National Center for Competency Testing

Monoclonal Antibody (mAb) Treatments

COURSE DESCRIPTION

The term “monoclonal antibodies” has frequently circulated in the news since the start of the COVID-19 pandemic. But did you know that monoclonal antibody technology dates back more than 30 years and has historically treated many conditions besides COVID-19? In fact, dozens of different monoclonal antibody treatments are FDA approved for use in conditions such as rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, Ebola, and different types of cancers. This course introduces the topic of monoclonal antibodies (mAbs) as therapeutic treatments and discusses in simplified terminology their history and development, the diseases they treat, and the immune system actions they involve.

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Ver 1

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COURSE TITLE: Monoclonal Antibody (mAb) Treatments

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OBJECTIVES

Upon completion of this continuing education course, the professional should be able to:

1. Name at least six conditions that can be treated with monoclonal antibodies (mAbs) and identify at least six of the most commonly use mAb treatments.
2. Describe the role of antibodies in the adaptive immune response and identify the type of white blood cell that produces them.
3. Define the terms pathogen, antigen, and epitope and describe how they're related.
4. Describe an antibody's structure.
5. Discuss an antibody's specificity and affinity for its antigen and how monoclonal antibodies take advantage of these properties.
6. Explain how an antibody can undergo weakened affinity for its antigen.
7. Name the first mAb treatment, what it was used for, and the year it achieved FDA approval.
8. Describe the purpose behind mAb treatments and name at least three scenarios in which mAb treatments might be useful.
9. Recall the three post-exposure mAb treatments for COVID-19, their target antigens, and their FDA status at the time of this course.

Disclaimer

The writers for NCCT continuing education courses attempt to provide factual information based on literature review and current professional practice. However, NCCT does not guarantee that the information contained in the continuing education courses is free from all errors and omissions.

Glossary

Innate immune response	The host defense mechanisms that act immediately at the onset of an infection. Is not adaptive to specific antigens and immune memory is not established.
Adaptive immune response	Tailored immune response by B cells and T cells mounted against a specific antigen at the time of the primary encounter. Antibodies are generated and immune memory is established. Requires several days for full response. Subsequent encounters with the same antigen results in immediate immune response.
Lymphocytes	A class of white blood cell, responsible for adaptive immune response. Main classes are B cells and T cells. Some lymphocytes also play a role in innate immunity.
Differentiation	The normal process by which a less specialized cell develops or matures to take on a more specialized form and function.
Plasma cell	A differentiated B cell that secretes antibody.
Memory B cell	A differentiated B cell that is long lived and antigen-specific. Produced during the initial exposure to the antigen. If the antigen is encountered again, memory B cells differentiate into antibody-producing plasma cells against the antigen.
Antibody (immunoglobulin)	A protein secreted by plasma cells (B cells) that is developed in response to a specific antigen. Can neutralize the antigen itself or aid in eliminating the antigen from the body. Each antibody binds only one specific antigen.
Pathogen	An agent that causes disease; usually a foreign invader such as a virus, bacteria, or fungus.
Antigen	Any molecular structure (usually proteins) on a pathogen, toxin, or cell that triggers the immune system to make antibodies against it. Antigens can be foreign or self (autoimmunity).
Epitope	The specific portion of an antigen that becomes bound by antibody. An epitope is the smallest part of an antigen that is recognized by the immune system.
Affinity	The strength with which an antibody binds to its epitope on an antigen. Antigen mutations can weaken affinity because the antibody no longer is a perfect fit for that epitope.
Specificity	The property of an antibody to recognize and bind to only one specific epitope on an antigen.
Monoclonal	Copies of or clones of something that are all identical. Mono = single; Clonal = clones/copies.

INTRODUCTION

Monoclonal antibodies (mAbs) are laboratory-developed proteins with many uses in medicine including research, diagnostics, and therapy. When used as therapy, mAbs treat disease by mimicking the immune system's response. Monoclonal antibody technology dates back more than 30 years and has been used therapeutically for many diseases. In fact, dozens of different mAb treatments are FDA approved to treat conditions such as rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, Ebola, and different types of cancers.

Monoclonal antibodies are developed by making clones (copies) of a specific antibody-producing B cell that targets the desired antigen (this process is explained in more detail later in the course). The desired antigen can be a particular disease-causing pathogen or cell protein. By cloning the B cell, millions of copies of the desired antibody can be produced. Treatments consist of injected doses of many identical copies of the antibody to neutralize or clear the antigen and lessen the disease symptoms.

Monoclonal antibodies mimic naturally-occurring antibodies and have several indications:

- Early in infectious disease, to prevent disease from becoming severe during the period of time that passes before the body can mount its own antibody response;
- In patients who lack prior vaccination against the pathogen or are severely immunocompromised and cannot form their own antibodies in sufficient numbers to fight off the pathogen themselves;
- To interrupt the disease process in patients with some chronic conditions (such as certain cancers or autoimmune diseases).

Before discussing monoclonal antibodies in detail, the following section lays the groundwork for understanding the concept behind mAb treatments: antibodies and the immune system.

ANTIBODIES & THE IMMUNE SYSTEM

The immune system is comprised of many components that work together to protect the body against disease. A large portion of immunology is beyond the scope of this course. Instead, this course focuses on the two specific immune system components that are most relevant to mAb technology: **B cells** and **antibodies.** Refer to the glossary on page 3 for definitions of the words in bold font throughout this section.

B cells and the adaptive immune response

B cells are antibody-producing immune system cells that fall under the class of white blood cells called **lymphocytes.** B cells and another type of lymphocyte called T cells are components of the **adaptive immune response**.

The adaptive immune response is an immune system action that forms in response to an exposure to something specific. For example, when a **pathogen** such as a virus is

encountered by the body for the first time, the adaptive immune response takes several days to fully organize and mount an attack against it. This delay is due to the immune system not having yet familiarity with this virus. The immune system must coordinate a specific response against this particular virus.

During the time it takes the immune system to build a virus-specific response, the virus is able to replicate and cause disease symptoms in the body. After several days, the immune response will become strong enough to clear the virus and the individual will recover. Memory B cells and memory T cells will be formed that linger for years, waiting to act if that same virus is encountered again. Generally, in an immunocompetent person, any subsequent exposure to that same virus will be resolved immediately and the individual is generally considered to be immune. This is a large part of the premise behind vaccination.

One of the most important steps of the adaptive immune response is the formation of **antibodies**. B cells produce antibodies that are specific a single pathogen; in fact, antibodies are so specific they actually respond to a distinct portion of a pathogen. This means an immune response against one pathogen can elicit the production of many distinct antibodies, each working against different portions of the pathogen. These portions of a pathogen that trigger antibody formation are called **antigens**, and a single pathogen likely consists of several antigens.

