Overview of therapeutic monoclonal antibodies

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INTRODUCTION — Immunoglobulin molecules (antibodies) are multifunctional components of the immune system. Antibodies facilitate numerous cellular and humoral reactions to a variety of antigens, including those of the host (self) and foreign substances.

Most antibodies produced as part of the normal immune response are polyclonal, meaning that they are produced by a number of distinct B lymphocytes, and, as a result, they each have a slightly different specificity for the target antigen (eg, by binding different epitopes or binding the same epitope with different affinities). However, it is possible to produce large quantities of an antibody from a single B-cell clone.

Since 1985, approximately 100 independent monoclonal antibodies (mAbs) have been designated as drugs. Available mAbs are directed against a large number of antigens and used for the treatment of immunologic diseases, reversal of drug effects, and cancer therapy. The World Health Organization (WHO), which is responsible for therapeutic mAb nomenclature, reported in 2017 that over 500 mAb names have been provided. (See 'Naming convention for therapeutic mAbs' below.)

This topic will provide an overview of therapeutic mAbs, including their mechanisms of action, production, modifications, nomenclature, administration, and adverse effects.

Separate topic reviews discuss clinical uses of polyclonal antibodies, including subcutaneous, intramuscular, and intravenous immune globulin products (SCIG, IMIG, and IVIG, respectively):

- **SCIG and IMIG** – (see "Subcutaneous and intramuscular immune globulin therapy" and "Immune globulin therapy in primary immunodeficiency")
- **IVIG** – (see "Overview of intravenous immune globulin (IVIG) therapy" and "Intravenous immune globulin: Adverse effects")

Separate reviews also discuss the basic principles of antibody genetics, immunoglobulin structure, and cellular and humoral immunity. (See "Structure of immunoglobulins" and "Immunoglobulin genetics" and "The humoral immune response" and "The adaptive cellular immune response".)

NAMING CONVENTION FOR THERAPEUTIC mAbs — A uniform naming convention for mAbs has been developed to facilitate global recognition of a unique name for each product. The name of the mAb specifies certain features such as proposed target, original host, modifications, and conjugation to other molecules. Naming rules from the International Nonproprietary Name (INN) expert group of the World Health Organization (WHO) were originally published in 1995 and have been updated periodically [1,2].

INN documents from the WHO published in 2014 and 2017 describe the classification for mAb names [1,3]. The mAb names consist of a prefix, two substems (reduced to one substem in the 2017 document), and a suffix (table 1).

- The prefix is referred to as "random"; it is intended to provide a unique, distinct drug name.
- The substems (also called "infixes") designate the target (eg, "ci" for cardiovascular, "so" for bone, "tu" for tumor) and the source (host) in which the antibody was originally produced (eg, "u" for human, "o" for mouse), as well as modifications (eg, "-xi-" for chimeric, "-zu-" for humanized). The second substem (which specifies the source of the antibody and whether it is humanized or chimeric) was eliminated in 2017 [3]. This change only applies to mAb names created after mid-2017; names created before that time will not be altered.

- The suffix for all mAbs is "mab." There are rare exceptions such as a few of the earliest mAb products that were produced before the "mab" stem was established in 1990 (eg, muromonab-CD3 [OKT3], digoxin immune Fab).

The rationale for eliminating the second substem that specifies the host included several concerns, such as the large number of antibody names being created, the use of the species information as a marketing tool despite lack of scientific support for true clinically important differences, and conceptual ambiguities that led to confusion, especially related to chimeric and humanized antibodies [3-5]. Thus, mAbs named after mid-2017 may have longer prefixes and shorter substems.

PRODUCTION METHODS AND SPECIAL MODIFICATIONS — mAbs are homogenous preparations of antibodies (or fragments of antibodies) in which every antibody in the product is identical in its protein sequence, and thus every antibody is expected to have the same antigen recognition site, affinity, biologic interactions, and downstream biologic effects. This distinguishes mAbs from polyclonal antibodies, which are heterogenous in protein sequence and recognize heterogeneous epitopes on an antigen.

Additional methods are used to modify and mass produce the mAb that is ultimately administered to patients as a medical therapy, as discussed in the following sections.

Initial antibody selection — A key to an effective mAb is the quality of the interaction between its hypervariable region (also called the complementarity-determining region [CDR]) and the target antigen. The choice of target antigen is usually based on the scientific understanding of disease mechanism and/or observation of disease-specific antibody effects in preclinical models or individual patients.

Also key to clinical efficacy and low toxicity are the downstream effects of antibody-antigen binding. These effects can be reduced by using antibodies that lack certain epitopes from foreign (eg, nonhuman) species, although immunogenicity of the mAb is complex (ie, it is not simply a matter of the number of amino acid residues).

Several approaches are used for the creation of antibodies that react with the desired target:

- **Immunize an animal** – An animal (typically a mouse or rat) may be immunized with the target antigen. This was the most popular (and the only technically feasible) method in the early days of mAb production. Candidate B cells for producing a therapeutic mAb with specificity for the target are obtained by harvesting spleen cells from the animal. An example of an mAb created by this method is muromonab-CD3 (Orthoclone OKT3).

  A serious risk with this approach is that some individuals exposed to mouse antibodies develop an immune response to the mouse antibody sequence. Once an individual develops a human-anti-mouse antibody, they generally cannot receive additional doses of the original mAb or other therapeutic mAbs with a similar murine sequence [6,7]. Thus, approaches were developed to engineer changes to the immunoglobulin molecule such as humanizing the antibody or creating a chimeric antibody; these are used in the majority of mAbs initially selected in animals. Mice have been engineered with human immunoglobulin loci in place of the endogenous mouse sequences, thus generating human antibodies in mice. (See 'Modifications' below.)

- **Obtain an existing antibody** – An existing antibody against a target antigen can be isolated from a patient. This method is especially applicable to cancer therapeutics because removal of a tumor and/or regional lymph nodes is often used in routine treatment. These tissues can be used to harvest tumor-infiltrating lymphocytes. Existing antibodies can also be isolated from peripheral blood, bone marrow, or other lymphoid tissues such as the spleen or tonsils [8]. Examples of this method include various investigational mAbs against viruses such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [9].

- **Screen a library** – A library of antibodies (constructed using molecular techniques or purchased) can be screened in vitro for binding to a target antigen. Libraries vary widely in their size and diversity. They can be generated using phage display or other combinatorial methods. With a phage display library, a large collection of sequences can be introduced into bacteriophage (a virus that infects bacteria) in a stoichiometry such that each bacteriophage clone produces a single antibody or antibody fragment [10]. The size and diversity of the library can be adjusted by the investigator. Larger more diverse libraries are more likely to produce a therapeutic mAb or an mAb fragment that has the highest affinity and specificity for the target antigen. Examples of therapeutic mAbs that were derived from a phage display library include adalimumab, raxibacumab, and belimumab [10].

