In the Know

Biologics 101 for Anesthesiologists

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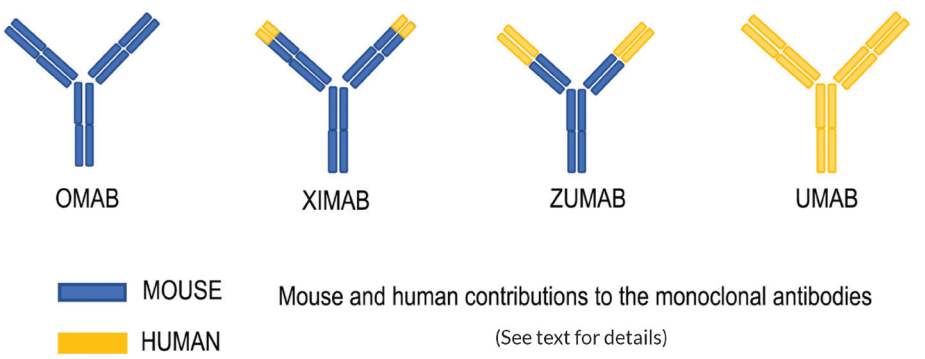
Over the past two decades, treatment strategies for various inflammatory and autoimmune conditions have evolved from the use of small molecule broad-spectrum immunomodulators to that of highly targeted antibody-based immunotherapies (*Nat Rev Immunol* 2021;21:680-6). Previously, glucocorticoids served as a key therapy for most of these conditions. However, this strategy demonstrated diminished benefit as a result of considerable off-target toxicities. Steroid-sparing agents such as methotrexate, azathioprine, and sulfasalazine provided modest benefits, albeit with some significant adverse events. Research in biochemistry and molecular biology allowed greater mechanistic understanding of these disease processes. Consequently, new targeted immunotherapies that act quickly and directly to interrupt inflammatory processes and tissue destruction have been developed. These new therapies include biologics and small molecules that target several cytokines, cytokine receptors, and other relevant immunologic pathways. In doing so, it was hoped that high response rates could be obtained with reduced toxicity profiles (*Nat Rev Immunol* 2021;21:680-6). In this brief update, we review the most frequently used monoclonal antibodies to treat a variety of conditions.

One of the most frequently employed methods of monoclonal antibody production was first described in 1975 by Köhler and Milstein (*Nature* 1975;256:495-7). This process requires the use of hybridomas, cellular fusions of antibody-generating B cells, and myeloma cells in immunized animals (frequently mice). Subsequent clonal expansion of the hybridoma cell line allows industrial production of the desired monoclonal antibodies. These mass-produced antibodies are currently used in numerous diagnostics and therapies. Advanced methods have been developed to create more humanized versions of monoclonal antibodies to reduce the hypersensitivity reactions, thereby increasing their clinical applicability (*Methods Mol Biol* 2012;901:149-59). Standard nomenclature of the monoclonal antibodies indicates their source with the suffix, as depicted in the Figure (*Hum Antibodies* 2019;27:37-51). Briefly, the suffix "omab" identifies mouse derived, "ximab" indicates chimeric combining murine and human antibody regions with 30%-35% murine contribution, "zumab" is humanized with <10% murine components, and "umab" are fully human monoclonal antibodies with no animal component (*J Genet Eng Biotechnol* 2021;19:159; *N Engl J Med* 2020;383:2255-73).

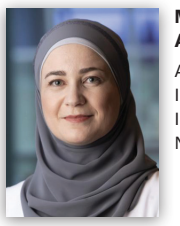
Figure: Monoclonal Antibodies Nomenclature



Another class of therapeutic biological products are called fusion proteins (mAbs 2015;7:456-60). These unnatural proteins are created by joining two or more genes coding separate proteins. These therapeutics frequently end with the suffix "cept."

It has been shown that cytokine cascade imbalances can initiate and propagate immune-driven inflammation, resulting in organ damage (*N Engl J Med* 2020;383:2255-73). Monoclonal antibodies have been used to suppress the cytokine action and mitigate cytokine storm-related morbidity and mortality; some key pathways that have been effectively targeted are summarized in Table 1. Listed below are examples of the main immunological targets for therapeutic monoclonal antibodies:

- Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine secreted by various immune cells, including activated macrophages. This cytokine mediates the acute inflammatory response to infectious agents and activates host cell responses, resulting in neutrophil recruitment and inflammatory response initiation. TNF-α inhibitors bind to the cytokine prior to receptor engagement, thus preventing an inflammatory response. These inhibitors are key therapies for psoriasis, rheumatoid and psoriatic arthritis, and inflammatory bowel disease and have demonstrated substantial improvement in disease-related symptoms and signs, including improvement in the quality of life. Currently approved anti-TNF-a monoclonal antibodies include infliximab, adalimumab, certolizumab, and golimumab (*Juntendo Medical Journal* 2020;66:34-7).
- Interleukin 1 (IL-1) and its receptor (IL-1R), including IL-1α and IL-1β, exert strong pro-inflammatory activities. At higher concentrations, both interleukins induce fever and acute phase reactions via IL-6 production. Examples of IL-1-mediated disease include hereditary autoinflammatory conditions, which arise from excess IL-1 signaling. These inherited disorders present predominantly as recurrent febrile episodes. IL-1 inhibitors have been used effectively for treatment of monogenic periodic fever syndromes (*Nat Rev Immunol* 2021;21:680-6).