To speak in even more detail, when antibodies bind to an antigen, they are actually binding to small portions of the antigen called **epitopes.** An epitope is the smallest part of an antigen that is recognizable by the immune system, and a single antigen can possess multiple epitopes.

Pathogen / antigen / epitope summary

To summarize**,** a pathogen can consist of a multitude of different antigens, and an antigen can have multiple different epitopes. This means that the body possesses an enormous amount of B cells. For every pathogen you ever recovered from in your lifetime, you have B cells that recognize different components of each one of those pathogens.

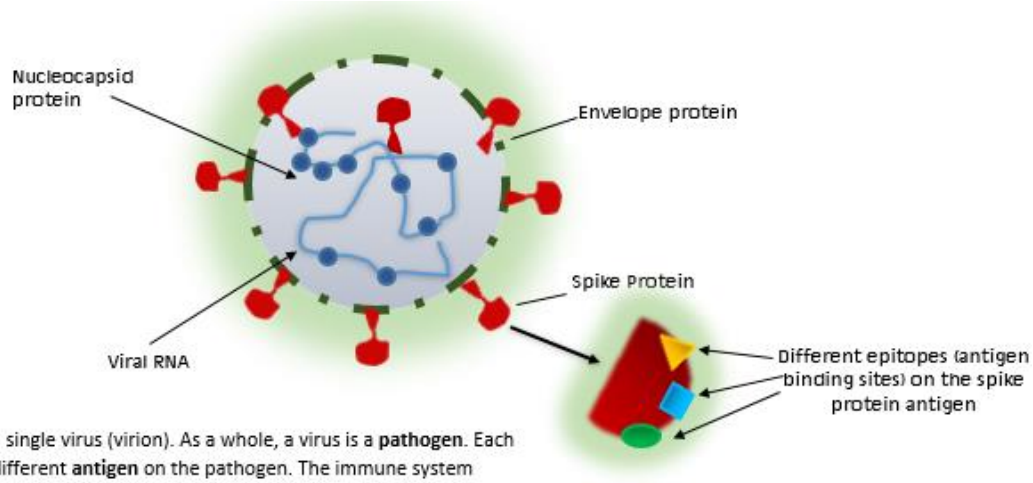
The immune system can also mount an immune response against antigens that don't necessarily originate from a pathogen, such as autoimmune conditions (where "self" becomes an antigen), toxins, cancer cells, or foreign cells (as with transfusions or organ transplants).

Remember, an antigen is the term for any molecular structure that elicits antibody formation against it – usually part of a pathogen, toxin, or cell. An epitope is the antibody's binding spot on the antigen. Epitopes vary in shape and physical properties.

Although they are different things, this course will sometimes use pathogen, antigen, and epitope interchangeably.

However, it's important to understand the relationship between the three terms:

Pathogen > antigen > epitope



This is a depiction of a single virus (virion). As a whole, a virus is a **pathogen**. Each protein represents a different **antigen** on the pathogen. The immune system naturally responds to, and forms antibodies against, the many different antigens on a single pathogen.

The enlarged spike protein portion to the right loosely depicts the different antibody binding sites that can exist on a single antigen. These antibody binding sites are called **epitopes**. Unique antibodies form in response to these specific epitopes. Epitopes vary in shape and physical properties.

B cell immune response in more detail

A not-yet activated B cell is a naïve B cell, which means that B cell has not yet encountered an antigen to activate it. When a naïve B cell encounters a new antigen for the first time, the B cell differentiates into either a **plasma cell** (which is an antibody-producing B cell) or a **memory B cell** (which hang around for years as a part of the immune memory and await future encounters with that same antigen; they can be quickly activated into plasma cells and multiplied). Both the plasma cells and the memory B cells are specific to that particular antigen.

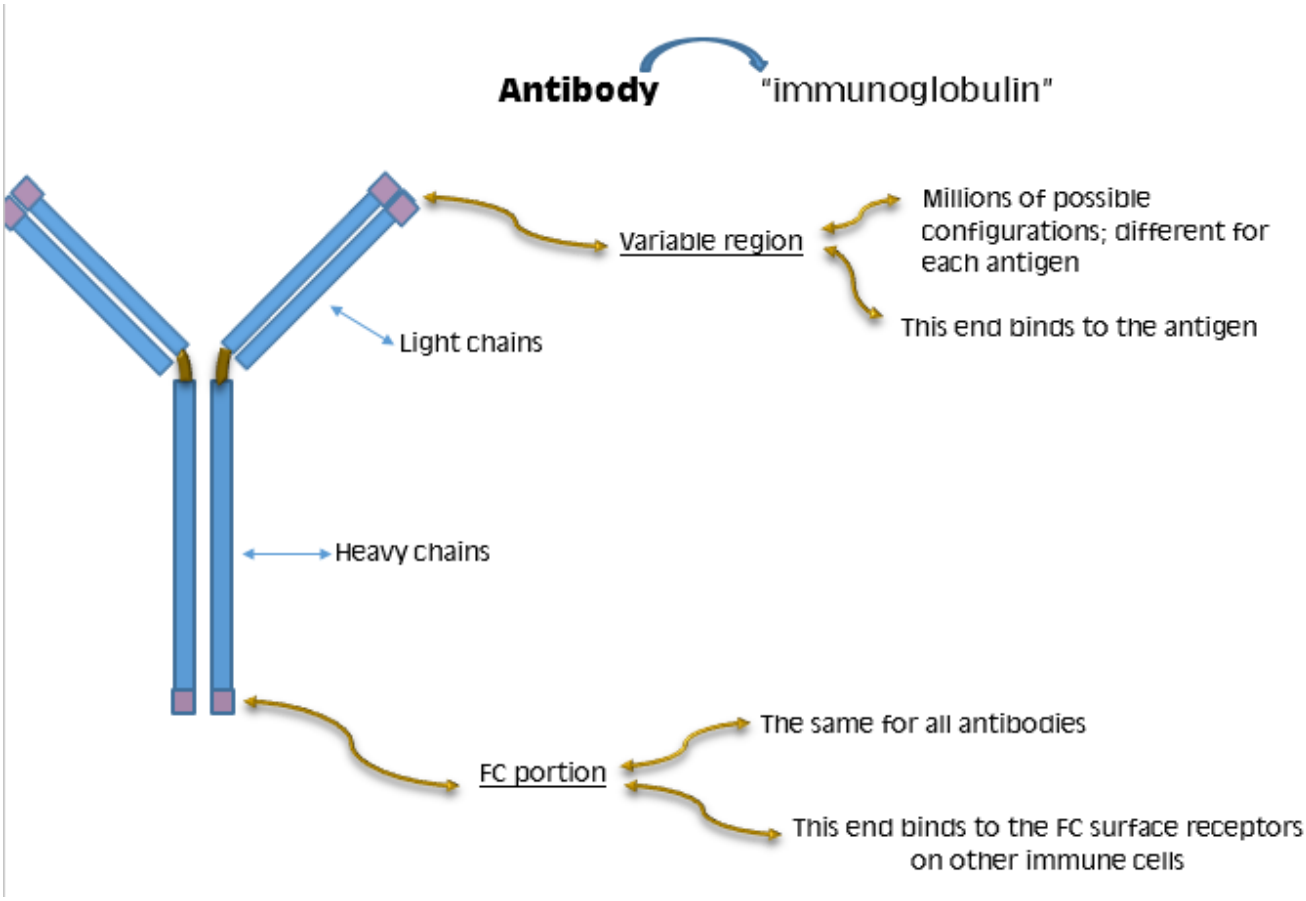
Plasma cells produce vast amounts of their specific antibody to help the immune system neutralize or destroy the antigen. However, once the antigen is cleared from the system, the amount of circulating antibody can wane. If the antigen is encountered again, the memory B cells that were sitting idly will differentiate into plasma cells and begin producing large amounts of antibody until the antigen is cleared again. The antibody response to a second encounter with the antigen occurs immediately. In the case of infectious disease with, say, a virus, this means the pathogen won't be able to become established, replicate, or cause disease and the individual is immune.

