Finding the Right Key

Using Antibody Therapy to Fight Infectious Disease

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Antibody immunotherapy is a modern treatment with a long history. As an alternative to traditional medicine, antibodies that fight infection are purified from recovered patients or engineered in laboratories. Hundreds of clinical trials are underway that assess the efficacy of antibody therapy for treating drug resistant infections and emerging pathogens, such as SARS-CoV-2.

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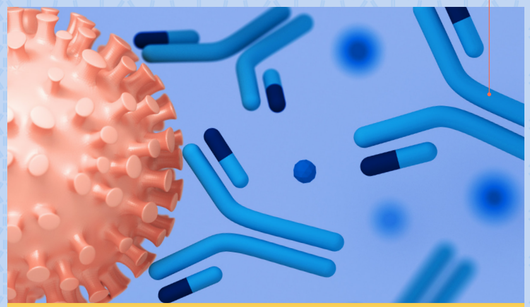
Antibody Basics

Antibodies enhance the immune response by binding to target antigens on foreign cells and particles. Pathogens display a variety of antigens made from proteins, polysaccharides, or nucleic acids.

Once antibodies bind their target, the immune system eliminates the foreign invader through several mechanisms, including recruitment and binding to phagocytic cells, direct cell lysis, and neutralization by coating the surface of antigenic particles.[1]

Each antibody is highly specific to a single antigen, like a unique key fitting into a single lock.



Antibodies binding antigen on virus

Origins of Antibody Therapy

In the 1890s, Emil von Behring and Kitasato Shibasaburo worked at the Institute for Infectious Diseases in Berlin to develop an antibody therapy for diphtheria. They immunized animals with the *Corynebacterium diphtheriae* toxin, collected their blood sera, and found that the sera protected other animals from the toxin's adverse effects. The sera, commonly referred to as antitoxin, contained antibodies that conferred passive immunity against diphtheria toxin. In 1901, Behring was awarded the first Nobel Prize in Physiology or Medicine for this work. [2]

Once scientists began to purify serum from sheep and cattle, physicians used antitoxins to treat infectious diseases.[3] Serum therapy reduced diphtheria mortality from 50% - 80% to less than 15.5%.[4]

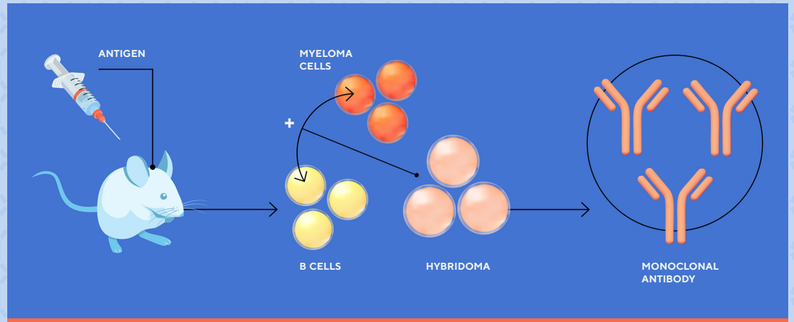
Famously, in 1925, an outbreak of diphtheria in Nome, Alaska, precipitated the need for a heroic delivery of antitoxin. A relay of sled dog teams transported the sera 674 miles in 5.5 days across the frigid Alaskan landscape to save the inhabitants of Nome.[5]

A Key Technique Paves the Way

Serum antibody therapy fell out of favor in the 1940s after antibiotics were discovered; however, scientists still saw promise in the technique, especially for cancer treatment. To develop potent cancer therapeutics, researchers needed to purify large amounts of monoclonal antibodies that targeted a single portion, or epitope, of an antigen.

In 1975, César Milstein and Georges J. F. Köhler from the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, developed the hybridoma technique for the large-scale production of monoclonal antibodies.[6] To form hybridomas, scientists first inject mice with an antigen.

After the mice mount an immune response, the scientists harvest antibody-producing B cells and select for specificity against the desired epitope. Scientists fuse the B cells to myeloma cells, forming an immortal cell hybrid that produces antigen-specific antibodies.