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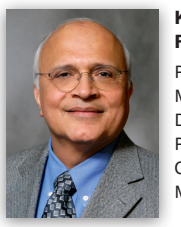

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Table 1: Monoclonal Antibodies (mABs) – Examples of Key Targets

Monoclonal antibodies		
Extracellular targets	**Membrane targets**	**Intracellular targets**
Interleukin 1	B-lymphocyte antigen 20	Janus activated kinase 1
Interleukin 6	B-lymphocyte antigen 22	Janus activated kinase 2
Tumor necrosis factor α	B-lymphocyte antigen 80/86	Janus activated kinase 3
Interleukin 4	Interleukin -17 RA	Bruton Tyrosine Kinase
Interleukin 6	Alpha 4 integrins	BDE 4
Interleukin 13	Interleukin 6R	Tyrosine kinase 2
Interferon-γ	INFR	
Interleukin 12	Interleukin 4R	
Interleukin 23	FCERI	
Interleukin 17		

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Some IL-1 inhibitors include anakinra, which is a recombinant form of the IL-1R antagonist protein, and canakinumab, a human monoclonal antibody against IL-1β (*Pediatr Rheumatol Online J* 2010;8:9; *N Engl J Med* 2009;360:2416-25).

- Interleukin 6 (IL-6) and the IL-6 receptor/IL-6R are produced by various innate and adaptive immune cells in response to infection or tissue injury. IL-6 stimulates the synthesis of acute phase reactants in the liver. It also promotes the maturation of neutrophils from bone marrow precursors and the growth of B cells, thereby contributing to immunocompetence against infectious agents. The success of the IL-6-targeting monoclonal antibody tocilizumab in treating inflammatory arthritis has allowed the identification of that cytokine as a key mediator of chronic inflammation in these patients (*Nat Immunol* 2015;16:448-57). Tocilizumab has also shown beneficial effects in the treatment of critically ill patients with COVID-19 and in cancer patients receiving new immunotherapies who experience cytokine release syndrome (*Blood* 2019;134:1783-6; *N Engl J Med* 2021;384:1491-1502; *Cancer J* 2014;20:119-22).
- Interferon gamma (INF-g) is produced by natural killer and T cells and activates macrophages to kill phagocytosed microbes. Uncontrolled activation of $CD8^+$ T cells leading to a cytokine storm is the hallmark of a potentially lethal disease called hemophagocytic lymphohistiocytosis. Targeted inhibition of INF-g using the monoclonal antibody emapalumab has recently shown remarkable efficacy in disease control (*Blood* 2019;134:1783-6).
- CD20 inhibitors. CD20 is a surface-bound protein expressed on B cells. The monoclonal antibody rituximab blocks CD20, resulting in B cell depletion and reduction of autoreactive antibodies. Rituximab has proven effective for the treatment of many autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, vasculitis, and chronic autoinflammatory polyneuropathy (*J Allergy Clin Immunol* 2010;125:S314-23). Additionally, this antibody has also received regulatory approval for the treatment of several hematologic malignancies, including non-Hodgkin's lymphoma, diffuse large B cell lymphoma, and chronic lymphocytic leukemia (*Br J Cancer* 2003;89:1389-94).
- Immune checkpoint inhibitors. Immune checkpoints, which include proteins such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein 1(PD1), and PD1 ligand (PDL1), play crucial roles in the regulation of T cell activity. CTLA-4 and PD1 are expressed on the surface of T cells and are essential in downregulating the immune system and thus promoting self-tolerance. PDL1 is overexpressed on the surface of malignant tumor cells, where it binds to PD1. This PD1-PDL1 interaction results in immunosuppression, which contributes to tumor immune evasion, possibly leading to treatment failure. Targeting the PD1/PDL1 pathway has shown clinical efficacy by augmenting T cell responses and increasing activity against several solid tumor malignancies (*Front Pharmacol* 2021;12:731798; *Front Immunol* 2021;11:619257; *ASA Monitor* 2022; 86:1,1-5).
- The vascular endothelial growth factor (VEGF) family of growth factors is critical for new blood vessel growth (angiogenesis). This process, which is important in wound repair, is also critical for solid tumor cancers, as rapidly growing tumors require a steady supply of nutrients and oxygen. Consequently, these tumors will often release growth factors such as VEGF to stimulate blood vessel production. Thus, the VEGF-VEGFR system is an important therapeutic target in cancer (*Genes Cancer* 2011;2:1097-105). In 2004, Bevacizumab was the first VEGF inhibitor to receive FDA approval (*Cold Spring Harb Perspect Med* 2012;2:a006577). Since then, a number of small-molecule multi-kinase inhibitors have been approved as anti-VEGF therapies.
- Human epidermal growth factor receptor-2 (HER2/neu, c-erbB2) is a membrane tyrosine kinase that is overexpressed in some patients with breast cancer. When activated, this receptor provides cells with potent proliferative and anti-apoptosis signals that drive tumor development and progression in these patients. Thus, HER2 is an attractive therapeutic target to halt tumor proliferation (*Arch Pathol Lab Med* 2011;135:55-62). In 1998, trastuzumab became the first HER2-targeting antibody approved for the treatment of patients with HER2+ breast cancer.