Once an mAb with a desired specificity has been obtained, it must be produced in large quantities for therapeutic use. The earliest production technology was to create a hybridoma (a cell-cell fusion) in which the antibody-producing cell is fused with a partner cell that has been immortalized. The partner usually used is a myeloma cell (a malignant B cell) that will

proliferate indefinitely in culture. For mAb production from a hybridoma, the myeloma cell line must be nonsecreting; otherwise, the hybridoma would also produce the antibodies from the myeloma cell line.

Once candidate hybridomas have been created, they must be screened for immortalization and antibody production. Screening for immortalization can be done using a method that takes advantage of a specialized growth medium (figure 1). In this method, the nonsecreting myeloma cell line has a defect in the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), which permits a cell to use xanthine and guanine as nucleotide precursors rather than synthesizing them de novo [11]. A cell with this enzyme defect will survive unless it is cultured in the presence of an inhibitor of de novo nucleotide synthesis such as aminopterin, which will render it unable to make any purine nucleotides. When the candidate hybridoma cell lines are cultured in the presence of aminopterin, only the lines that have successfully fused and contain HGPRT from the fusion partner will survive because they can use hypoxanthine to make purine nucleotides. Thymidine is also added to the culture medium since its synthesis is inhibited by aminopterin. This selection medium is referred to as HAT medium (hypoxanthine, aminopterin, thymidine). Screening for antibody production can be done using an immunoassay on the cell supernatant for binding to the target antigen.

Other methods have been developed for immortalization such as transfection with an immortalizing virus or production in an immortal cell culture line such as Chinese hamster ovary (CHO) cells [8].

Mass production — Once a source of the desired mAb (hybridoma, cell line, or other system) has been established, production must be scaled up to accommodate clinical use. A requirement for several grams of mAb per patient is not unusual. mAbs are large multimeric proteins (typical molecular weight, approximately 150 kilodaltons [kD]), and their proper functioning requires a number of post-translational modifications, including glycosylation and formation of disulfide bonds [8]. Thus, a eukaryotic production system that carries out normal eukaryotic post-translational modifications is used.

The major method of mAb production is using cultured cells such as CHO cells [6]. Alternative eukaryotic cell lines for mAb production are under consideration, such as yeast, which grow faster than mammalian cells [6]. Quality controls and purification steps are used to ensure a homogenous product with defined potency that is free of endotoxin and/or host cell proteins. Potency is assayed using an immunoassay or a cell-based assay.

Modifications

Fab fragments and single-chain antibodies — The use of antibody fragments instead of full-length antibodies may enhance pharmacokinetic properties and/or the efficiency of penetration into tissues or tumor masses (since fragments are smaller) [10]. Fragments typically have a single valence (binding site) for the antigen, rather than two valences that are characteristic of full-length antibodies. The following types of antibody fragments have been created, typically using molecular biology techniques in the laboratory:

- **Fragment antigen binding (Fab)** – Also called Fab fragments, these consist of a variable domain and the first constant region each of heavy and light chain
- **Single-chain variable fragment (scFv)** – An scFv consists of a light chain and heavy chain variable region joined by a linker peptide
- **Single-domain antibody (sdAb)** – An sdAb is an antibody fragment consisting of a light chain variable region or heavy chain variable region

A popular method for producing these fragments is use of a phage display library that can be used to screen large collections of potential antibody fragments for their binding to the antigen and other desired properties [10]. (See 'Initial antibody selection' above.)

Fab fragments lack the Fc component of the antibody (the remainder of the heavy chain) and thus are not capable of interacting with Fc receptors or activating complement. Thus, alone, they typically are not appropriate for indications that depend on cell killing. Examples of clinical applications include the following:

- Ranibizumab is a recombinant humanized mAb Fab fragment that binds to and inhibits human vascular endothelial growth factor A (VEGF-A). Ranibizumab inhibits the binding of VEGF to its receptors and thereby suppresses neovascularization and slows vision loss. This agent is used in the treatment of some forms of age-related macular degeneration. (See "Age-related macular degeneration: Treatment and prevention", section on 'Ranibizumab'.)
- Abciximab is a Fab antibody fragment derived from a chimeric human-murine mAb (7E3) that binds to platelet IIb/IIIa receptors, resulting in steric hindrance and thus inhibition of platelet aggregation. Abciximab is used in unstable

angina and reduction of thrombosis in various coronary stenting procedures. (See "Early trials of platelet glycoprotein IIb/IIIa receptor inhibitors in coronary heart disease", section on 'Abciximab'.)

Humanized and chimeric mAbs — mAbs originally derived from a nonhuman species (eg, mouse, rat) can be "humanized" to various degrees by engineering amino acid substitutions that make them more similar to the human sequence. This is done using recombinant DNA technologies.

In principle, the more similar an mAb is to human-derived sequences shared among many individuals, the less likely it is to elicit an immune reaction against the mAb. Potential adverse effects of immunogenicity include infusion reactions and reduced efficacy, although these are not easily predicted. (See 'Infusion reactions' below and 'Resistance' below.)

However, not all amino acid residues or groups of residues are similar in their immunogenicity. Further, it has become increasingly challenging to clarify what constitutes a chimeric antibody versus what constitutes a humanized antibody (eg, how many amino acid residues need to be changed for an antibody to qualify as humanized), and definitions have evolved over time [5]. In general, humanized mAbs contain segments from nonhuman sources in the complementarity-determining region (CDR) interspersed among human-derived segments in the constant regions of the immunoglobulin heavy and light chains. Chimeric antibodies are generally those in which the Fc part of the immunoglobulin molecule (but not the CDR) is of a human sequence. In general, chimeric mAbs and humanized antibodies contain >65 and >90 percent human sequence, respectively. In addition, several technologies exist to generate fully humanized antibodies for therapeutic use.

Prior to mid-2017, an mAb that had been humanized was designated by inclusion of the stem "zu" in its name (eg, trastu**zu**mab), and chimeric mAbs were designated as chimeric by the addition of "xi" (eg, ritu**xi**mab). However, as noted above, ongoing issues with accurately classifying an mAb as humanized or chimeric and the potential for these designations to be used as a marketing tool in the absence of scientific support for reduced immunogenicity of the nonhuman components have led to the decision that antibodies named after mid-2017 will not contain the "zu" and "xi" stems in their generic names. (See 'Naming convention for therapeutic mAbs' above.)

