Evolution and Emergence of Therapeutic Monoclonal Antibodies

What Cardiologists Need to Know

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The concept of using antibodies for the treatment of disease dates back to the 1890s, when Emil Adolf von Behring discovered the ability of small doses of diphtheria or tetanus toxin to produce transferable immunity between animals via serum[1] (later attributed to the presence of antibodies). However, it was not until the early 1960s that structural characteristics of antibodies were described,[2,3] with the following decade marking the discovery of methods for producing monoclonal antibodies (mAbs), including the hybridoma technique.[4,5] In 1986, the first mAb, muromonab-CD3, was approved[5] for treating steroid-resistant acute allograft rejection in renal transplant recipients. The first fully human mAb (adalimumab) was approved for treating rheumatoid arthritis in 2002.[5] As of March 2012, the number of US Food and Drug Administration–approved, actively marketed therapeutic mAbs for use in oncology/hematology, immunomodulatory settings, and other miscellaneous conditions is approaching 30 (Table 1). Most of the recently approved biologics are fully human mAbs, and cancer and immunologic disorders continue to be the focus of investigational therapeutic mAbs[6] (estimated at >500 across various stages of development).[7]

This review provides an overview of the emergence and use of mAbs as therapeutics, including a discussion of their mechanism of action, delivery, clearance, and overall safety. Key differentiating aspects between mAbs and small-molecule therapeutics are also highlighted, along with a brief summary on the use of mAbs in the cardiology arena.

Background

Antibody Structure and Function

Antibodies, also known as immunoglobulins (Igs), are B-cell–produced molecules composed of 4 polypeptide chains (2 heavy and 2 light chains) that come together to form their characteristic Y shape (Figure 1).[8] They can circulate in soluble form or can be bound to the B-cell membrane as part of the B-cell receptor. There are 5 antibody isotypes distinguished by differences in their heavy chains: isotypes IgM, IgD, IgA, IgE, and IgG.[8] Primary antibody responses are mediated by IgM. Secreted IgM is a multivalent molecule made up of 5 or 6 full IgM antibodies, and it contributes to phagocytosis through efficient activation of the complement system. IgD is universally expressed on naive B cells. Secreted IgA is a dimer of 2 full IgA antibodies and is the primary Ig in external secretions such as saliva, tears, colostrum, and breast milk. IgE functions mainly in the lung and skin and plays a fundamental role in hypersensitivity or allergic reactions, reflecting high-affinity binding to mast cells and basophils. IgG typically functions in the secondary phase of an immune response. It is the most abundant antibody, accounting for ≈80% of antibodies in humans.[9] There are 4 IgG subclasses (IgG1–IgG4) in humans that vary in abundance in serum and in binding affinity to the crystallizable fragment (Fc) receptors on immune cells. IgG1 is the most abundant IgG subclass, followed by IgG2, IgG3, and IgG4.[8] Except for IgG3, which has an elimination half-life of ≈7 days, the IgG subtypes have elimination half-lives of ≈20 to 21 days.[9] Therefore, IgG is the most common class of Igs used as the structural basis for the production/generation of therapeutic mAbs.

Generation of Monoclonal Antibodies

Early hybridoma technology, developed by fusing immortal mouse myeloma cells and splenic B cells from hyperimmune animals, allowed the development of fully murine mAbs during the 1970s.[4] From the accumulating clinical experience with the murine anti-CD3 mAb muromonab, it was apparent that the host immune response and the poor pharmacokinetics of mouse antibodies in humans were serving as barriers to the efficacy of long-term and repeated administration.[10] Investigators then sought to develop recombinant DNA strategies that would result in more humanized, less immunogenic mAbs (Figure 2). The initial modification was a chimeric antibody in which the variable region of the antibody had mouse sequences and the remaining sequences were human, thereby reducing but not totally eliminating the risk of immunogenicity compared with mouse antibodies.[10,11] The next phase of development was designed to generate humanized mAbs by substituting rodent sequences for human sequences except for those found within the antigen-binding complementarity determining regions.[10] The first chimeric (abciximab, for percutaneous coronary intervention) and humanized (daclizumab, to prevent rejection in organ transplantation) mAbs were introduced into the US marketplace in 1994 and 1997, respectively.[5]

Initially, the production of fully human mAbs was hampered by challenges related to a lack of a stable human myeloma fusion partner and concerns about human immunization.