It's important to understand that a pathogen can mutate enough for memory cells to not recognize its antigens in the future. This is why one individual can become sick with influenza (the flu) multiple times in their life. Alternatively, a pathogen's partial antigenic mutation can still elicit an immune response, but a weaker one. For example, the specific epitopes on a pathogen's antigens can undergo enough of a molecular reconfiguration that weakened **affinity** results. Weakened affinity means the antibodies no longer tightly bind to the antigen because the epitope is no longer a perfect fit. This can result in the immune system's inability to immediately clear a pathogen upon a subsequent exposure. It's possible, however, that a milder form of disease might occur in this case, as some partial immune protection could still exist.

Antibody structure

Antibodies are also called immunoglobulins. An antibody's structure consists of the following components: two identical heavy chains and two smaller identical light chains.

Antibodies form a shape like a capital letter "Y".



The **FC portion** of the antibody, also called the **constant region**, is located at the end of the heavy chains and is generally the same among all antibodies. The FC portion of an antibody binds to the cells of the immune system to trigger immune cell actions that destroy and clear the pathogen. The immune cells have a corresponding FC receptor that binds to the FC portion of the antibody.

The top of the Y contains the **variable region** of the antibody. This is the end of an antibody that is specific for a particular antigen's epitope and only binds to that epitope. This end of an antibody has millions of possible configurations, and each configuration is specific for binding to the corresponding configuration of the molecular structure of the epitope it matches. The variability of this variable region is the reason for the great diversity of specificities among antibodies.

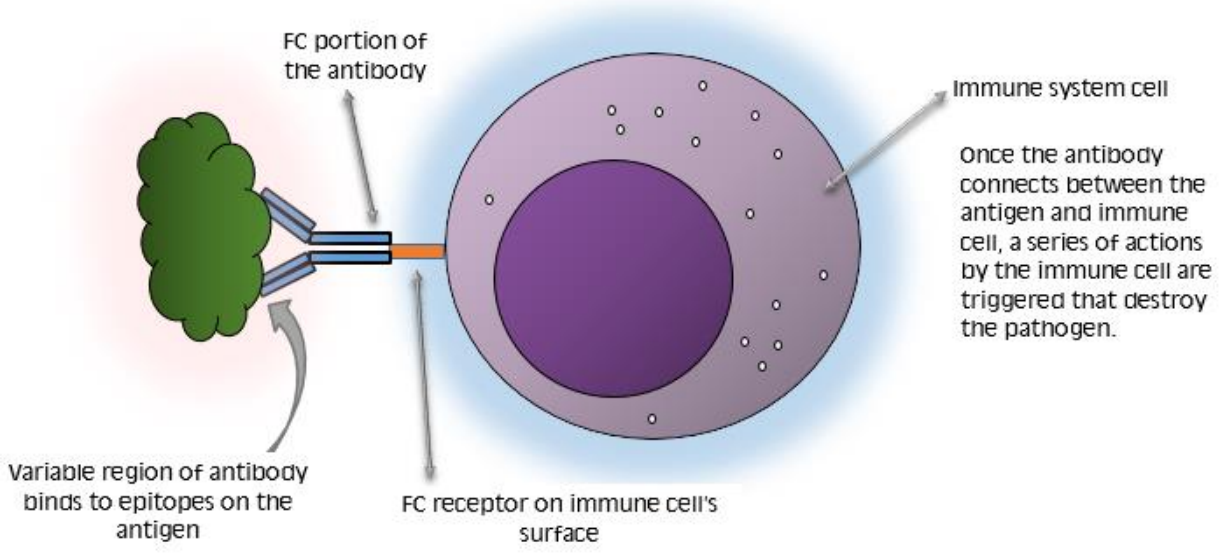


Illustration of an antibody bound to both an antigen and an immune system cell at the FC portion/receptor junction

What exactly do antibodies do?

Once an antibody binds to an antigen, they have several different types of actions they can take. Sometimes antibodies work alone to neutralize a toxin or pathogen. Other times they aid the rest of the immune system in the destruction and clearance of cells or pathogens. The following describes several different possible antibody actions.

- Antibodies bind their variable region to the epitope on the antigen and form an antigen/antibody complex. Then, the FC portion of the antibody will bind to an immune system cell. This action sets off a cascade of immune system reactions that destroy the pathogen and clear it from the body.

- Antibodies attach their variable regions to receptors on the surface of the antigen and neutralize the pathogen or toxin themselves by disrupting their function. Ex: antibodies can bind to a site on a virus that blocks the virus from entering cells (viruses must enter cells in order to replicate and cause disease).

- Antibodies bind their variable region to antigens and cause the antigens to clump together, which can slow the pathogens down.

- Multiple antibodies can coat themselves over an antigen (called opsonization) in order to make the pathogen visible to other immune cells, which then engulf or destroy the offending pathogen.