Hybridoma Technique

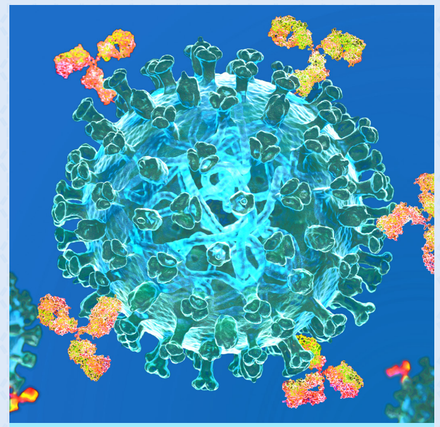
Current Monoclonal Antibody Therapies for Infectious Diseases

For decades, antibody therapy lagged due to the low cost and availability of antibiotics. However, the bacterial drug resistance crisis and emergence of novel infectious diseases have caused an explosion of antibody clinical trials and approved therapies.[11, 12]

According to clinicaltrials.gov, as of 2020 over 300 antibody clinical trials are active and recruiting around the world to test potential treatments against well-known agents of disease, such as *Staphylococcus aureus, Escherichia coli*, HIV, and malaria, and pathogens that cause emerging diseases, such as Zika virus, Ebola virus, Chikungunya virus, and SARS-CoV-2.

SPOTLIGHT ON COVID-19

Because of the COVID-19 pandemic, researchers are rapidly generating treatment options for SARS-CoV-2 infection, including monoclonal antibody therapies. Clinical trials are underway for virus-neutralizing antibodies that bind to the viral spike protein that attaches to host cells. Scientists are generating human antibodies from genetically engineered mice and cows immunized with the spike protein. Researchers are also employing convalescent plasma therapy, which isolates sera from people who have survived COVID-19 infection and uses bioinformatics to screen the samples for promising candidates.[13]



SARS-CoV-2 with Antibodies

Monoclonal Antibodies Make Their Mark

The first monoclonal antibodies produced from hybridomas were not clinically successful because they did not effectively recruit host effectors and they often elicited an anti-mouse immune response.[7] As a result, scientists now employ several techniques using human antibodies to increase efficacy:

1 ENGINEERED ANTIBODIES

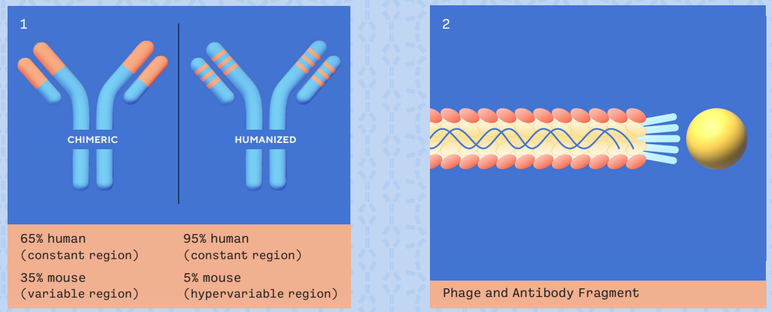
Genetic engineering produces chimeric and humanized antibodies that fuse mouse and human regions.[8]

2 PHAGE DISPLAY

This in vitro method selects for antibodies that have a high affinity for a target antigen. Scientists engineer bacteriophages to express human antibodies on their surface and apply them to a solid surface with antigen fragments. Once the antibodies attach to their targets, scientists isolate and amplify bound phages.[9]

3 TRANSGENIC ANIMALS

Mice or other animals are engineered to have fully human antibody repertoires. Their immune systems produce human antibodies in response to an antigen, and the antibody-secreting B cells are immortalized via the hybridoma technique.[10]



Phage and Antibody Fragment

Mouse Producing Human Antibodies

Monoclonal Antibodies for Treating Infectious Diseases [11,12]

PATHOGEN	TARGET	NAME	TYPE OF MAB	U.S. APPROVAL
Ebola Virus	3 Glycoprotein Epitopes	REGN-EB3	Mix of 3 Human	In Review
Human Immunodeficiency Virus (HIV)	CCR5 T Cell Receptor	Leronlimab	Humanized	In Review
Human Immunodeficiency Virus (HIV)	CD4 T Cell Receptor	Ibalizumab	Humanized	2018
Clostridium difficile (C. diff)	Enterotoxin B	Bezlotoxumab	Human	2016
Bacillus anthracis (Anthrax)	Anthrax Toxin Protective Antigen	Obiltoxaximab	Chimeric	2016
Bacillus anthracis (Anthrax)	Anthrax Toxin Protective Antigen	Raxibacumab	Human	2012