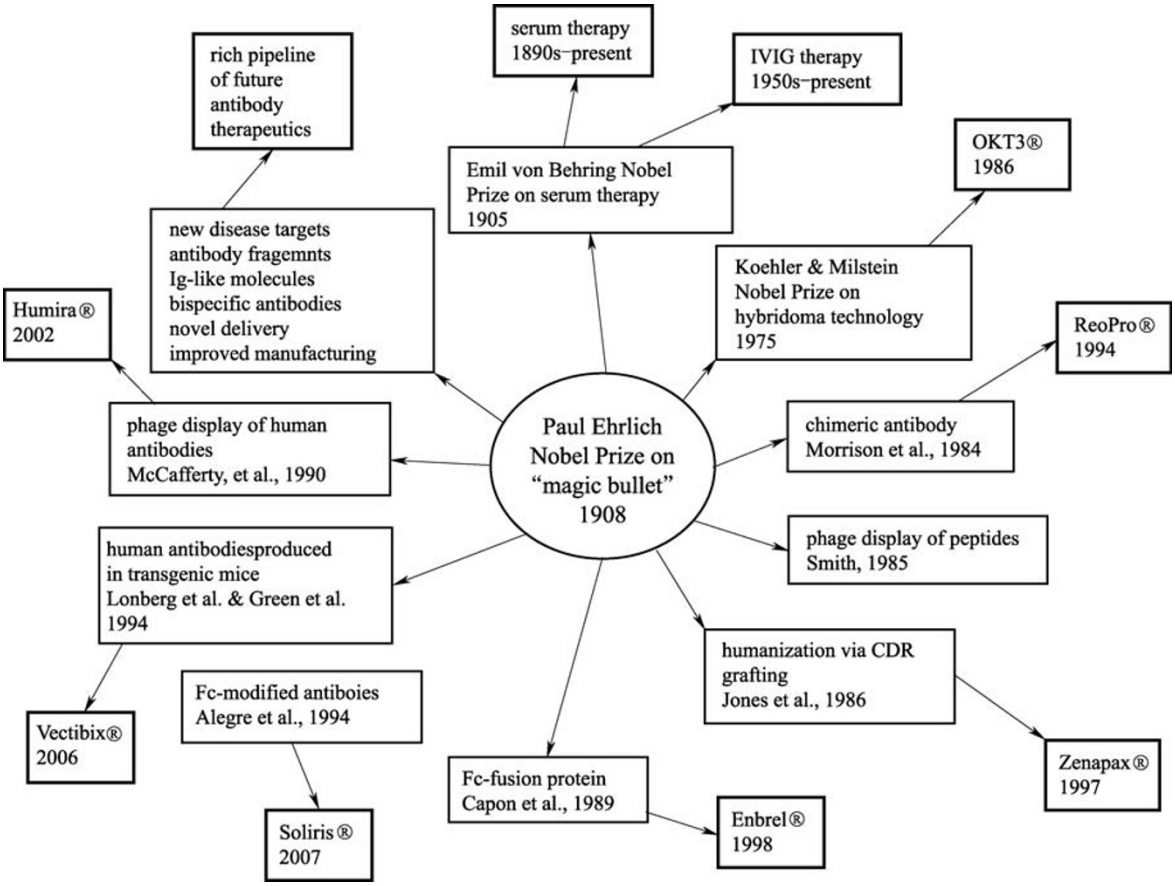

Figure 2. History of antibody therapeutics. Green boxes represent scientific and technology milestones. Blue boxes are antibody therapeutics developed as a result of the scientific and technology breakthroughs.

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 lymphoma	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/ozogamicin Mylotarg Wyeth	2000	oncology	acute myelogenous leukemia	CD33	humanized IgG4 conjugated 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 Erbitux 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

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