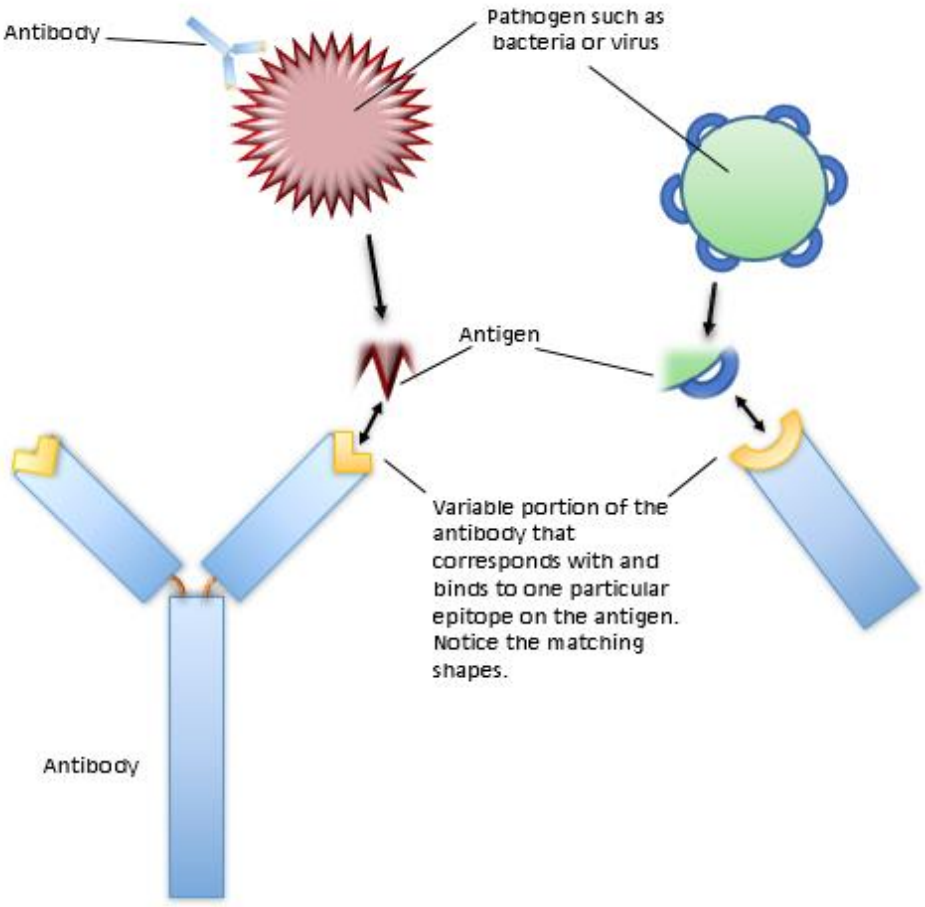


Illustration that demonstrates how an antibody's variable region has specificity for a particular antigen.

MONOCLONAL ANTIBODY (mAb) TREATMENTS

Now that antibody structure and function have been discussed, the concept behind monoclonal antibodies (mAbs) can be described. Monoclonal antibody technology takes advantage of the specificity and affinity of an antibody toward its corresponding antigen. Antibodies against a specific antigen can be mass produced. From here they can be developed into therapeutics for the treatment of disease, or reagents that detect and quantify the antigen in patient specimens. In fact, many laboratory tests use antibodies this way, both in research and diagnostics.

When antibodies are lab-developed, they must be carefully produced by making many copies of a single antibody of the desired specificity. Since these antibodies are all identical, they are called **monoclonal antibodies**. The word monoclonal means "single clone." Monoclonal antibodies (mAbs) are produced from a single lab-grown, antibody-producing B cell that is multiplied over and over. The goal is to harvest a specific type of B cell that will produce a large amount of antibody of the desired specificity.

When used as treatments, mAbs are injected into the patient usually either intravenously or subcutaneously. Once the dose is in a patient's body, the antibodies go

to work immediately to begin binding the offending antigen, resulting in neutralization or destruction just as your own antibodies would.

The purpose of mAb treatments is to “fill in” during a time when a patient’s own antibodies are inadequate, or to fight a disease that the patient’s immune system cannot. As stated earlier in the course, mAbs mimic naturally-occurring antibodies and have uses as treatments in several scenarios:

- Early in infectious disease, to prevent disease from becoming severe during the period of time that passes before the body can mount its own antibody response;
- In patients who lack prior vaccination to the pathogen or are severely immunocompromised and cannot form their own antibodies in sufficient numbers to fight off the pathogen themselves;
- To interrupt the disease process in patients with some chronic conditions (such as certain cancers or autoimmune disease).

Some Common mAb Treatments in Use Today

Dozens of different mAb treatments are FDA approved for several conditions, such as rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, Ebola, and different types of cancers. Following is a list with descriptions of some commonly used mAb treatments.

- **Rituximab**- FDA approved in 1997. Targets the CD20 protein on the surface of B cells. Given the topic of B cells in this course, it may seem curious that there is a monoclonal antibody treatment directed at B cells themselves. However, in some cancers related to the B cells, such as some non-Hodgkins lymphomas, Rituximab causes the immune system to target and destroy B cells, which are mostly malfunctioning malignant B cells that were otherwise proliferating uncontrollably. This destroys the cancer cells, but also acts as an immunosuppressant. However, since antibody-producing plasma cells do not express CD20, individuals who are treated with Rituximab can still produce their own antibodies. Normal populations of circulating B cells are usually restored within one year. Rituximab is also used in some autoimmune conditions, such as rheumatoid arthritis.

- **Alemtuzumab** – Fully FDA approved in 2007 (in use since 2001). Targets the CD52 protein on T cells and B cells. Used to treat MS and B-cell chronic lymphocytic leukemia.

- **Trastuzumab** – FDA approved in 1998. Targets Her2 receptor protein on the surface of cancerous cells of the breast. Causes immune cells to attack and destroy cells associated with the Her2 protein in metastatic breast cancer.

- **Infliximab**, and **Adalimumab** – (initially FDA approved in 1998 and 2002, respectively). Target a cytokine (a signaling chemical in the body) called tumor necrosis factor alpha (TNFα). This cytokine contributes to inflammatory processes, such as those associated with inflammatory bowel disease (IBD),

rheumatoid arthritis, and psoriasis. These monoclonal antibody treatments help to limit the inflammation associated with these conditions.

- **Ranibizumab** – FDA approved in 2006. Targets vascular endothelial growth factor A (VEGF A), which is a growth factor that stimulates the development of new blood vessels. This treatment is useful for some cases of macular degeneration, and is injected directly into the patient's eye. This can help to slow the development of new blood vessels in the retina of those with age-related macular degeneration.