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Table 1. Marketed Therapeutic Monoclonal Antibodies With Food and Drug Administration–Approved Indications* (as of December 2012)

Agent	Binding Target	Mechanism of Action†	Type of Antibody	Indication(s)
Oncology				
Alemtuzumab (Campath)	CD52	ADCC, CDC	Humanized	CLL
Bevacizumab (Avastin)	VEGF	Ag	Humanized	CRC, non–small-cell lung and renal cell carcinomas, glioblastoma
Brentuximab vedotin (Adcetris)	CD30	ADC	Chimeric, with MMAE (microtubule-disrupting agent)	HL, systemic anaplastic large-cell lymphoma
Cetuximab (Erbitux)	EGFR	Ag, ADCC	Chimeric	CRC, squamous cell carcinoma of the head and neck
Ibritumomab (Zevalin)	CD20	Ag (delivery of radionuclide)	Murine, with yttrium-90 or indium-111	NHL
Ipilimumab (Yervoy)	CTLA-4	Ag	Human	Melanoma
Ofatumumab (Arzerra)	CD20	Ag, ADCC, CDC	Human	CLL
Panitumumab (Vectibix)	EGFR	Ag	Human	CRC
Pertuzumab (Perjeta)	HER2	Ag, ADCC	Humanized	Breast cancer
Rituximab (Rituxan)	CD20	Ag, ADCC, CDC	Chimeric	NHL, CLL
Tositumomab (Bexxar)	CD20	Ag (delivery of radionuclide), possibly ADCC and CDC	Murine, with iodine-131	NHL
Trastuzumab (Herceptin)	HER2	Ag, ADCC	Humanized	Breast cancer, gastric or gastroesophageal junction adenocarcinoma
Immunomodulatory settings				
Adalimumab (Humira)	TNFα	Ag, ADCC, CDC[38]	Human	RA, PsA, AS, CD, PsO, JIA
Basiliximab (Simulect)	CD25	Ag	Chimeric	Organ (kidney) transplantation rejection
Belimumab (Benlysta)	Soluble human BlyS	Ag	Human	Systemic lupus erythematosus
Canakinumab (Ilaris)	IL-1β	Ag	Human	Cryopyrin-associated periodic syndrome
Certolizumab pegol (Cimzia)	TNFα	Ag	Humanized pegylated Fab fragment	RA, CD
Golimumab (Simponi)	TNFα	Ag, ADCC, CDC[38]	Human	RA, PsA, AS
Infliximab (Remicade)	TNFα	Ag, ADCC, CDC[38]	Chimeric	RA, PsA, AS, CD, ulcerative colitis, PsO
Natalizumab (Tysabri)	α4-Integrin	Ag	Humanized	Multiple sclerosis, CD
Omalizumab (Xolair)	IgE	Ag	Humanized	Allergic asthma
Rituximab (Rituxan)	CD20	Ag, ADCC, CDC	Chimeric	RA, Wegener granulomatosis, microscopic polyangiitis
Tocilizumab (Actemra)	IL-6 receptor	Ag	Humanized	RA, systemic JIA
Ustekinumab (Stelara)	p40 Subunit of IL-12 and IL-23	Ag	Human	PsO
Cardiology				
Abciximab (ReoPro)	Glycoprotein IIb/IIIa	Ag	Chimeric Fab	Percutaneous coronary intervention
Other				
Denosumab (Prolia, Xgeva)	RANKL	Ag	Human	High fracture risk from PMO, CRPC, or aromatase inhibitor–treated breast cancer
Eculizumab (Soliris)	Complement protein C5	Ag	Humanized	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome
Palivizumab (Synagis)	RSV F protein	Ag	Humanized	RSV infection
Ranibizumab (Lucentis)	VEGF-A	Ag	Humanized	Wet age-related macular degeneration, macular edema postretinal vein occlusion
Raxibacumab (ABthrax)	Bacillus anthracis toxin	Ag	Human	Inhalation anthrax

ADC indicates antibody drug conjugate; ADCC, antibody-dependent cell cytotoxicity; Ag, antigen-mediated (direct) mechanism; AS, ankylosing spondylitis; BlyS, B-lymphocyte stimulator; CD, Crohn disease; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; Fab, antigen-binding fragment; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; IgE, immunoglobulin E; IL, interleukin; JIA, juvenile idiopathic arthritis; MMAE, monomethyl auristatin E; NHL, non-Hodgkin lymphoma; PMO, postmenopausal osteoporosis; PsA, psoriatic arthritis; PsO, plaque psoriasis; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor κ-B ligand; RSV, respiratory syncytial virus; TNFα, tumor necrosis factor-α; and VEGF, vascular endothelial growth factor.

*Not including diagnostic monoclonal antibodies or therapeutic products that had been granted approval but have since been withdrawn from the US market. Four agents—muromonab-CD3 and daclizumab (both for commercial reasons), efalizumab (for safety concerns), and gemtuzumab ozogamicin (for safety concerns and futility in prolonging survival in a confirmatory trial in acute myeloid leukemia)—were withdrawn from the US marketplace in 2008.

†Mechanisms of action listed in this table are the primary mechanism of action based on the manufacturers' product monographs or on additional information when noted.

