ILD Collaborative

A Patient-Physician Collaborative for the Understanding, Management, and Treatment of Interstitial Lung Diseases

# From Convalescent Plasma to Monoclonal Antibodies

## Combination Prevention in Pandemics

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# Active versus Passive Immunity

*Active immunity* is acquired through the body's own immune response to an infectious agent, either directly through infection, or through vaccination. The immune system develops a memory that helps it defend against another infection with the same agent.

*Passive immunity* is acquired through receiving infusions of antibodies against the infectious agent. This from of immunity does not activate one's immune system and is less durable. It may be achieved through infusions of *convalescent plasma,* or *monoclonal antibodies.*

# Convalescent Plasma

Milestone 4 1890

## Serum power

The transfer of blood sera from individuals who had recovered from an infectious disease to individuals with ongoing infection with the same pathogen was first described for tetanus and diphtheria; this approach is still used today as a first-line therapy against arising viral infections for which few or no treatments exist. Read More

By Alison Farrell


Credit: SSPL / Getty Images

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**Nature Milestones in Vaccines: Serum Power**
*https://www.nature.com/articles/d42859-020-00009-4*

# Convalescent Plasma

Plasma is the straw-colored, clear part of the blood that is free of cells and cell fragments. It makes up about 55% of the blood, and contains water (~90%), salts, enzymes, *antibodies*, and other proteins.

Following recovery from an infection, antibodies against the infectious agent are found in the plasma of the convalescing patient.

Convalescent plasma can be used to treat, or actively vaccinate, people who are sick with, or susceptible to the infection.

# Convalescent Plasma

## Convalescent plasma and COVID-19

The blood of recovered COVID-19 patients contains proteins called antibodies developed by the immune system to fight the SARS-CoV-2 virus. Antibodies are found in the blood plasma, which can be collected and used to treat other COVID-19 patients with a **convalescent plasma** transfusion that is safe and has few side effects.

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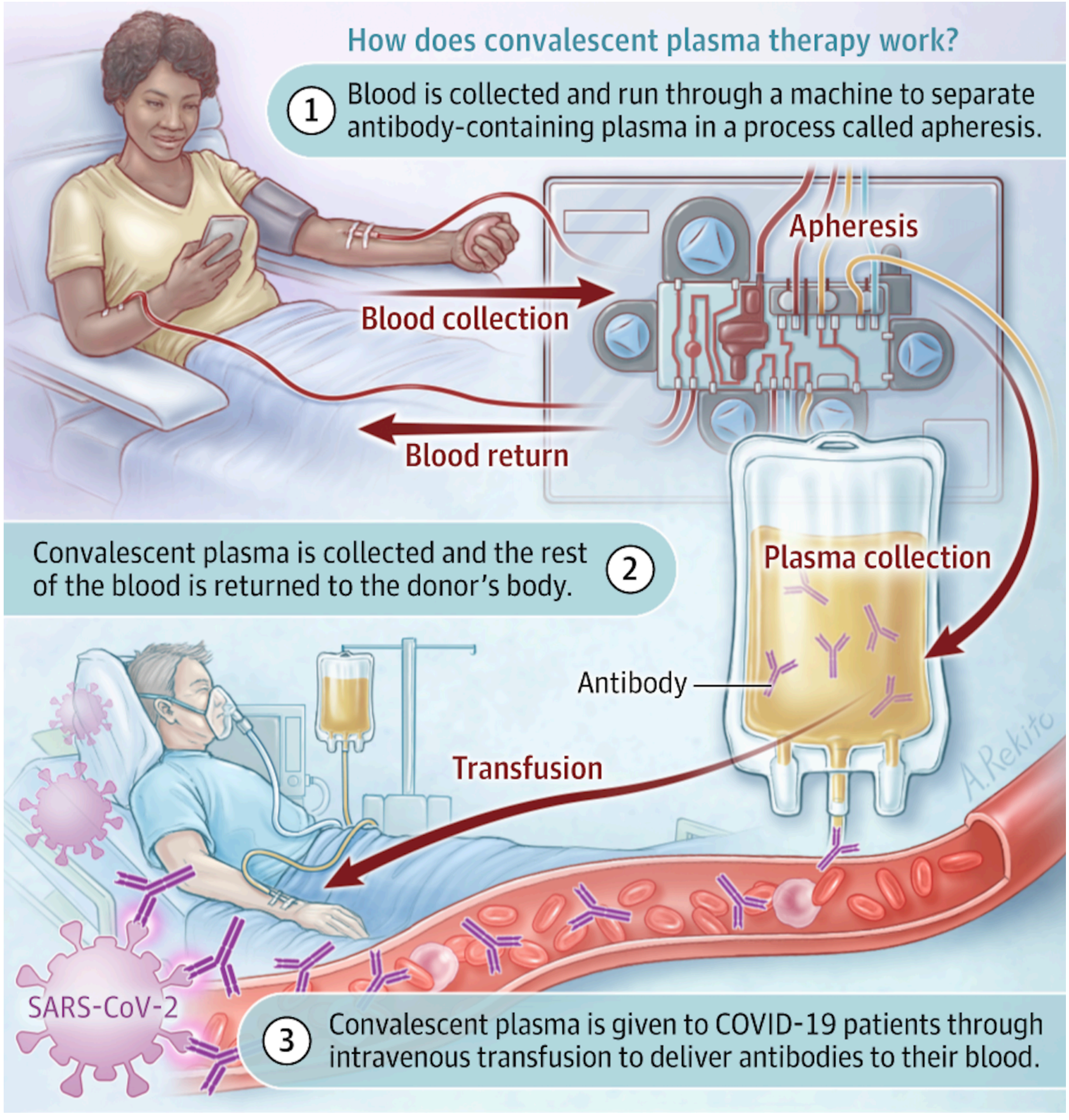
**Convalescent Plasma and COVID-19**
*https://jamanetwork.com/journals/jama/fullarticle/2767351*