Bifunctional antibodies — Bifunctional antibodies (also called "bispecific" antibodies) are mAbs in which the two different valences (heavy-light chain CDR pairs) of the antibody bind to two different antigens. This allows the antibody to bring two different antigens (or two cells, or a protein and a cell) into close physical proximity, which in turn may carry out a new function. Examples of bifunctional mAbs include the following:

- Emicizumab binds to two coagulation factors (factor IXa and factor X), taking the place of activated factor VIII (factor VIIIa) in the coagulation cascade (figure 2). This mAb is available for prophylaxis against bleeding in certain individuals with hemophilia A. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab'.)

- Catumaxomab binds to the T-cell surface molecule CD3 and epithelial cell adhesion molecule (EpCAM), a tumor cell surface marker; it also has an Fc region that can bind to an Fc receptor on macrophages, natural killer (NK) cells, or dendritic cells. This combination of antigen binding in a single molecule has the potential to recruit T cells and antigen-presenting cells to a tumor and to elicit an anti-tumor immune response. Efficacy has been shown in malignant ascites. (See "Malignancy-related ascites", section on 'Tumor-targeted treatment'.)

- Blinatumomab binds to CD3 on T cells and the cell surface protein CD19, present on precursor B-cell acute lymphoblastic leukemia (ALL) cells, potentially recruiting cytotoxic T cells to kill the ALL cells. (See "Treatment of relapsed or refractory acute lymphoblastic leukemia in adults", section on 'Blinatumomab'.)

Other bispecific mAbs are under development for a number of indications, including various tumor types and inflammatory conditions [12,13].

Drug or toxin conjugation — mAbs can be used to deliver a drug or a toxin to a specific site, which may be especially useful for cell killing in cancer therapy or antimicrobial applications. Drugs or toxins are typically attached to the immunoglobulin molecule using covalent binding to prevent their premature dissociation before reaching the target cell. Early-generation drug conjugates had heterogenous ratios of drug to antibody, but subsequent methods for ensuring more consistent stoichiometry have been developed, including engineered alternate amino acids that selectively bind the drug [14].

Antigenized antibodies — Antigenization is an investigational approach in which an mAb can be engineered to deliver an antigen (eg, as a vaccine). This is done by replacing part of the antibody polypeptide with a fragment of a microbial antigen. Any sequence can be inserted into various portions of the antibody molecule. Antigenized mAbs are

potentially useful as vaccines since they have a longer serum half-life compared with the isolated antigen fragment and may be better tolerated than some microbial fragments.

The successful presentation of microbial peptides contained in antibody molecules has been shown in a variety of animal systems (eg, for influenza virus in mice) [15]. However, this potentially promising technology has not advanced beyond animal studies. For example, using recombinant DNA methods, a bovine herpes virus B-cell epitope was grafted onto a bovine immunoglobulin molecule. This antigenized antibody was used to immunize cows and generate antibodies against the virus [16].

BIOSIMILAR mAbs — Biosimilar drugs are biologic therapies that are highly similar to the reference product in clinical potency and toxicity but may have slight differences in components that do not appear to affect their clinical efficacy or toxicity [17]. Biosimilar mAbs are being developed as the patents expire on existing products. Examples include mAbs similar to infliximab and adalimumab, which target tumor necrosis factor (TNF). Since mAbs have many functionalities, it is especially important to determine how potency, efficacy, and toxicity compare with the reference product. (See "Overview of biologic agents and kinase inhibitors in the rheumatic diseases", section on 'Biosimilars for biologic agents'.)

Biosimilar mAbs are named as the reference drug plus a four-letter suffix that consists of four unique and meaningless lowercase letters [18]. As an example, a biosimilar for the mAb infliximab is named infliximab-dyyb.

IgG1 FUSION PROTEINS — Immunoglobulin G1 (IgG1) fusion proteins (also referred to as Fc-fusion proteins) are biologic therapies that take advantage of some of the properties of the immunoglobulin Fc region such as enhanced half-life. IgG1 fusion proteins do not have an antigen-binding complementarity-determining region (CDR) and thus do not have a biologic target in the same sense that mAbs do, although the protein to which Fc is fused often does have a specific biologic function that is being manipulated.

The following are examples of IgG1 fusion proteins in clinical use:

- Etanercept is a fusion of two soluble tumor necrosis factor (TNF)-alpha receptors with the Fc portion of IgG. The two TNF receptors make it bivalent (ie, one etanercept molecule binds two TNF molecules). It is used to inhibit TNF-alpha in various immunologic and rheumatologic disorders. (See "Overview of biologic agents and kinase inhibitors in the rheumatic diseases", section on 'TNF inhibition'.)

- Recombinant human factor VIII fused to the Fc portion of IgG (rFVIII-Fc) is a form of factor VIII supplementation that can be used in individuals with hemophilia A. A corresponding product is available for hemophilia B (FIX-Fc). These fusion proteins have longer half-lives than the corresponding factor proteins without Fc fusion. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Longer lasting recombinant factor VIII' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Longer-lasting recombinant factor IX'.)

Some of these fusion proteins can be identified by the suffix "-cept"; others contain "Fc" in their names.

MECHANISM OF ACTION

General principles of mAb activity — mAbs are biologic substances, and, as such, each mAb may have unique aspects to its mechanism of action. The following discussion is an overview of the general principles of how therapeutic mAbs sequester or destroy their targets.

One of the key distinguishing attributes of mAbs is their affinity for the target antigen, which is determined by the variable region/complementarity-determining region (CDR). Antibodies with greater affinity can be selected in the laboratory. Affinity is quantified by calculating the association constant for binding between the antibody and a single monovalent antigen in vitro [19]. When the antibody is bivalent (eg, full-length), this affinity is amplified (eg, 10^{18} [a virtually irreversible binding reaction] rather than 10^{9} L/mol). Antibody affinities are most often in the range of 10^{5} to 10^{11} L/mol (picomolar to nanomolar affinity).

Another key attribute of mAbs is their ability to recruit other immune cells and molecules (such as complement), both of which can promote killing of target cells. This recruitment is mediated by the Fc (fragment crystallizable) portion of the antibody (figure 3), which includes the heavy-chain second and third constant regions.

Target is a cell surface antigen — The desired effect of an mAb directed against a cell surface antigen may involve blocking the function of a cell surface receptor or killing of the target cell.