Generation of fully human therapeutic mAbs was made possible by the development of phage-display platforms and, more recently, by transgenic mouse platforms.[12,13] Adalimumab, the first fully human anti–tumor necrosis factor-α mAb to reach the US marketplace, was developed with the use of phage display.[14] Several recently approved mAbs, including panitumumab (for the treatment of colorectal cancer) and ipilimumab (for the treatment of metastatic melanoma), were produced by use of XenoMouse or UltiMAb transgenic mouse technology, respectively (Figure 3).[15,16]

Therapeutic Monoclonal Antibodies

Mechanisms of Action

Antibodies mediate their actions by various types of direct or indirect effects. Direct effects may be conferred by binding with cell surface receptors, membrane-bound (or associated) proteins, growth factors, or circulating proteins. By binding to the antigen (target), antibodies can modulate cells.[17] Most therapeutic mAbs use the variable regions to produce a direct effect on target biology (Table 1).

In addition to the biological activity provided through the variable region binding directly to the specific antigen, some antibodies have a mechanism of action that is indirectly mediated through the Fc region of the antibody.[17] Indirect antibody effects occur when antibodies bind to the targeted cells and stimulate the recruitment of effector cells with the capacity for antibody-dependent cellular cytotoxicity or phagocytosis such as natural killer cells and monocytes/macrophages, respectively.[17,18] For trastuzumab and rituximab, which act via both direct and indirect pathways, there is clinical evidence to support that the Fc-mediated effector activity is functional in vivo.[19,20] A second indirect method by which antibodies may promote cell death is complement-dependent cytotoxicity, in which antibody binding to the target cell results in activation of the complement cascade. The degree to which a mAb is able to mediate antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity depends on its IgG subclass.[18] Indirect antibody effects can also be mediated through the conjugation of mAbs to drugs, toxins, radioisotopes, or cytokines (known as immunoconjugation) and permit the specialized delivery of therapeutic or diagnostic agents.[18] For example, brentuximab vedotin, an anti-CD30 antibody conjugated to the microtubule inhibitor monomethyl auristatin E, causes apoptosis in CD30-expressing target cells.[21]

Delivery and Biodistribution

Therapeutic mAbs are administered parenterally by intravenous, subcutaneous, or intramuscular routes.[22] The