Table 2: *Commonly Employed Monoclonal Medications

Antibody	Trade name	Target antigen	Examples of FDA-approved indications
infliximab	Remicade	TNF-α	*RA, psoriatic arthritis, Crohn's disease, ulcerative colitis
adalimumab	Humira	TNF-α	*RA, psoriatic arthritis, Crohn's disease, juvenile idiopathic arthritis
certolizumab	Cimzia	TNF-α	
golimumab	Simponi	TNF-α	
nivolumab	Opdivo	PD1	Various cancers such as melanoma, esophageal cancer, urethral cancer, and non-small cell lung cancer
pembrolizumab	Keytruda	PD1	Various cancers, including melanoma, non-small cell lung cancer, advanced breast, and uterine cancers
denosumab	Xgeva	RANK-L**	Osteoporosis, bone loss associated with cancer
emapalumab	Gamifant	IFN-γ	Hemophagocytic lympho-histiocytosis
canakinumab	Ilaris	IL-1B	Familial periodic fever syndromes
daclizumab	Zenapax	IL-2Ra	Prophylaxis of acute organ rejection in renal transplant recipients
dupilumab	Dupixent	IL-4Ra	Atopic dermatitis
tocilizumab	Actemra	IL-6Ra	*RA, Castleman disease
ustekinumab	Stelara	P40 subunit of IL12&IL23	Plaque Psoriasis
daratumumab	Darzalex	CD38	Multiple myeloma
belimumab	Benlysta	B cell activating factor	Systemic lupus erythematosus
bevacizumab	Avastin	VEGF	Colorectal cancer, cervical cancers
eculizumab	Soliris	C5	Paroxysmal nocturnal hemoglobinuria
omalizumab	Xolair	FCERI	Asthma
rituximab	Rituxan	CD20	Autoimmune disease, B-ALL
vedolizumab	Entyvio	α4β7 integrin	Ulcerative colitis and Crohn's disease
pertuzumab	Perjeta	HER2	Breast cancer
trastuzumab	Trazimera	HER2	Breast cancer

*Rheumatoid arthritis (asamonitor.pub/3xfsXOy)
**Receptor activator of nuclear factor kappa beta ligand (RANKL), important for osteoclast differentiation.

The therapeutic reach of monoclonal antibodies extends to multiple other conditions such as some neurologic disorders, innate immune disorders, infectious diseases, and cardiovascular conditions. They have been commonly used in the treatment of solid tumor and hematologic malignancies, achieving immune suppression by direct killing of tumor cells and by blocking growth factor receptor signaling, while simultaneously fostering a long-lasting effector immune response against tumor cells. Table 2 lists several monoclonal antibodies that are used in the control of other diseases.

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A thorough understanding of cellular signaling pathways underlying these conditions can help clinicians choose the proper therapy that specifically targets these pathways. This is important, because blocking of these pathways, in addition to halting the pathology, may also alter essential functions. For example, targeting pro-inflammatory cytokines can lessen the body's ability to fight infections. Tuberculosis can be reactivated with the use of some biologics. Therefore, it is important to rule out tuberculosis infection before starting treatment. Monitoring for other infections, particularly in immunocompromised patients, is essential for patient safety. Live attenuated vaccines should be avoided during active treatment with monoclonal antibody therapeutics.

Other side effects may include hypersensitivity reactions. The development of humanized monoclonal antibodies has significantly reduced the incidence of allergic reactions. Another negative for these therapies is their high cost, making them unavailable for many in need. Additionally, there is the possibility of interaction with anesthetics. There is one case report of a patient developing transverse myelitis following a spinal anesthetic for transurethral resection of the prostate. This patient was on obinutuzumab for follicular lymphoma (*Reg Anesth Pain Med* 2021;46:828-30). Another monoclonal antibody, trastuzumab, has been reported to induce reversible cardiotoxicity when used as immunotherapy in patients with malignancies (*Cancers (Basel)* 2021;13:4797).

In conclusion, the use of monoclonal antibodies has improved the treatment of patients with previously difficult-to-treat inflammatory and autoimmune diseases. These therapies have also provided significant benefit to patients with some malignancies. Their administration requires complete evaluation and close monitoring for cardiac and other toxicities and reactivation of dormant infections. ■