- In some cases the target antigen may be a cell surface receptor, and mAb binding may block the normal/physiologic ligand from binding the receptor, thus interfering with receptor function and in turn preventing cell proliferation or

survival. Examples include mAbs directed against the epidermal growth factor receptor (EGFR) or the receptor tyrosine kinase erbB-2 (also known as HER2).

- In other cases, the target may be a tumor cell or a B-cell clone that produces an autoantibody (eg, an antiplatelet antibody in immune thrombocytopenia [ITP]). The mechanism of cell killing may involve recruitment of complement proteins, phagocytes, or natural killer (NK) cells, which can promote immune-mediated destruction of the cell(s) expressing the target antigen on their surface.

  Recruitment of immune mediators generally occurs through interactions with the Fc portion of the mAb. Fc receptors can modulate the cell killing effects of mAbs by recruiting effector cells to effect antibody-dependent cellular cytotoxicity (ADCC) or antibody-mediated phagocytosis by monocytes/macrophages [20]. Fc receptors can also promote cell death via complement-dependent cytotoxicity (CDC), in which mAb binding to target cells results in the activation of the complement cascade. Some antibodies have features of both ADCC and CDC, and in some cases, mAbs can be further engineered to alter their Fc binding to enhance cell death [21,22]. Complement activation can have both agonistic and antagonistic effects on CDC and ADCC, and it is unclear which mechanisms are most responsible for eliminating malignant cells. Target cell killing can also be enhanced by using the antibody as a vehicle to deliver a toxin or cytotoxic drug directly to the target cell using an mAb-drug or mAb-toxin conjugate. (See 'Drug or toxin conjugation' above.)

  Fc receptors are expressed on lymphocytes, neutrophils, monocytes, dendritic cells, and epithelial cells [23]. Fc receptors can be engineered to bind specific receptors on subpopulations of cells or to have specific glycoprotein modifications. The properties of the Fc portion can vary depending on antibody isotype (eg, immunoglobulin G [IgG], IgA, or IgM). Most therapeutic mAbs are IgG1, which has been well-characterized for its half-life and effector functions, including complement fixation. The Fc portion may bind complement C1q and activate the classical pathway of the complement cascade, or it may bind to receptors on antigen-presenting cells, leading to phagocytosis. The Fc portion can activate or suppress B cells, depending on the antigen and timing of interactions.

Investigational approaches are being tested for the generation of mAbs against intracellular proteins, which could potentially greatly expand the available targets and methods of cell killing. Examples include engineering mAbs to be internalized by endosomal pathways [24].

Additional information about specific Fc receptors on various cell types and mechanisms of complement activation and phagocytosis are discussed in other topic reviews. (See "Mast cells: Surface receptors and signal transduction" and "NK cell deficiency syndromes: Clinical manifestations and diagnosis", section on 'Functions' and "Complement pathways" and "The humoral immune response".)

Target is a plasma protein or drug — Antigen binding and sequestration of the protein away from its normal binding partners may be sufficient for the efficacy of an mAb directed against a soluble molecule such as a plasma protein or a medication.

Examples of plasma proteins that are targeted by mAbs include:

- **Tumor necrosis factor (TNF)** – Adalimumab, afelimomab, certolizumab pegol, golimumab, infliximab, and others (see "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects", section on 'TNF-alpha antagonists')
- **Vascular endothelial growth factor (VEGF)** – Bevacizumab (see "Overview of angiogenesis inhibitors", section on 'Anti-VEGF antibodies' and "Age-related macular degeneration: Treatment and prevention", section on 'Treatment of wet AMD')

Examples of drugs that are targeted by therapeutic mAbs include:

- Dabigatran (anticoagulant) – Idarucizumab (see "Management of bleeding in patients receiving direct oral anticoagulants", section on 'Dabigatran reversal')
- Digoxin (antiarrhythmic agent) – Digoxin immune Fab (see "Digitalis (cardiac glycoside) poisoning", section on 'Antidotal therapy with antibody (Fab) fragments')

When bound to the mAb, these drugs are unable to interact with their normal targets and are essentially neutralized. They are eventually cleared from the body by macrophages, via Fc-mediated uptake and lysosomal degradation [25].

INDICATIONS — Indications for mAbs are discussed in separate topic reviews on specific disorders. Some examples include the following:

- **Hematologic malignancies** – (see "Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia" and "Initial treatment of advanced stage (III/IV) follicular lymphoma" and "Initial treatment of acute promyelocytic leukemia in adults")

- **Solid tumors** – (see "Adjuvant systemic therapy for HER2-positive breast cancer" and "Systemic therapy for advanced non-small cell lung cancer with an activating mutation in the epidermal growth factor receptor" and "Immunotherapy of advanced melanoma with immune checkpoint inhibition")

- **Autoimmune disorders or disorders with an immune component** – (see "Treatment of progressive multiple sclerosis in adults", section on 'Immune-modulating treatments' and "Alternatives to methotrexate for the initial treatment of rheumatoid arthritis in adults" and "Immune thrombocytopenia (ITP) in adults: Second-line and subsequent therapies")

- **Hypercholesterolemia** – (see "PCSK9 inhibitors: Pharmacology, adverse effects, and use")

- **Asthma** – (see "An overview of asthma management", section on 'Severe persistent (Step 4 or 5)' and "Anti-IgE therapy", section on 'Omalizumab therapy in asthma')

- **Osteoporosis** – (see "Denosumab for osteoporosis")

- **Inflammatory bowel disease** – (see "Overview of the management of Crohn disease in children and adolescents" and "Overview of the medical management of severe or refractory Crohn disease in adults")

- **Allograft rejection** – (see "Liver transplantation in adults: Overview of immunosuppression", section on 'Monoclonal antibodies' and "Treatment of acute T cell-mediated (cellular) rejection of the renal allograft", section on 'Banff grade II or III rejection')

- **Infectious organisms** – (see "Clostridium difficile in adults: Treatment", section on 'Alternative therapies')

- **Drug reversal** – (see "Digitalis (cardiac glycoside) poisoning", section on 'Antidotal therapy with antibody (Fab) fragments' and "Management of bleeding in patients receiving direct oral anticoagulants", section on 'Dabigatran reversal')

These examples are only intended to provide a sense of settings in which an individual may be receiving a therapeutic mAb; they are not an exhaustive list. New indications for existing mAbs as well as new mAbs directed against additional target antigens are expected as disease mechanisms are elucidated, microbial antigens are identified, and new drugs are created.

ADMINISTRATION — Maintaining appropriate levels of the mAb requires a dose and administration schedule that takes into account the pharmacokinetics of the specific antibody and minimizes premature removal of the antibody (eg, by plasmapheresis).