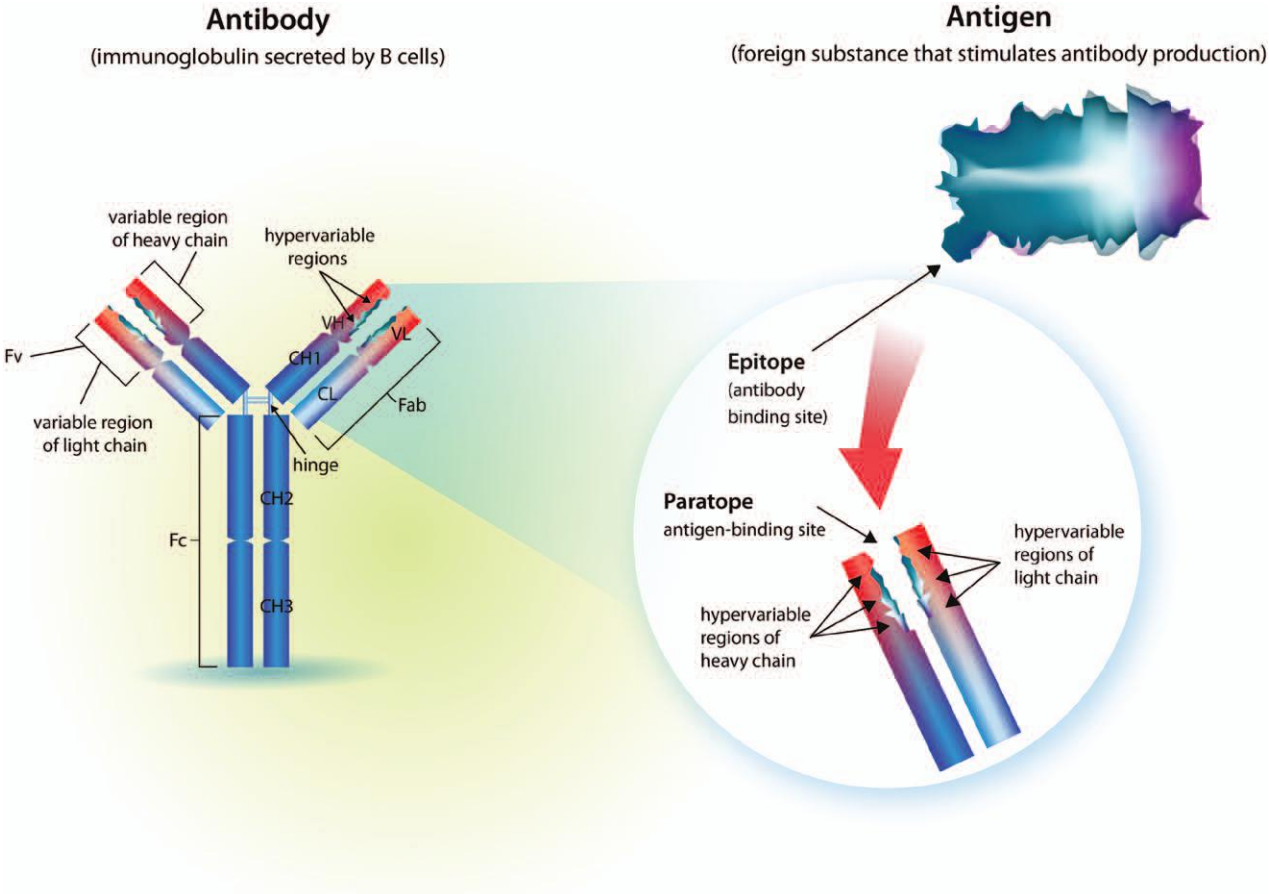

Figure 1. Antibody structure. The hypervariable regions (VH and VL) of the antigen-binding fragment (Fab) region of the antibody specifically bind an antigen. The crystallizable fragment (Fc) region of the antibody is responsible for effector function by binding the Fc receptors on effector cells, linking the humoral (antibody) response to a cellular response. CH indicates heavy chain, constant domain; CL, light chain, constant domain; Fv, variable fragment; VH, heavy chain, variable domain; and VL, light chain, variable domain.

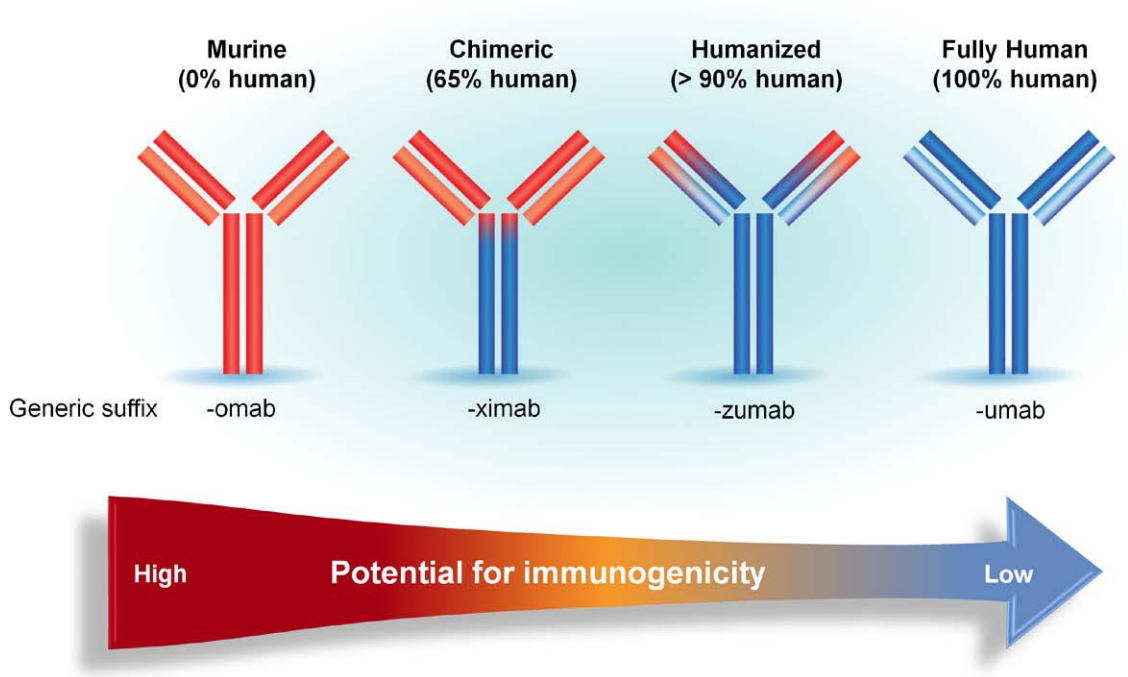

Figure 2. Humanization of therapeutic antibodies has reduced their immunogenicity.

intravenous route is the most common for mAbs to date and is advantageous with respect to the speed of systemic delivery, complete bioavailability, and ability to deliver high volumes. It has shortcomings, however, related to convenience, cost, and a potential for triggering infusion reactions. These limitations have fueled interest in administration via extravascular routes, mostly in subcutaneous and intramuscular delivery.[22] These methods have lower bioavailability (24%–95%)[23] but provide the advantages of self-administration in the home setting and lower rates of adverse events related to drug infusion. Whereas therapeutic antibodies can access most tissues in the body, although at varying degrees, they do not passively cross the blood-brain barrier to penetrate the central nervous system.[24]