How does convalescent plasma therapy work?
1 Blood is collected and run through a machine to separate antibody-containing plasma in a process called apheresis.
Apheresis
Blood collection
Blood return
Plasma collection
Convalescent plasma is collected and the rest of the blood is returned to the donor's body.
2
Antibody
Transfusion
A.Rekito
SARS-CoV-2
3 Convalescent plasma is given to COVID-19 patients through intravenous transfusion to deliver antibodies to their blood.

# Convalescent Plasma for COVID-19

"Recommendation (October 9, 2020): There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19."

"Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway; a list is available at *ClinicalTrials.gov*."

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**NIH COVID-19 Treatment Guidelines: Convalescent Plasma**
*https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma/*

# “Magic Bullets” in the Plasma

Credit: AWP / Alamy Stock Photo

1897

## Standardized unit for diphtheria antitoxin

Serum varies greatly in its content of antitoxin — and hence potency — between samples. Working at the Institute for Infectious Diseases in Berlin, Paul Ehrlich developed a standardized unit of diphtheria antitoxin allowing for more consistent treatment by physicians.

Related Article
https://www.sciencehistory.org/historical-profile/paul-ehrlich

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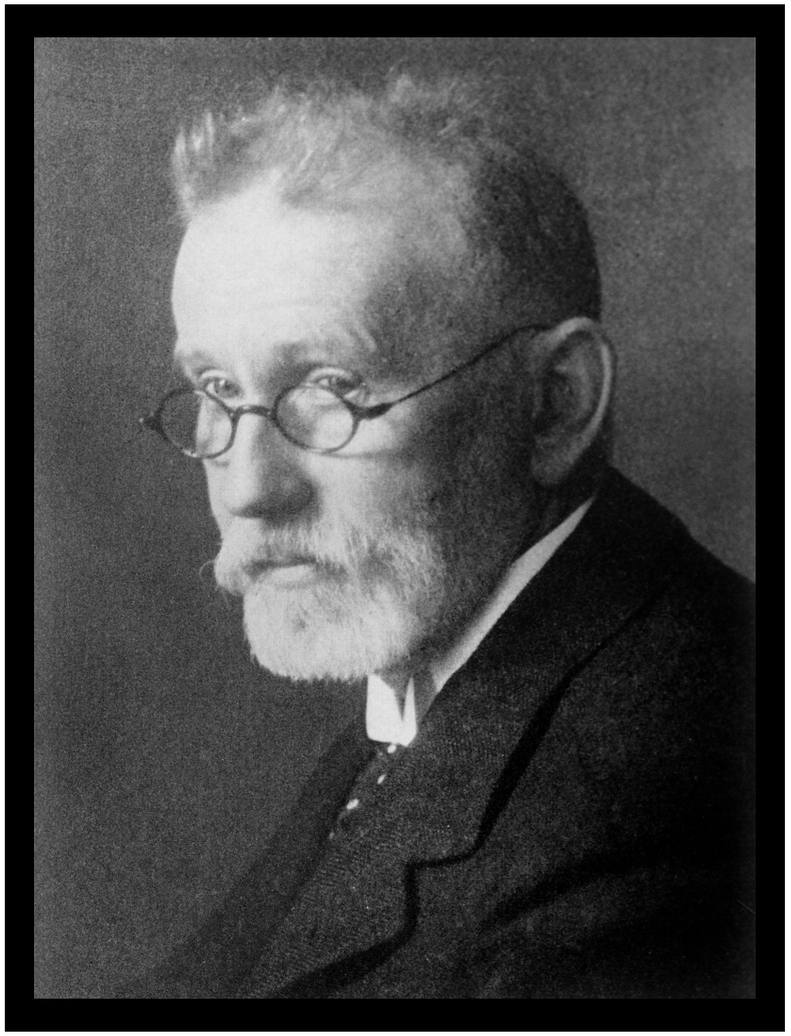
**Nature Milestones in Vaccines**
*https://www.nature.com/immersive/d42859-020-00005-8*

# “Magic Bullets” in the Plasma



**Experimentelle Untersuchungen über Immunität.**

*Ehrlich P.*

*Dtsch. med. Wochenschr.* 1891;17(1218)

# “Magic Bullets” in the Plasma

**Paul Ehrlich (1854-1915):** “Early in his career Ehrlich began to develop a chemical structure theory to explain the immune response. He saw toxins and antitoxins as chemical substances at a time when little was known about their exact nature.”

“Ehrlich supposed that living cells have side chains—a shorter chain or group of atoms attached to a principal chain in a molecule. These side chains can link with particular toxins.”