Dose, route, and pharmacokinetics — Some mAbs are given in a fixed dose, and some are dosed according to body weight, as discussed in separate topic reviews. (See "Dosing of anticancer agents in adults", section on 'Newer targeted therapies'.)

mAbs are proteins, so they cannot be administered orally. Some are administered intravenously (eg, infliximab), some can be administered subcutaneously (eg, emicizumab), and some can be administered by either route (eg, rituximab, in different formulations). Intramuscular use has also been reported (eg, palivizumab). The major determinants of the optimal administration route include the greater and more rapid bioavailability with intravenous use, balanced by avoidance of intravenous access for the subcutaneous route [26]. Antibodies injected subcutaneously are taken up by lymphatic channels and may not reach maximum plasma concentration for several days. The mAb should be given by the route that was used to establish clinical efficacy and safety for the specific indication, unless given in the context of a clinical trial.

Once an mAb is in the circulation, it leaves the vasculature by hydrostatic and osmotic pressure, which may differ in different tissues [26]. Retention in tissues depends on affinity for the target. Most mAbs are eliminated by reticuloendothelial macrophages. The half-lives of mAbs are quite variable, from two days to several weeks. Binding to the receptor FcRn (Fc-receptor of the neonate, expressed on many adult cell types) increases the half-life of human and humanized mAbs of the immunoglobulin G (IgG) class (see 'Modifications' above). The covalent attachment of polyethylene glycol (PEG) has been used to extend the half-life of an mAb (see "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects", section on 'Pegylated Fab' fragment'). The duration of biologic activity may differ substantially from the half-life due to different effects on and properties of the target cell.

As might be expected from the varying indications for mAbs and their diverse properties, the frequency of administration is mAb-dependent. As a general rule, antibodies are relatively stable in the circulation and can be given approximately once per week or at greater intervals. There are exceptions for which doses are given at more frequent intervals (eg, alemtuzumab, given in escalating doses on alternate days) or less frequent intervals (eg, rituximab maintenance therapy following treatment of a B-cell malignancy).

Co-administration of more than one mAb — It is possible to co-administer more than one mAb, although this should only be done in situations in which the combination has been demonstrated to have greater efficacy (or similar efficacy with reduced toxicity) than one of the mAbs alone. In principle, the mAbs could be directed against the same target, two different targets on the same cell, or two independent cell types.

Evidence for greater efficacy of two mAbs has been demonstrated in the following solid tumor examples:

- The combination of ipilimumab and nivolumab is used in melanoma for combined targeting of the costimulatory receptor cytotoxic T lymphocyte antigen 4 (CTLA4) and the immune checkpoint receptor program death 1 (PD-1), both of which are thought to augment the anti-tumor immune response. This combination has greater efficacy and greater toxicity (mostly gastrointestinal and hepatic) than either mAb alone. (See "Immunotherapy of advanced melanoma with immune checkpoint inhibition", section on 'Ipilimumab plus nivolumab'.)

- The combination of pertuzumab and trastuzumab is used in HER2-positive breast cancer, along with a taxane. Both mAbs target the HER2 receptor. The combination of both mAbs plus a taxane has greater efficacy and toxicity (eg, febrile neutropenia, diarrhea, skin changes) than trastuzumab plus a taxane but no increased rate of left ventricular dysfunction. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Trastuzumab plus pertuzumab plus a taxane'.)

Evidence for **lack** of a synergistic or additive effect has been demonstrated in trials in metastatic colorectal cancer that have evaluated combined treatment using the anti-epidermal growth factor receptor (EGFR) panitumumab together with mAbs that target the vascular endothelial growth factor (VEGF). (See "Systemic chemotherapy for metastatic colorectal cancer: Completed clinical trials", section on 'Dual antibody therapy'.)

Clinical trials testing other mAb combinations in other tumor types are ongoing [27].

Timing related to plasmapheresis or plasma exchange — Plasmapheresis and plasma exchange remove circulating proteins from the circulation, including mAbs. Thus, attention must be paid to the timing of administration of a therapeutic mAb with the plasmapheresis procedure.

Examples of conditions for which this consideration may be relevant include the following:

- Granulomatosis with polyangiitis (GPA) may be treated with plasmapheresis and rituximab. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis and microscopic polyangiitis", section on 'Role of plasma exchange'.)

- Complement-mediated thrombotic microangiopathy (C-TMA; also called complement-mediated hemolytic-uremic syndrome [HUS]) may be treated with plasma exchange and eculizumab. (See "Complement-mediated hemolytic uremic syndrome", section on 'Treatment'.)

While plasmapheresis may remove a portion of an mAb, there is evidence that certain mAbs may retain efficacy despite removal of a significant amount of the mAb, perhaps because the dose exceeds the capacity for complete removal and/or the interactions with the target occur with extremely rapid kinetics [28]. In addition, mAbs rapidly distribute beyond the intravascular space, so the amount of mAb removed by plasmapheresis is a fraction of the total tissue-distributed and target-bound mAb. (See "Acquired TTP: Treatment of refractory or relapsed disease", section on 'Rituximab'.)

In other cases, removal of the mAb by plasmapheresis may be a desired effect. An example is an individual who has an adverse effect from an mAb such as progressive multifocal leukoencephalopathy (PML) from natalizumab; this may be reversed by performing plasmapheresis to decrease the concentration of natalizumab and restore immune effector function [29]. (See "Natalizumab for relapsing-remitting multiple sclerosis in adults".)

If plasmapheresis is inadvertently performed immediately after administration of a therapeutic mAb, the treating clinician must decide whether it is necessary to administer another dose of the mAb or wait until the next scheduled dose. Often extra doses are not given. Factors to consider include the disease severity, number of doses administered previously, and time interval between administration of the mAb and initiation of the plasmapheresis procedure. In many cases, the

sufficient quantities of the mAb may have reached their intended target despite removal of some of the antibodies during the plasmapheresis procedure.

In contrast to plasmapheresis, which removes plasma proteins, hemodialysis does not remove mAbs from the circulation.

ADVERSE EVENTS — mAbs are made using recombinant biotechnology. Thus, they do not carry infectious risks associated with polyclonal antibody preparations from human plasma. However, they are biologic products and can elicit a number of immune-mediated and other reactions and adverse events (AEs) [30]. Thus, these therapies should not be prescribed without the requisite expertise in their use and appropriate facilities for treating potentially serious reactions. Individuals treated with mAb-based therapies should be made aware of potential AEs and given instructions to follow and contact information should they occur. The prescribing information for the specific mAb should be consulted for a complete list of AEs.