Elimination Mechanisms

There are 2 primary ways that mAbs are eliminated from the circulation: antigen-specific target-mediated disposition and nonspecific elimination via phagocytic cells and endothelial cells of the reticuloendothelial system.[25] Target-mediated disposition is the process by which antibodies bind antigens and are subsequently cleared via endocytosis and lysosomal degradation.[25] Because the target-mediated clearance mechanism is dependent on antigen binding, which is primarily membrane bound, the process is saturable and thus nonlinear.[25] The reticuloendothelial system clears both antigen-bound and free mAbs, is not saturable, and thus is linear. Depending on the antibody and its target, these 2 clearance mechanisms occur in parallel.[25] The liver and kidneys are not thought to play significant roles in the metabolism or excretion of mAbs except under pathological conditions that lead to disruption or injury to the endothelial lining of the glomeruli (eg, glomerulonephritis).

Research efforts over 5 decades have characterized the key role of the Fc receptor of the neonate in the absorption, tissue distribution, and elimination of IgG.[22,24] Fc receptor of the neonate is believed to rescue IgG from the endosome, thereby reducing the rate of metabolism and elimination via the reticuloendothelial system. Fc receptor of the neonate is expressed on phagocytic and endothelial cells and limits clearance by recycling the antibody from the endosome back to the serum via pH-dependent binding.[22] Accordingly, from a therapeutic standpoint, the short half-life of murine mAbs is a reflection of the low affinity that human Fc receptors of the neonate have for murine IgG.[22,26]

Safety Considerations

Depending on the antibody characteristics and its biological target, mAbs carry the risk of immune reactions and adverse effects. There are 2 general classes of potential toxicities associated with mAb therapy: target-related toxicity and modality-related toxicity.[27] Target-related toxicities are mechanism based, resulting from mAb-antigen binding that is specific for the mAb therapies directed against that particular target. For example, anti–tumor necrosis factor-α mAbs that are used to treat inflammatory conditions may induce immunosuppression and lead to infections as a consequence of inhibiting tumor necrosis factor-α (an innate mediator of the immune response).[28,29] Toxicities may also arise from mAb interactions with the target antigen on tissues other than the intended target. For example, dermatologic toxicities such as skin rash, pruritus, and erythema are characteristic of the inhibition of epidermal growth factor receptor on epithelial cells in the skin by the anti–epidermal growth factor receptor mAbs cetuximab and panitumumab, which reflects the wide expression of epidermal growth factor receptor on these cells in addition to the intended expression of epidermal growth factor receptor on the tumor cell target.[27,30–32]