# “Magic Bullets” in the Plasma

“According to Ehrlich, a cell under threat from foreign bodies grows more side chains, more than are necessary to lock in foreign bodies in its immediate vicinity.”

“These ‘extra’ side chains break off to become antibodies and circulate throughout the body. It was these antibodies, in search of toxins, that Ehrlich first described as magic bullets.”

# Monoclonal Antibodies

In his paper, Ehrlich hypothesized that if if two substances give rise to two different antibodies, then they themselves must be different.

We now know that each B cell makes one type of antibody. A B cell can be isolated and cloned experimentally to make lots of copies of it.

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**Experimentelle Untersuchungen über Immunität.**
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# Monoclonal Antibodies

All the cloned B cells will make the same type of antibody. This antibody is then called a *monoclonal antibody.*

In the last two decades monoclonal antibodies have been used to bind specifically to inflammatory proteins in autoimmune diseases, or to cancer cells.

Effective antibiotics and vaccines have lessened the need to develop monoclonal antibodies against infectious agents.

# Monoclonal Antibodies for SARS-CoV-2

In response to the continued challenge in making an HIV vaccine, in recent years there has been interest in developing monoclonal antibodies against HIV. That has set the stage to develop monoclonal antibodies against SARS-CoV-2.

At least two different private drug companies — Eli Lilly and Company and Regeneron Pharmaceuticals, Inc. — are now conducting human clinical trials on monoclonal antibodies.