Monoclonal Antibody Nomenclature

Monoclonal antibodies are named based on a specific structure developed by the International Nonproprietary Names Working Group, under the direction of the World Health Organization.

The suffix —mab is a common stem for all monoclonal antibodies.

History and Development of mAbs

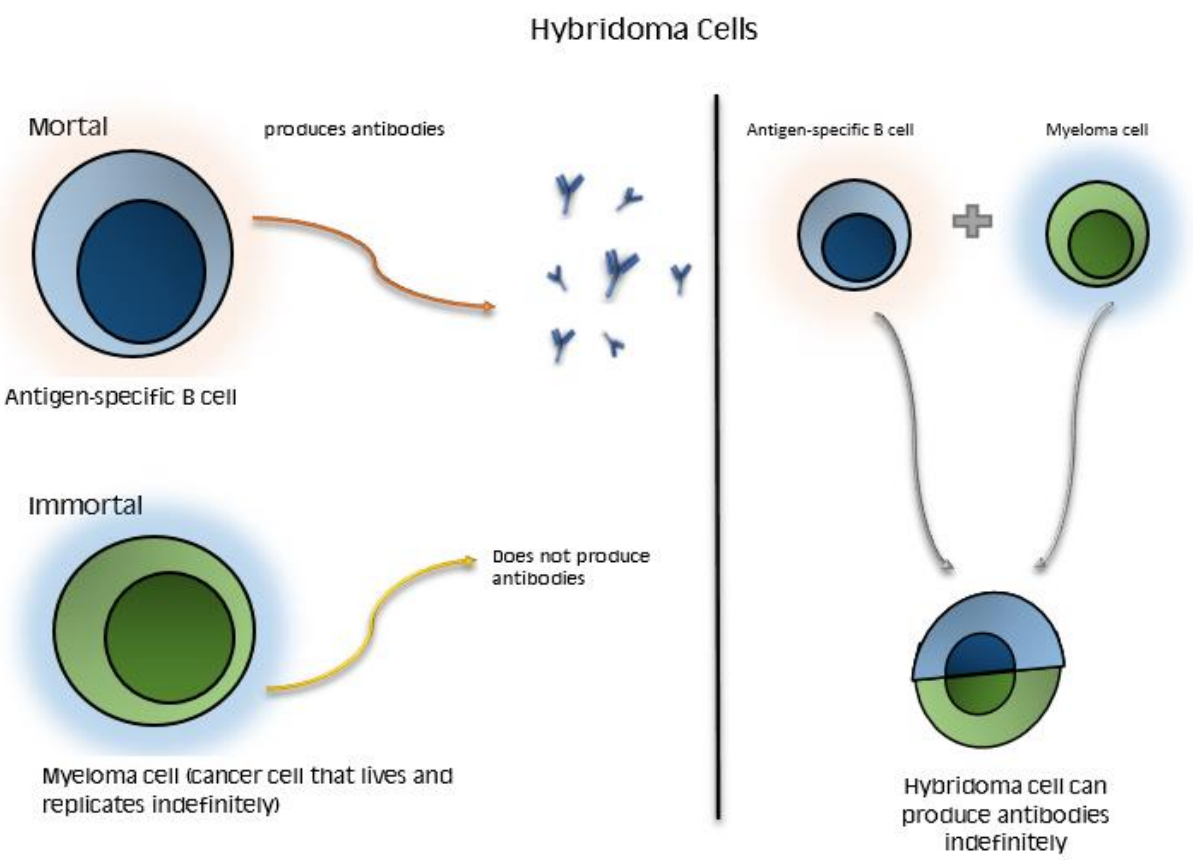
History

The first monoclonal antibody (mAb) was generated in 1975 and, shortly after, the first successful use of mAbs as a therapeutic took place during a kidney transplant to stop the recipient from rejecting the donor kidney. In this case, mouse-derived monoclonal antibodies were directed at the CD3 protein on the recipient's own T-cells which blocked the T-cell action that initiates rejection of the donor's organ. This immunosuppressive mAb treatment was FDA approved in 1986 under the name muromonab-CD3 (and has since been withdrawn from the U.S. market in 2010). The CD3 protein on the recipient's own cells are the target antigen for this mAb treatment.

Techniques for development

Monoclonal antibodies are developed in biotechnology laboratories. The majority of techniques for developing mAbs are complex and beyond the scope of this course. One technology, a common method called **hybridoma technology**, is briefly described below.

Hybridoma technology - A mouse is injected with an antigen that provokes a B cell response by the mouse's immune system. These B-cells are harvested from the mouse and, in a cell culture, are fused with immortal B-cell cancer cells (myeloma cells) to produce a hybrid cell line called a hybridoma. The hybridoma has the antibody producing ability of the B-cell (antibodies directed against the intended antigen) plus the myeloma's longevity and ability to mass produce the single desired antibody. A hybridoma is then gown in culture to produce clones (genetically identical replicas) of itself.



Undesired immune responses may occur in patients receiving antibodies that contain nonhuman (typically mouse) components. This means that a human's immune system perceives the mouse antibodies as foreign and might form its own antibodies against the mouse monoclonal antibodies, in order to eliminate them. This is undesirable. To reduce this problem, **chimeric** monoclonal antibodies have been developed that combine mouse variable regions (the portion that binds with the antigen) with human constant regions (the FC portion that binds to the patient's immune cells). This lessens the likelihood of human rejection of the monoclonal antibody treatment in the body.

Advancements have humanized monoclonal antibodies even further, where only a portion of the variable region remains of mouse origin. Furthermore, fully humanized monoclonal antibodies can now be made from human hybridomas or from mice whose antibody genes that have been replaced with human genes.

All four types of monoclonal antibodies (mouse, chimeric, humanized, and fully human) have been used therapeutically.

Monoclonal Antibodies for Post-Exposure Treatment of COVID-19

The COVID-19 emergency of 2020 and 2021 led to the development of monoclonal antibody products targeting SARS-CoV-2, the virus that causes COVID-19. Post-exposure monoclonal antibody treatments for COVID-19 are intended for patients who meet the following requirements:

- 12 years of age and older weighing at least 40 kg (Exception: the Bamlanivimab and etesevimab combination was authorized for neonates).
- At high risk for progression to severe COVID-19, including hospitalization or death, **and:**
    - not fully vaccinated **or** not expected to mount an adequate immune response to SARS-CoV-2 vaccination (for example, people with immunocompromising conditions, including those taking immunosuppressive medications), **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC).
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes or prisons).