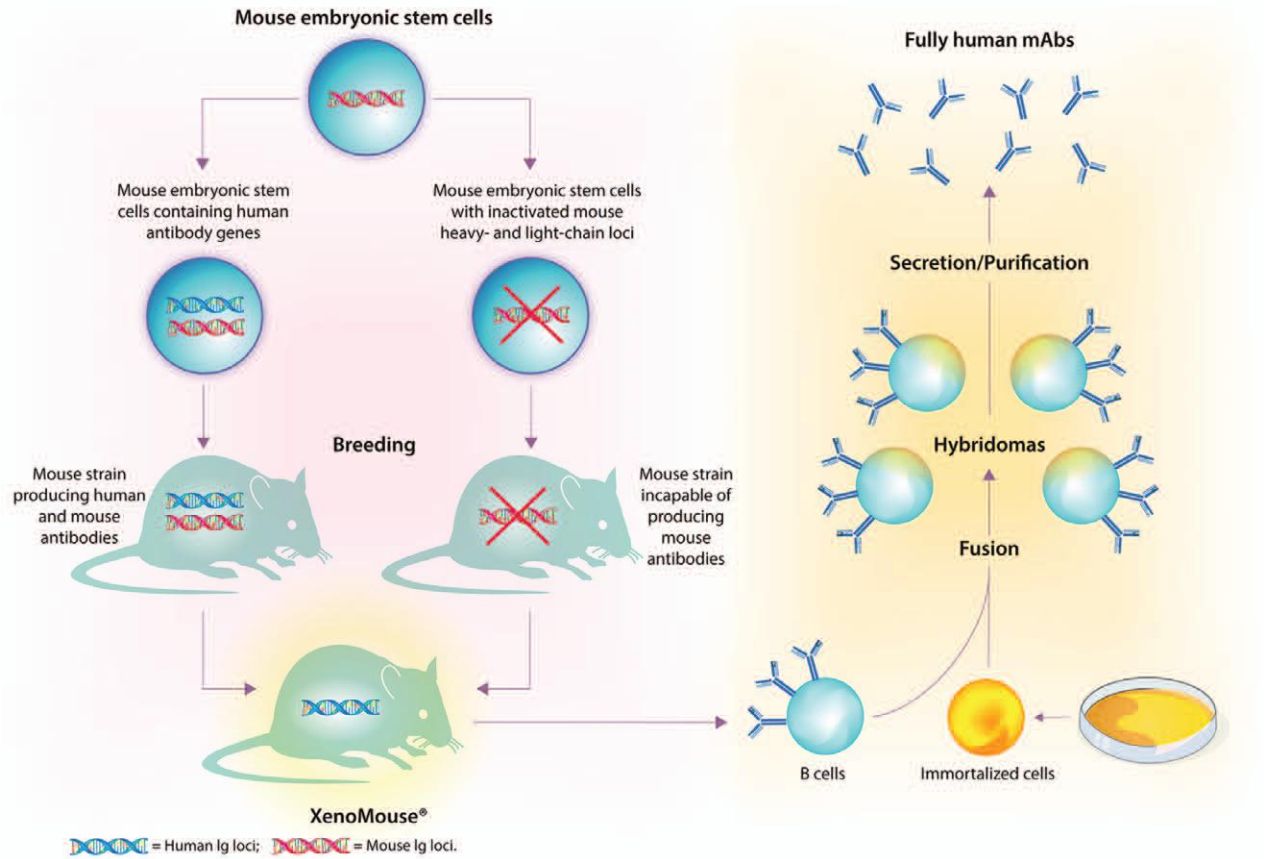

Figure 3. Making human monoclonal antibodies (mAbs): XenoMouse Hybridoma Technology. Initially, endogenous mouse immunoglobulin (Ig; heavy and light chain) gene loci were functionally inactivated in embryonic stem (ES) cells by gene-targeted deletion and used to generate mice homozygous for the necessary deletions. Crossbreeding of these mice resulted in mice homozygous for these deletions, rendering them incapable of producing mouse immunoglobulin. Then, yeast artificial chromosomes containing either human heavy- or light-chain DNA were introduced into ES cells. Crossbreeding of the mice derived from these ES cells resulted in transgenic mice producing both human and mouse antibodies. The mice incapable of producing mouse immunoglobulin were crossbred with the transgenic mice (containing both human and mouse antibodies), resulting in the XenoMouse strain that expresses fully human antibodies and is unable to produce mouse antibodies. Antibody-producing B cells, isolated from the spleen of an immunized XenoMouse, are used to produce hybridomas, wherein the B cells are fused with an immortal cell line. Finally, fully human mAbs are produced through the use of hybridoma technology. Results of this technology are favorable from a supply standpoint because each hybridoma can produce large quantities of identical fully human antibodies that can be cultured indefinitely and screened to identify antibodies of desired specificity, affinity, and target activity.[15,16]

Modality-related toxicities are target-independent and can occur acutely at the time of injection, or can develop through the prolonged treatment with the antibody. Target-independent, modality-related toxicities include various types of acute immune reactions such as rare events of hypersensitivity reactions or cytokine-release syndrome and more common events such as infusion-related reactions and injection-site reactions.[30,33] Infusion reactions can arise because of the mAb or its formulation (eg, excipients); can manifest as fever, nausea, chills, and hypotension, among other symptoms; and are the result of cytokine release. They may be difficult to distinguish from type I hypersensitivity reactions, which typically occur at mAb re-exposure.[34] For mAbs administered via the subcutaneous route, pruritus, erythema, induration, and swelling are relatively common injection-site manifestations that typically appear within minutes to 2 days of administration and are mostly benign and self-limiting with continued therapy.[35]

In contrast to the more acute types of modality-related reactions discussed in the previous paragraph, immunogenicity represents a delayed hypersensitivity that occurs in a longer time frame that can have an impact on the therapeutic efficacy of the mAb. The development of human antibodies against murine or chimeric mAbs, also referred to as an anti-antibody response, was one of the most important therapeutic limitations of early mAb therapy. As with any drug class, development of an immune response against a therapy can affect its efficacy and safety; mAbs are no different. Anti-antibody responses have been implicated in reduced target binding and therapeutic effect, altered clearance and pharmacokinetics, and infusion reactions of various degrees of severity.[10,12,36] Consequently, in a clinical trial setting, patient samples are evaluated for the presence of neutralizing antibodies to the therapeutic mAb that may be associated with loss of efficacy or adverse events and nonneutralizing antibodies that may affect the biodistribution and elimination of the therapeutic mAb.