Infusion reactions — Infusion reactions are reactions that typically occur in the first one to two hours of starting an infusion. They can occur in response to biologic therapies such as mAbs as well as to other systemic therapies. They can affect any organ system and can range from mildly irritating injection-site reactions, increases in body temperature, or pruritus, to potentially life-threatening anaphylaxis. Mild reactions are common.

The immunogenicity of mAbs derived from nonhuman species can lead to the development of anti-mAb antibodies, which are sometimes associated with acute hypersensitivity reactions. While the majority of anti-mAb antibodies are immunoglobulin G (IgG) and can limit the availability and half-life of the drug, those of the IgE isotype can also mediate immediate swelling and anaphylaxis after repeated exposures. Strategies such as desensitization to modify these adverse reactions have been tried. Many times these acute hypersensitivity reactions can be confused with cytokine release syndromes (CRS), which are largely dependent on the amount and type of target cell rather than the characteristics of the therapeutic mAb. (See 'Cytokine release syndrome' below.)

The management of infusion reactions depends on the severity of the reaction and the urgency needed for treatment of the underlying condition. Mild reactions can often be managed by early recognition and prompt intervention. Often, the mAb can be continued after temporarily stopping it; use of a slower infusion rate or concomitant therapy with antipyretics or antihistamines may be helpful. Information specific to the disorder being treated should be consulted.

A separate discussion of infusion reactions to mAbs used to treat hematologic malignancies and solid tumors includes additional information about reactions to specific antibodies, along with recommendations for management, prevention, rechallenge, and desensitization. (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy".)

Other immune-related AEs — In addition to infusion reactions, other immune-related AEs include a number of dermatologic, gastrointestinal, endocrine, and other inflammatory reactions related to alterations of the normal immune balance between immune activity and immune tolerance [30]. As an example, skin reactions may occur during the use of certain mAbs for cancer therapy. (See "Cutaneous side effects of molecularly targeted therapy and other biologic agents used for cancer therapy", section on 'Monoclonal antibodies'.)

In some cases, concomitant administration of an immunosuppressive medication such as a glucocorticoid may reduce these immune-related AEs.

Infections and autoimmunity are a potential risk after administration of any mAb that reduces immune function, including those that target antigens on B and T lymphocytes [7]. Cytokine release syndrome (CRS) is a severe immune reaction that may occur in individuals being treated for certain malignancies. (See 'Cytokine release syndrome' below.)

Undesired effects related to the target antigen — In some cases, AEs may be directly related to the biology of the target antigen. As examples:

- The mAb abciximab, which blocks platelet aggregation by blocking the function of platelet glycoprotein IIb/IIIa, can cause bleeding. (See "Early trials of platelet glycoprotein IIb/IIIa receptor inhibitors in coronary heart disease", section on 'Adverse effects'.)
- The mAb cetuximab, which inhibits epidermal growth factor receptor (EGFR), can cause dermatologic toxicity. (See "Acneiform eruption secondary to epidermal growth factor receptor (EGFR) inhibitors".)
- The mAb trastuzumab, which targets the HER2 receptor, can cause cardiotoxicity that is thought to be related to a role for HER2 in cardiomyocyte survival. (See "Cardiotoxicity of trastuzumab and other HER2-targeted agents", section on 'Pathophysiology of cardiotoxicity'.)

Cytokine release syndrome — CRS is a severe immune reaction that occurs in response to immunotherapy for certain cancers (eg, lymphoid malignancies), in which positive feedback leads to progressive elevation in inflammatory cytokines by T lymphocytes [7]. It can occur in response to a therapeutic mAb or other immune-based therapies such as chimeric antigen receptor (CAR)-T cells. (See "Principles of cancer immunotherapy", section on 'Chimeric antigen receptors'.)

Some consider CRS an extreme form of an infusion reaction. CRS may be accompanied by fever, headache, nausea, malaise, hypotension, rash, chills, dyspnea, and tachycardia. Elevations in serum aminotransferases and bilirubin can be seen, and, in some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome, and a hemophagocytic lymphohistiocytosis-like syndrome have been reported. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

The largest risk factor for CRS is tumor load. The antibodies most likely to cause CRS are those that promote T-lymphocyte activation. As examples:

- Blinatumomab, a bifunctional mAb that binds to the T-cell surface protein CD3 and the cell surface marker CD19, present on precursor B-cell acute lymphoblastic leukemia (ALL) cells (see 'Bifunctional antibodies' above). In one series of 189 individuals treated with blinatumomab, 60 percent had fever, 28 percent had febrile neutropenia, and 2 percent had grade 3 CRS [31].

- Nivolumab, an mAb that binds to and inhibits the programmed death-1 (PD-1) protein that is expressed on T cells, B cells, and natural killer (NK) cells; its ligand (PD-L1) is expressed on tumor cells and is thought to interfere with cytotoxic T-cell effector function (see "Principles of cancer immunotherapy", section on 'PD-1 and PD ligand 1/2'). A case report has described CRS after a single dose of nivolumab in an individual with Hodgkin disease; the patient recovered, had a dramatic reduction in tumor size, and was able to receive additional doses [32].

- Rituximab, an mAb that targets CD20 on B lymphocytes, has been reported to cause CRS, particularly in individuals with B-cell malignancies who have bulky disease. Rare cases of CRS associated with rituximab in other settings have been reported [33]. (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Rituximab'.)

Prophylaxis for CRS (eg, premedication with acetaminophen and diphenhydramine) is sometimes incorporated into therapy protocols. Management of CRS depends on the severity (table 2) and may include interruption of the infusion, symptomatic treatment, intravenous fluids, and ventilator and/or pressor support [34]. The mAb tocilizumab, directed against interleukin (IL)-6, has been effective in treating CRS related to chimeric antigen receptor (CAR)-T cells, which, unlike an mAb, cannot be discontinued once they have been infused [34].

RESISTANCE — The concept of drug resistance is not usually applied to mAbs, but in some cases, it has been observed.

- In some cases, resistance is due to altered biology of the disease (eg, individual with cancer for whom an mAb was initially effective but later became ineffective).

- In other cases, reduced efficacy may be due to the development of neutralizing antibodies by the patient's immune system that are directed against the therapeutic mAb. This has been seen with certain mAbs, as discussed in separate topic reviews. Examples include mAbs directed against the following:

    - Tumor necrosis factor (TNF)-alpha. (See "Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases", section on 'Anti-drug antibodies'.)

    - Epidermal growth factor receptor (EGFR). (See "Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations", section on 'RAS/BRAF wild-type tumors'.)