Monoclonal antibodies are not authorized for use in the following patients:

- hospitalized due to COVID-19
- require oxygen therapy due to COVID-19
- require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

The goal of these treatment is to help prevent hospitalizations, reduce viral loads, and lessen disease severity. Post-exposure monoclonal antibody treatments are to be administered early in the COVID-19 disease process, and are more effective the earlier they are administered. Treatment is not effective for people who are already hospitalized or severely ill with COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Monoclonal antibody treatments for COVID-19 are designed to target the SARS-CoV-2 outer spike protein, meaning the spike protein is the antigen. The viral spike protein is what attaches the virus to the human cell and allows viral entry into the cell. These mAbs block viral entry to the cells, which neutralizes the virus.

The blood of recovered COVID-19 patients provide a source of antibodies that can be harvested and mass produced into monoclonal treatments for others. A recovered patient would have multiple unique antibodies that bind different epitopes on the spike protein antigen. From here, scientists use different techniques to determine which of these antibodies are the best candidates for mass production and viral neutralization.

The FDA strongly recommends COVID-19 mAbs be designed to target more than one SARS-CoV-2 epitope. This is to lessen the likelihood that a viral variant could escape the drug due to spike protein mutations.

At the time of this course, three separate post-exposure mAb treatments have received FDA Emergency Use Authorization (EUA) for COVID-19.

Post-Exposure Monoclonal Antibody Treatment	Disease	Target epitope on pathogen	FDA Status
REGEN-CoV (Casirivimab and Imdevimab)	COVID-19	Certain epitopes on the spike protein receptor binding domain (RBD) of SARS-CoV-2 virus	Emergency Use Authorization 11/21/2020 (revised 1/24/22 due to omicron variant)
Bamlanivimab and Etesevimab	COVID-19	Certain epitopes on the spike protein receptor binding domain (RBD) of SARS-CoV-2 virus	Emergency Use Authorization 2/9/2021 (revised 1/24/22 due to omicron variant)
Sotrovimab	COVID-19	Certain epitopes on the spike protein receptor binding domain (RBD) of SARS-CoV-2 virus	Emergency Use Authorization 5/26/2021, still in use at the time of this course

COVID-19 post-exposure monoclonal antibodies in more detail

- **Bamlanivimab** and E**tesevimab** bind to different but overlapping epitopes in the receptor binding domain (RBD) of the spike protein. Using both antibodies together is expected to reduce the risk of viral resistance.

- **Casirivimab** and **Imdevimab (REGEN-COV)** bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2.

- **Sotrovimab** binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 virus. Sotrovimab inhibits a step that occurs after virus attachment to the host's cell but prior to viral entry into the cell.

Update

On January 24, 2022, the Food and Drug Administration (FDA) revised the emergency use authorizations (EUA) for two COVID-19 monoclonal antibody treatments:

- Regeneron's REGEN-COV (**Casirivimab** and **Imdevimab**)
- Lilly's **Bamlanivimab** and **Etesevimab** (administered together)

The FDA reported that variant mutations in the epitopes of the SARS-CoV-2 virus's S protein (spike protein) has resulted in weakened affinity of the mAbs toward their target

antigens. This has caused these mAb treatments to suffer reduced effectiveness against certain variants, such as the omicron. At the time of this course, Centers for Disease Control and Prevention (CDC) is reporting the omicron variant to be the dominant circulating variant in the United States.

The FDA issued the following statement on January 24, 2022:

> "…these treatments are highly unlikely to be active against the omicron variant, which is circulating at a very high frequency throughout the United States, these treatments are not authorized for use in any U.S. states, territories, and jurisdictions at this time. In the future, if patients in certain geographic regions are likely to be infected or exposed to a variant that is susceptible to these treatments, then use of these treatments may be authorized in these regions."

Both of these treatments consist of two mAb drugs designed to target different epitopes on the spike protein antigen. These treatments were developed this way in order to safeguard against mutational virus escape, however, FDA has announced that these treatments still lost effectiveness against the predominant variant at the time of this course (omicron).

Also at the time of this course, GlaxoSmithKline/Vir Biotechnology, Inc's **Sotrovimab** is still in use and believed to be effective in treating the omicron variant. Sotrovimab targets a highly conserved epitope on the virus's spike protein antigen that is present across the entire family of SARS-like coronaviruses.

The EUA revisions issued by the FDA on January 24, 2022 provide a great example of how individual epitopes (antibody binding sites) on an antigen can change enough to affect the affinity of its corresponding antibody.

FDA update regarding the BA.2 omicron sub-variant: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization

At the time of this course, no COVID-19 monoclonal antibody treatments have been granted FDA approval. These drugs have only been granted emergency use authorization (EUA), which can be revised at any time.

Monoclonal Antibodies for Pre-Exposure Prophylaxis of COVID-19

Monoclonal antibodies can also be used as a "temporary vaccine" in those with weak immune systems (who will not form their own antibodies after vaccination). They only have a temporary effect because the immune system would be relying on injected antibodies, which have a limited life span of around 3-4 months.

Prophylactic monoclonal antibody treatments could effectively prevent infection, at least for a time. Vaccines take a while to work (several days), and might not work at all in older patients, such as those in nursing homes. A pre-exposure prophylactic monoclonal antibody treatment could help high-risk older populations prevent infection.

Pre-exposure prophylactic treatments against COVID-19 are recommended for patients who meet the following indications:

- Adults and pediatric individuals (12 years of age and older weighing at least 40 kg);
- Not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**:
  - Moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

One product is available for pre-exposure prophylaxis of COVID-19 under FDA emergency use authorization (EUA):

- **Evusheld** (**tixagevimab** and **cilgavimab**) - (EUA granted 12/8/2021)

Monoclonal Antibody Treatment Adverse Reactions

Monoclonal antibody treatments are a drug and are not without side effects. There are many types of monoclonal antibody treatments and their associated adverse reactions can vary depending on the mechanism of action of the monoclonal antibodies and the antigen they target.

Some non-severe possible adverse reactions include:

- Fever
- Chills
- Weakness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Rashes

Localized injection site reactions can occur after subcutaneous administration of mAbs. When administered intravenously, infusion reactions can occur. Infusion reactions are characterized as flushing, fever/chills, back or abdominal pain, nausea/vomiting, pruritus, or skin rashes. These reactions typically occur within 60 minutes of starting the infusion and typically do not become life-threatening. If an infusion reaction occurs, the infusion should be stopped. Once the symptoms resolve, the infusion can be resumed at a slower rate.

Allergic reactions are also possible in some patients. Although rare, anaphylaxis is life-threatening. Anaphylaxis must be distinguished from non-severe infusion-related

reactions. Anaphylaxis involves a rash, tongue or lip swelling, difficulty breathing, and low blood pressure.