Over time, the gradual replacement of murine protein sequence content in mAbs with human sequence content (ultimately leading to the generation and use of fully human

Table 2. Comparison of Small-Molecule and Monoclonal Antibody Therapeutics

	Small Molecule	Monoclonal Antibody
Size, kDa	≈0.5	≈150
Structure	Chemical entity	Immunoglobulin
Method of production	Controlled chemical synthesis; easily controlled	Purification from cell culture media; more complex
Target	Intracellular or extracellular	Extracellular
Target specificity	Low(er)	High
Metabolism	Hepatic/renal	RES, target-mediated disposition
Administration	Oral	Parenteral
Dosing	Approximately daily	Approximately Q2W–Q4W
Can cross blood-brain barrier	Potentially	No

Q2W indicates every 2 weeks; Q4W, every 4 weeks; and RES, reticuloendothelial system.

mAbs, which were developed in part to further reduce immunogenicity) has resulted in a lower propensity of mAb-associated anti-antibody responses.[36] In a literature review focused on the incidences of anti-antibody responses with various types of mAbs, marked reactions were associated with 84% of murine products (human anti-mouse antibody reactions) and 40% of chimeric products (human anti-chimeric antibody reactions) but only with 9% of humanized products (human anti-humanized antibody reactions).[36] Extrinsic factors also contribute to the development of immune responses such as aggregate formation, adjuvant-like contaminants, administration protocol, comedication, and even the treated disorder.[34] Overall, immune responses are considerably reduced with the use of fully human mAbs; however, there is always a risk of developing anti-antibody responses, even with fully human mAbs.

Monoclonal Antibodies Versus Small-Molecule Therapeutics

Therapeutic mAbs provide a novel approach to the treatment of disease. The success of this approach is attributed, at least in part, to the high specificity with which they bind to target antigens.[17] This feature has important implications for the development of large-molecule drugs for use in cardiology. In addition, because binding is restricted to the extracellular domain of transmembrane proteins or circulating proteins, mAbs are unlikely to affect human ether-a-go-go–related gene activity and to impact ECG parameters, unlike small-molecule therapeutics (Table 2).[17,26,37,38] Because mAbs do not undergo hepatic or renal metabolism, they also have a lower propensity for drug interactions.[7,17,39,40] Finally, the steps needed for the production, purification, and evaluation of mAbs are distinctly different from those necessary for chemically produced small-molecule pharmaceuticals.[41] Whereas reproducible standards are available to facilitate the manufacturing of small molecules, the production of mAbs is complicated by the inherent heterogeneity in their composition and other challenges, including those related to host cell contaminants and identification of the optimal cell line and growth conditions.[41] Improvements in technologies have enabled a fuller understanding of manufacturing processes and their impact on product quality and attributes, as well as the knowledge of how to control the process and product attributes.[42]

Clinical Update in Cardiology

Historically, major arenas for the development and clinical use of mAbs have been in the oncology, hematology, rheumatology, and immunomodulatory settings (Table 1). Monoclonal antibodies that are approved by the Food and Drug Administration for therapeutic use in cardiology include the aforementioned fully murine muromonab-CD3, the chimeric anti-glycoprotein IIb/IIIa antigen-binding fragment (Fab) abciximab (for percutaneous coronary intervention), and the sheep polyclonal digoxin immune Fab (for digoxin toxicity). Several early clinical trials of the murine anti-CD3 mAb muromonab in which small numbers of heart transplant recipients were treated with steroid-resistant acute rejection demonstrated notably high response rates.[43] However, as mentioned previously, there were shortcomings with respect to the development of anti-drug antibodies, cytokine release syndrome, hypersensitivity reactions, infections, and other adverse events associated with muromonab.[44] This fueled the search for alternatives with improved safety profiles to address these limitations. In the setting of induction (rather than rescue of acute rejection), recent results of a randomized trial of muromonab versus the chimeric anti-CD25 mAb basiliximab and retrospective analyses examining muromonab versus basiliximab in heart transplantation recipients suggest that targeting CD25, a component of the interleukin-2 receptor on activated T and B cells, confers similar antirejection efficacy but with lower complication rates.[45,46]

In recent years, clinical evaluation of mAbs for cardiovascular indications has intensified outside the area of heart transplantation, including the prevention of thrombosis and treatment of hypercholesterolemia, as discussed below. Abciximab, which binds glycoprotein IIb/IIIa and prevents platelet adhesion to fibrinogen and corresponding platelet aggregation, significantly reduces the short-term reinfarction rate and mortality when used as adjunctive therapy for ST-segment–elevation myocardial infarction.[47] Recent prospective clinical trial data have also emerged to suggest additional benefits for intracoronary bolus administration or in-ambulance use of abciximab.[48,49] Data from a meta-analysis suggest that abciximab and small-molecule and peptide-based glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide, respectively) provide similar benefits in primary percutaneous coronary intervention in terms of postprocedural flow grade, ST-segment resolution, mortality, and early reinfarction.[50]

Table 3. Efficacy of Fully Human Anti-PCSK9 Monoclonal Antibodies on LDL-C in Phase 2 Trials