    - Proprotein convertase subtilisin/kexin type 9 (PCSK9). (See "PCSK9 inhibitors: Pharmacology, adverse effects, and use", section on 'Immunologic and allergic effects'.)

It is important to note that not all alterations in cell signaling cause mAbs to become ineffective and not all anti-mAb antibodies cause the mAb to be neutralized.

SUMMARY

- Numerous therapeutic monoclonal antibodies (mAbs) have been produced to treat an increasing number of medical conditions. The nomenclature has been standardized such that the name of the antibody provides information about the target and identifies the therapy as an mAb. Naming conventions have been updated (table 1) to account for technologic changes and distinction among sound-alikes. (See 'Naming convention for therapeutic mAbs' above.)

- Several technologies are available for selecting mAbs that recognize the target antigen and for producing the selected mAb for clinical use. Molecular engineering can be used to make further modifications, including generation of antibody fragments, humanization of antibodies produced in animals, generation of bifunctional antibodies that bring together two separate antigens, and/or conjugation of the mAb to a drug or toxin. (See 'Production methods and special modifications' above.)

- The mechanism of action for an mAb may involve immune modulation and/or cell killing; this may be achieved by blocking a physiologic ligand-receptor interaction or by recruiting immune cells and proteins (eg, phagocytes, natural killer [NK] cells, complement) that can kill the target cell. In other cases, the mAb may act by sequestering a plasma protein or drug and preventing it from interacting with its ligand. (See 'Mechanism of action' above.)

- Clinical indications for mAbs include treatment of hematologic malignancies, solid tumors, immune disorders, hypercholesterolemia, asthma, osteoporosis, inflammatory bowel disease, and infections; as well as bypassing the function of normal scaffold proteins and reversing the activity of a drug. Links to selected topic reviews that discuss these indications are provided above. (See 'Indications' above.)

- Important aspects of mAb administration include attention to the dose, route, and potential drug interactions; general principles are discussed above. In certain conditions, more than one mAb may be administered to the same patient. A patient can undergo plasmapheresis and receive an mAb, but the timing should minimize removal of the mAb by the plasmapheresis procedure. (See 'Administration' above.)

- Potential adverse effects of certain mAbs include infusion reactions, cytokine release syndrome, immune-related effects, infections, autoimmunity, and/or effects related to the target antigen that are not a desired part of therapy. (See 'Adverse events' above and "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy".)

- Resistance to the therapeutic effects of mAbs is rare but can occur, either due to altered disease biology or to development of neutralizing antibodies by the patient's immune system. (See 'Resistance' above.)

- Separate topic reviews discuss therapeutic polyclonal antibody preparations including subcutaneous, intramuscular, and intravenous immune globulin (SCIG, IMIG, and IVIG). (See "Subcutaneous and intramuscular immune globulin therapy" and "Immune globulin therapy in primary immunodeficiency" and "Overview of intravenous immune globulin (IVIG) therapy" and "Intravenous immune globulin: Adverse effects".)

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Topic 3970 Version 17.0

GRAPHICS

Therapeutic monoclonal antibody nomenclature

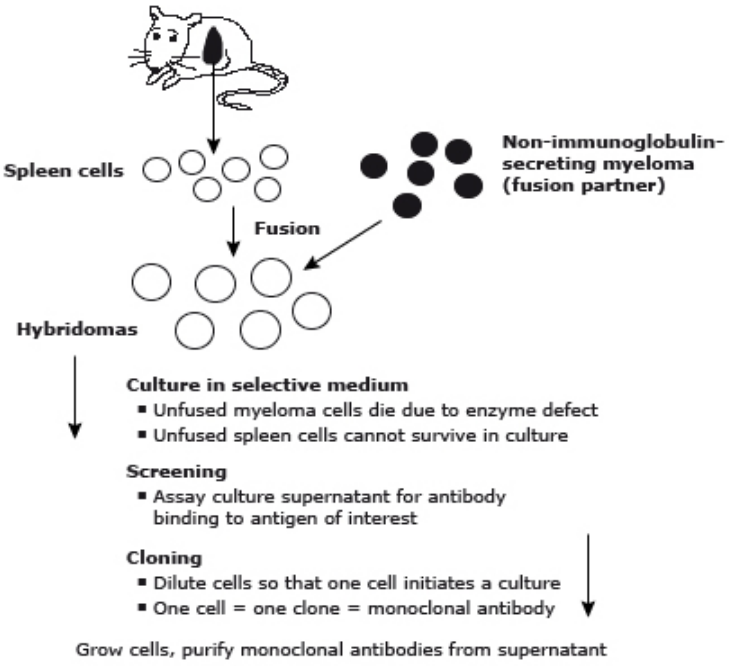
Prefix	Substem A = Target*		Substem B = Source¶		Suffix
	Substem	Definition	Substem	Definition	
Random and distinctive	-ami	Amyloid protein	-a	Rat	-mab
	-ba	Bacterial protein	-axo	Rat-mouse	
	-ci	Cardiovascular	-e	Hamster	
	-fung	Fungal protein	-i	Primate	
	-gros	Skeletal muscle	-o	Mouse	
	-ki	Interleukin	-u	Human	
	-li	Immuno-modulating	-xi	Chimeric	
	-ne	Neural	-xizu	Chimeric-humanized	
	-os	Bone	-zu	Humanized	
	-toxa	Toxin			
	-ta	Tumor antigen			
	-vi	Viral antigen			

Refer to UpToDate and Lexicomp for general information about therapeutic mAbs and specific dosing for individual products.

mAb: monoclonal antibody.
* The final letter may be omitted if it interferes with pronunciation; this is expected not to be an issue with substems created after mid-2017 since substem B will no longer be used.
¶ The use of substem B was eliminated in mid-2017. mAbs created before this time use substems A and B; mAbs created after this time only use substem A.