Possible severe mAb adverse reactions include:

- Acute anaphylaxis
- Serum sickness
- Development of antibodies against the mAbs,
- Cytokine storms

For COVID-19, mAb therapy is not indicated in severe cases requiring hospitalization, as the treatments may be associated with worse outcomes for patients requiring high-flow oxygen or mechanical ventilation.

CONCLUSION

Monoclonal antibody (mAb) treatments take advantage of the specificity and affinity of an antibody toward its target antigen and have many uses across the field of medicine. The COVID-19 pandemic brought therapeutic mAbs to the forefront of many news cycles and conversations, but mAbs have a 30 year history of treating many diseases that were once difficult to manage. New uses for mAb treatments are always in development and mAbs will almost certainly continue to have a place in medicine long after the pandemic comes to an end.

Addendum

Following is a list of FDA approved mAb treatments at the time of this course (January 2022)

mAb Treatment	Route	Target antigen	Disease
abciximab	intravenous	GPIIb/IIIa	Percutaneous coronary intervention
adalimumab	subcutaneous	TNF	Rheumatoid arthritis
adalimumab-atto	subcutaneous	TNF	Rheumatoid arthritis Juvenile idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Crohn's disease Ulcerative colitis Plaque psoriasis
ado-trastuzumab emtansine	intravenous	HER2	Metastatic breast cancer
alemtuzumab	intravenous	CD52	B-cell chronic lymphocytic leukemia
alirocumab	subcutaneous	PCSK9	Heterozygous familial hypercholesterolemia Refractory hypercholesterolemia
atezolizumab	intravenous	PD-L1	Urothelial carcinoma Metastatic non-small cell lung cancer

avelumab	intravenous	PD-L1	Metastatic Merkel cell carcinoma
basiliximab	intravenous	IL2RA	Prophylaxis of acute organ rejection in renal transplant
belimumab	intravenous	BLyS	Systemic lupus erythematosus
bevacizumab	intravenous	VEGF	Metastatic colorectal cancer
bezlotoxumab	intravenous	Clostridium difficile toxin B	Prevent recurrence of Clostridium difficile infection
blinatumomab	intravenous	CD19	Precursor B-cell acute lymphoblastic leukemia
brentuximab vedotin	intravenous	CD30	Hodgkin lymphoma Anaplastic large-cell lymphoma
brodalumab	subcutaneous	IL17RA	Plaque psoriasis
canakinumab	subcutaneous	IL1B	Cryopyrin-associated periodic syndrome
capromab pendetide	intravenous	PSMA	Diagnostic imaging agent in newly diagnosed prostate cancer or post-prostatectomy
certolizumab pegol	subcutaneous	TNF	Crohn's disease
cetuximab	intravenous	EGFR	Metastatic colorectal carcinoma
daclizumab	intravenous	IL2RA	Prophylaxis of acute organ rejection in renal transplant
daclizumab	subcutaneous	IL2R	Multiple sclerosis
daratumumab	intravenous	CD38	Multiple myeloma
denosumab	subcutaneous	RANKL	Postmenopausal women with osteoporosis
dinutuximab	intravenous	GD2	Pediatric high-risk neuroblastoma
dupilumab	subcutaneous	IL4RA	Atopic dermatitis, asthma
durvalumab	intravenous	PD-L1	Urothelial carcinoma
eculizumab	intravenous	Complement component 5	Paroxysmal nocturnal hemoglobinuria
elotuzumab	intravenous	SLAMF7	Multiple myeloma
evolocumab	subcutaneous	PCSK9	Heterozygous familial hypercholesterolemia Refractory hypercholesterolemia
golimumab	subcutaneous	TNF	Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis
golimumab	intravenous	TNF	Rheumatoid arthritis
ibritumomab tiuxetan	intravenous	CD20	Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma
idarucizumab	intravenous	dabigatran	Emergency reversal of anticoagulant dabigatran
infliximab	intravenous	TNF alpha	Crohn's disease

infliximab-abda	intravenous	TNF	Crohn's disease Ulcerative colitis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis
infliximab-dyyb	intravenous	TNF	Crohn's disease Ulcerative colitis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis
ipilimumab	intravenous	CTLA-4	Metastatic melanoma
ixekizumab	subcutaneous	IL17A	Plaque psoriasis
mepolizumab	subcutaneous	IL5	Severe asthma
natalizumab	intravenous	alpha-4 integrin	Multiple sclerosis
necitumumab	intravenous	EGFR	Metastatic squamous non-small cell lung carcinoma
nivolumab	intravenous	PD-1	Metastatic melanoma
nivolumab	intravenous	PD-1	Metastatic squamous non-small cell lung carcinoma
obiltoxaximab	intravenous	Protective antigen of the Anthrax toxin	Inhalational anthrax
obinutuzumab	intravenous	CD20	Chronic lymphocytic leukemia
ocrelizumab	intravenous	CD20	Multiple sclerosis
ofatumumab	intravenous	CD20	Chronic lymphocytic leukemia
olaratumab	intravenous	PDGFRA	Soft tissue sarcoma
omalizumab	subcutaneous	IgE	Moderate to severe persistent asthma
palivizumab	intramuscular	F protein of RSV	Respiratory syncytial virus
panitumumab	intravenous	EGFR	Metastatic colorectal cancer
pembrolizumab	intravenous	PD-1	Metastatic melanoma
pertuzumab	intravenous	HER2	Metastatic breast cancer
ramucirumab	intravenous	VEGFR2	Gastric cancer
ranibizumab	intravitreal injection	VEGFR1 VEGFR2	Wet age-related macular degeneration
raxibacumab	intravenous	Protective antigen of Bacillus anthracis	Inhalational anthrax
reslizumab	intravenous	IL5	Severe asthma
rituximab	intravenous	CD20	B-cell non-Hodgkin's lymphoma
secukinumab	subcutaneous	IL17A	Plaque psoriasis
siltuximab	intravenous	IL6	Multicentric Castleman's disease
tocilizumab	Intravenous subcutaneous	IL6R	Rheumatoid arthritis Polyarticular juvenile idiopathic arthritis Systemic juvenile idiopathic arthritis
tocilizumab	intravenous	IL6R	Rheumatoid arthritis
trastuzumab	intravenous	HER2	Metastatic breast cancer