	AMG145				REGN727/SAR236553		
	Monotherapy (MENDEL)[57]	Combination Therapy (LAPLACE)[58]	HeFH (RUTHERFORD)[59]	Statin Intolerant (GAUSS)[60]	Combination Therapy[64]	Combination Therapy[61]	HeFH[63]
Patient population	LDL-C ≥2.6 and <4.9 mmol/L (≥100 and <190 mg/dL)	LDL-C ≥2.2 mmol/L (≥85 mg/dL)	HeFH LDL-C ≥2.6 mmol/L (≥100 mg/dL)	Statin intolerance, LDL-C ≥100 mg/dL	LDL-C ≥2.6 mmol/L (≥100 mg/dL)	LDL-C ≥2.6 mmol/L (≥100 mg/dL)	HeFH or non-FH, LDL-C ≥2.6 mmol/L (≥100 mg/dL)
Background therapy	None	Statin±EZE	Statin±EZE	No or low-dose statin±EZE	ATV	ATV	Statin±EZE
Patients, n	406	631	167	160	92	183	77
Mean LDL-C change vs baseline at 12 wk, %							
Treatment	−39 to −51	−42 to −66*	−43 to −55	−41 to −63	−66 to −73†	−40 to −72	−29 to −68
Placebo/ control	−3.7 to +4.5	NA	+1.1	−14.8	−17.3†	−5.1	−10.7

ATV indicates atorvastatin; EZE, ezetimibe; GAUSS, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects; HeFH, heterozygous familial hypercholesterolemia; LAPLACE, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; LDL-C, low-density lipoprotein cholesterol; MENDEL, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels; NA, not available; and RUTHERFORD, Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder.

*Mean change vs placebo.

†Results at 8 weeks.

The development and use of mAbs for treating hypercholesterolemia is based on the role of the proprotein convertase subtilisin/kexin type 9 (PCSK9) in cholesterol metabolism as a mediator of hepatic low-density lipoprotein receptor degradation.[51–55] Available short-term phase 2 clinical trial data for 2 fully human anti-PCSK9 mAbs, AMG145 and REGN727/SAR236553, showed that these agents produced dose-dependent reductions in low-density lipoprotein cholesterol in diverse patient populations (Table 3), were generally well tolerated, and have no identified severe or serious safety issues.[56–64] A humanized anti-PCSK9 mAb, RN316, showed reductions in low-density lipoprotein cholesterol levels ranging from 33% to 84% relative to baseline in patients with hypercholesterolemia in single-dose phase 1 studies[65] and up to 66% relative to baseline in a multiple-dose phase 1 study.[66] Another mAb directed against PCSK9, MPSK3169A/RG7652, is undergoing evaluation in a phase 2 study in patients with coronary heart disease or a high risk of coronary heart disease[67]; however, no data are currently available for this agent.

An additional group of antibody therapeutics has recently emerged to address inflammation in cardiovascular diseases. Studies indicate that the proinflammatory cytokine interleukin-1 plays an important role in atherosclerosis and atherothrombosis.[68] Interleukin-1β levels are elevated in the coronary arteries of patients with coronary atherosclerosis relative to coronary arteries from patients with nonischemic cardiomyopathy[69] and in patients with acute coronary syndrome.[70,71] Therefore, interleukin-1β inhibition is being evaluated as a possible method to reduce cardiovascular risk. Three anti–interleukin-1β antibodies have entered into clinical trials, with canakinumab being tested in myocardial infarction, stroke, and cardiovascular death in patients with increased C-reactive protein levels[72]; gevokizumab being tested for acute coronary syndrome[73]; and LY-2189102 being tested for an as-yet unspecified cardiovascular disease.[74] To test the role of infiltrating lymphocytes in saphenous vein graft disease, a P-selectin antibody, RO4905417, is currently being examined in a clinical trial in patients undergoing coronary artery bypass surgery.[75] A third approach, to block inflammation induced by oxidized low-density lipoprotein using RG7418 (BI-204), recently failed to reduce inflammation markers in a phase 2 trial of atherosclerotic patients.[76]

Summary

Monoclonal antibodies are among the fastest-growing therapeutics and are being developed for a broad range of indications, from cancer to infectious diseases to cardiovascular diseases, including hypercholesterolemia. They provide novel opportunities for the treatment of human diseases in that they offer (in contrast to small-molecule drugs) high target specificity, do not undergo hepatic or renal metabolism, and allow less frequent, albeit parenteral, administration. From a safety perspective, mAbs in development today have been engineered to reduce the risk of target-related and modality-related adverse effects. Evolution of the mAb field has facilitated the transition from murine and chimeric mAbs to humanized and, most recently, fully human mAbs in an effort to reduce the risk of immunogenicity. Fully human mAbs directed against interleukin-1β and PCSK9 are under active investigation in

the cardiovascular field. Given the considerable burden of cardiovascular disease in industrialized countries, results from ongoing studies will add to current evidence for the use of mAbs in cardiology applications.

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Disclosures

Drs Foltz, Karow, and Wasserman are employees and stockholders of Amgen Inc.

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