Graphic 114279 Version 1.0

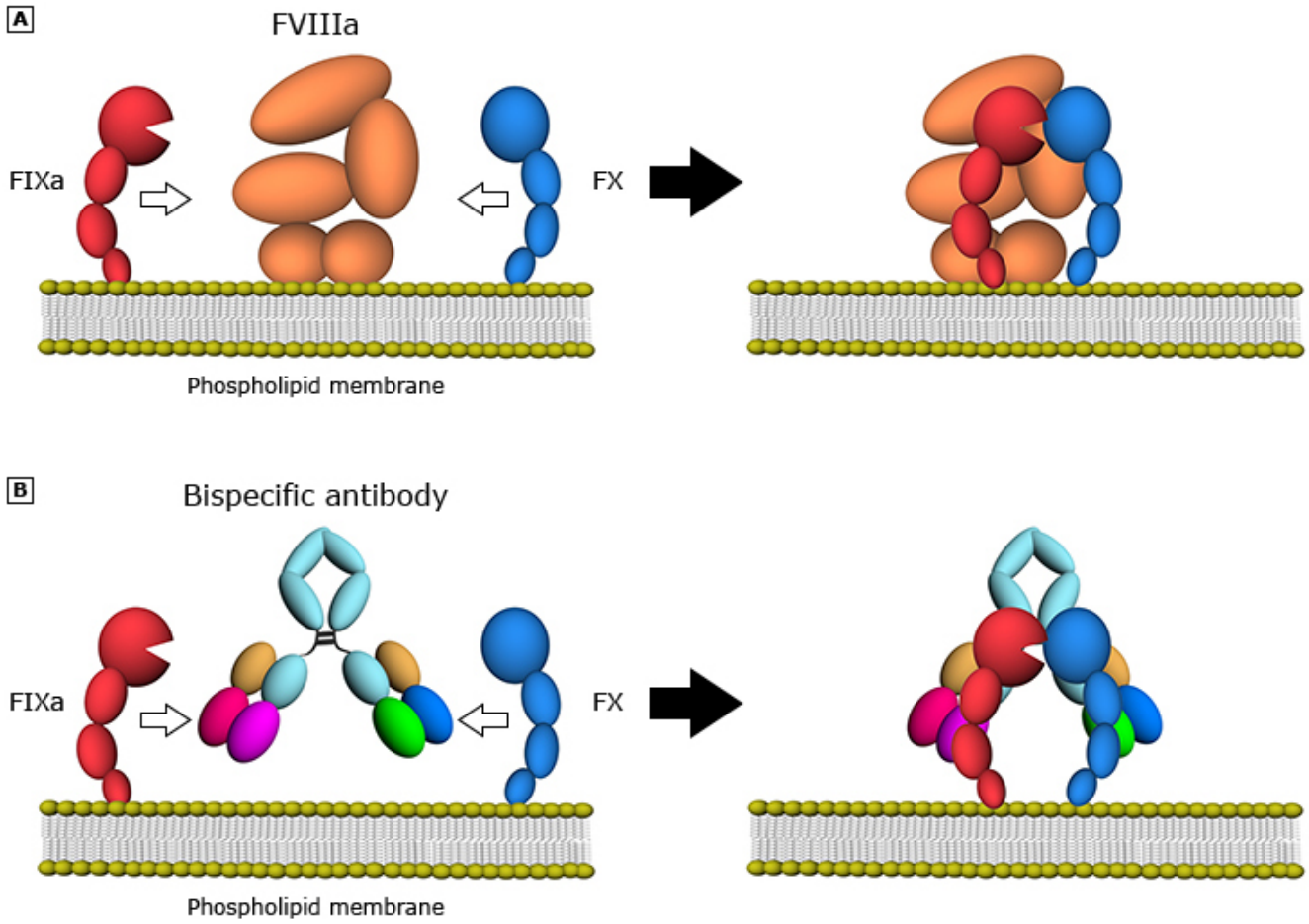
Method of monoclonal antibody production using hybridoma technology



In this method, an animal is immunized with a protein (or antigen) of interest. Spleen or lymph node cells are harvested and fused with a nonsecreting myeloma cell to create a hybridoma. Successfully fused cells can be selected in specialized media that only allows the hybridomas to survive. The candidate hybridomas are grown in culture, and the culture supernatants are screened for antibodies that bind to the target antigen. Cells are cloned by limiting dilution to yield a homogenous population. Refer to UpToDate for details of this method and for other methods of producing therapeutic monoclonal antibodies.

Graphic 71530 Version 3.0

Bispecific antibody that could be used to replace the function of FVIIIa

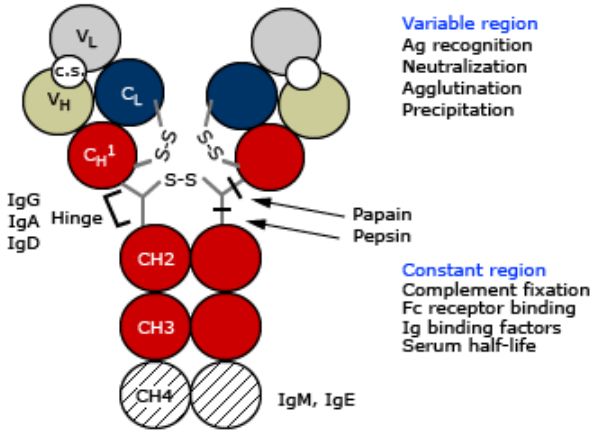


Refer to UpToDate content on treatment of hemophilia for further details.
(A) In normal hemostasis, FVIIIa (orange) forms a complex with FIXa (red) and promotes interaction between FIXa and FX (blue) by binding to both factors on the phospholipid membrane.
(B) A bispecific antibody that can simultaneously bind to FIXa (red) and FX (blue) could mimic the activity of FVIIIa and promote interaction between FIXa and FX on the phospholipid membrane.

FVIIIa: activated coagulation factor VIII (eight); FIXa: activated coagulation factor IX (nine); FX: coagulation factor X (ten).

Graphic 107801 Version 2.0

Antibody (immunoglobulin) structure



An immunoglobulin molecule is composed of four chains: two identical light chains, shown on the inner aspects of the molecule (in blue and gray), and two identical heavy chains, shown along the outer aspect of the molecule (in red and tan). Each chain is made up of immunoglobulin domains, represented as circles, and contains an internal disulfide bond (not shown). There are usually multiple disulfide bonds linking the two H chains in the hinge region and also a disulfide linking the H and L chains. Only IgG, IgA, and IgD have distinct hinge regions, and only IgM and IgE have four H chain domains. The points of cleavage of the enzymes pepsin and papain are shown. The CS is formed by structures contributed by the variable regions of both the heavy chain (VH) and light chain (VL).

VL: variable region of the light chain; CS: combining site; CL: constant region of the light chain; VH: variable region of the heavy chain; CH: constant region of the heavy chain; Ig: immunoglobulin.

Graphic 56393 Version 12.0

NCI CTCAE v4.0 cytokine release syndrome

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death

Cytokine release syndrome is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.

NSAIDs: nonsteroidal anti-inflammatory drugs; IV: intravenous.

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed August 3, 2017).

Graphic 114251 Version 1.0

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