ustekinumab	subcutaneous	IL12 IL23	Plaque psoriasis
ustekinumab	Subcutaneous intravenous	IL12 IL23	Plaque psoriasis Psoriatic arthritis Crohn's disease
vedolizumab	intravenous	integrin receptor	Ulcerative colitis Crohn's disease
sarilumab	subcutaneous	IL6R	Rheumatoid arthritis
rituximab and hyaluronidase	subcutaneous	CD20	Follicular lymphoma Diffuse large B-cell lymphoma Chronic lymphocytic leukemia
guselkumab	subcutaneous	IL23	Plaque psoriasis
inotuzumab ozogamicin	intravenous	CD22	Precursor B-cell acute lymphoblastic leukemia
adalimumab-adbm	subcutaneous	TNF	Rheumatoid arthritis Juvenile idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Crohn's disease Ulcerative colitis Plaque psoriasis
gemtuzumab ozogamicin	intravenous	CD33	Acute myeloid leukemia
bevacizumab-awwb	intravenous	VEGF	Metastatic colorectal cancer Non-squamous Non-small-cell lung carcinoma Glioblastoma Metastatic renal cell carcinoma Cervical cancer
benralizumab	subcutaneous	interleukin-5 receptor alpha subunit	Severe asthma, eosinophilic phenotype
emicizumab-kxwh	subcutaneous	Factor IXa, Factor X	Hemophilia A (congenital Factor VIII deficiency) with Factor VIII inhibitors.
trastuzumab-dkst	intravenous	HER2	HER2-overexpressing breast cancer, metaststic gastric or gastroesophageal junction adenocarcinoma
infliximab-qbtx	intravenous	TNF	Crohn's disease Ulcerative colitis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis
ibalizumab-uiyk	intravenous	CD4	HIV
tildrakizumab-asmn	subcutaneous	IL23	Plaque psoriasis
burosumab-twza	subcutaneous	FGF23	X-linked hypophosphatemia
erenumab-aooe	subcutaneous	CGRP receptor	Migraine headache prevention

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TEST QUESTIONS

Monoclonal Antibody (mAb) Treatments #1220422

Directions:

- Answer sheets: Read the instructions to assure you correctly complete the answer sheets.
- Online: Log in to your User Account on the NCCT website www.ncctinc.com.
  - **NOTE:** If the online test questions differ from the course test that follows the reading material, the CE course you are using is outdated or the question has been revised since you downloaded it. The online question is the most current and it should be answered accordingly.
- Select the response that best completes each sentence or answers each question from *the information presented in the course*.
- If you are having difficulty answering a question, go to www.ncctinc.com and select *Forms/Documents*. Then select *CE Updates and Revisions* to see if course content and/or a test questions have been revised. If you do not have access to the internet, call Customer Service at 800-875-4404.

1. Monoclonal antibody (mAb) treatments can be used to treat which of the following conditions?

   a. COVID-19
   b. Some autoimmune conditions
   c. Some cancers
   d. All of the above

2. Lymphocytes called _____ produce antibodies as a part of the _____ immune response.

   a. B cells; innate
   b. B cells; adaptive
   c. T cells; innate
   d. T cells; adaptive

3. When a pathogen such as a virus is encountered by the body for the first time, how long does the adaptive immune response take fully organize and mount an attack against it?

   a. Immediate
   b. Several days
   c. Several weeks
   d. Several months

4. An antigen is any substance that can elicit antibody formation against it. Which of the following can contain antigens?

    a. A pathogen, such as a virus or bacteria
    b. A cell (foreign or self, or cancer)
    c. A toxin
    d. All of the above

5. A pathogen can consist of a multitude of different antigens, and an antigen can have multiple different epitopes where antibodies can bind. This means many unique antibodies can form against a single pathogen.

    a. True
    b. False

6. What does it mean for an antibody to have weakened affinity for its antigen?

    a. The antibody no longer tightly binds to its antigen because a mutation of the epitope caused it to no longer be a perfect fit.
    b. The antibody no longer tightly binds to its antigen because a mutation of the antibody caused it to no longer be a perfect fit.
    c. The antigen no longer tightly binds to its epitope because a mutation of the antibody caused it to no longer be a perfect fit.
    d. The antigen no longer tightly binds to its epitope because a mutation of the antigen caused it to no longer be a perfect fit.

7. Which of the following is true about antibody structure?

    a. The constant region has millions of possible configurations and binds to a specific antigen's epitope; the FC portion is mostly the same for all antibodies and binds to immune cells
    b. The FC portion has millions of possible configurations and binds to a specific antigen's epitope; the variable region is mostly the same for all antibodies and binds to immune cells
    c. The variable region has millions of possible configurations and binds to a specific antigen's epitope; the FC portion is mostly the same for all antibodies and binds to immune cells
    d. The FC portion has millions of possible configurations and binds to a specific antigen's epitope; the constant region is mostly the same for all antibodies and binds to immune cells.

8. Which of the following is a scenario in which monoclonal antibody treatments might be useful?

    a. In the early stage of an infection in patients at risk of developing severe disease.
    b. In patients with certain cancers or autoimmune diseases.
    c. Both A and B
    d. Neither A nor B

9. Rituximab is a commonly administered therapeutic monoclonal antibody treatment. What condition does it treat?

    a. COVID-19
    b. Inflammatory bowel disease
    c. Breast cancer
    d. Some non-Hodgkins lymphomas

10. What was the first monoclonal antibody treatment used for and when was it FDA approved?

    a. To prevent a recipient's immune system from rejecting a donor's kidney, FDA approved in 1986.
    b. To destroy non-Hodgkins lymphoma cancer cells, FDA approved in 1997.
    c. To prevent severe COVID-19 disease, FDA approved in 2021.
    d. To prevent a recipient's immune system from rejecting a donor's kidney, but no monoclonal antibody treatments are FDA approved.

11. In January 2022 what reason did the FDA give for revising the emergency use authorization (EUA) of two different COVID-19 post-exposure mAb treatments?

    a. Mutations on the target epitopes of the virus's nucleocapsid protein resulted in the mAbs having stronger affinity for their target antigen and therefore reduced effectiveness.
    b. Mutations on the target epitopes of the virus's spike protein resulted in the mAbs having stronger affinity for their target antigen and therefore reduced effectiveness.
    c. Mutations on the target epitopes of the virus's nucleocapsid protein resulted in the mAbs having weaker affinity for their target antigen and therefore reduced effectiveness.
    d. Mutations on the target epitopes of the virus's spike protein resulted in the mAbs having weaker affinity for their target antigen and therefore reduced effectiveness.

End of Test

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Course Title: Monoclonal Antibody (mAb) Treatments Course #: 1220422

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COURSE CONTENT

____Yes ____No 3. Were you satisfied with this course?

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____Yes ____No 5. Was this CE course written at the right level for the practicing professional?

VALUE

____Yes ____No 6. Did you learn anything new?

____Yes ____No ____Maybe 7. Did you learn anything you might use at work?

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