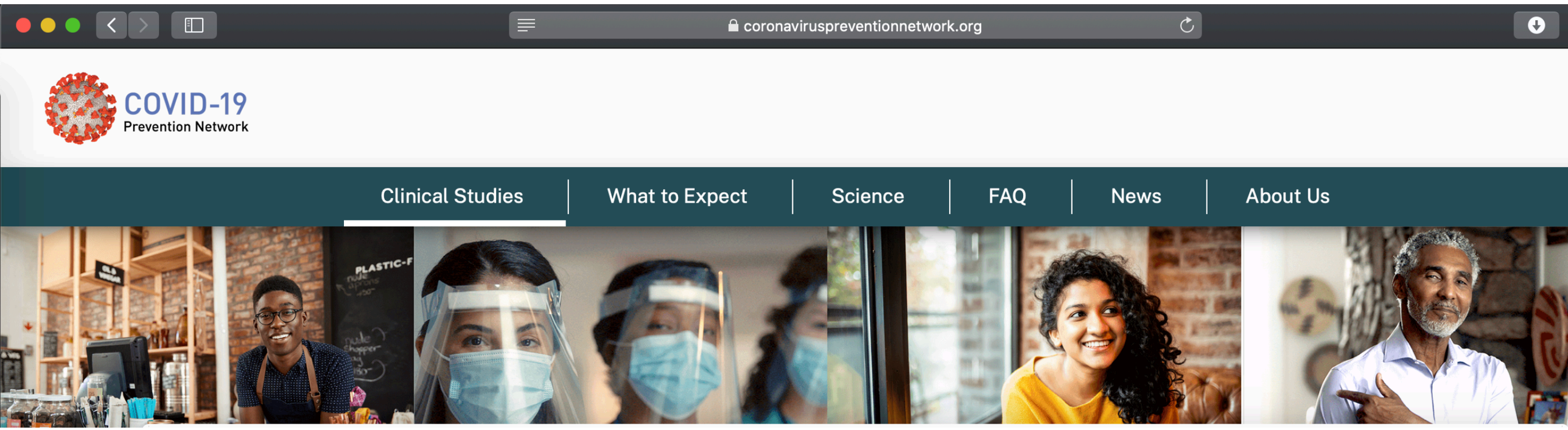
# Monoclonal Antibodies for SARS-CoV-2

## Phase 3 Randomized Control Trials

The trials are testing monoclonal antibodies both for prevention (household study) and treatment (skilled nursing facilities study).

The trials can be conducted much faster and with much fewer people than vaccine trials. If the antibodies show benefit, they will do so immediately after being given, and they are only tested on people who are already sick or at high risk of exposure.

# Monoclonal Antibodies for SARS-CoV-2




## COVID-19 Prevention Network

*https://www.coronaviruspreventionnetwork.org/understanding-clinical-studies/*

# Regeneron's 10933 and 10987 Antibodies, the REGN-COV2 Study

REGN-COV-2 is testing a combination of two antibodies called REGN10933 and REGN10987 to see whether they are able to prevent acquisition of SARS-CoV-2. This study will enroll approximately 2,000 adults in the United States who are living in the same household as a person who has recently tested positive for SARS-CoV-2. This will include about 1,700 participants who test SARS-CoV-2 negative at enrollment and about 300 participants who have a positive SARS-CoV-2 test result but do not have any COVID-19 symptoms.

The REGN10933 and REGN10987 antibodies are designed to bind to SARS-CoV-2 and prevent the virus from entering healthy cells. The antibodies were made in a lab by the pharmaceutical company Regeneron. REGN10933 and REGN10987 cannot give you SARS-CoV-2, nor will they make you sick with COVID-19.

Learn more about the study and the antibodies used:

- Visit www.regeneron.com/covid19 or ClinicalTrials.gov - NCT04452318 for additional information about the study.

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**COVID-19 Prevention Network**
*https://www.coronaviruspreventionnetwork.org/understanding-clinical-studies/*

# Eli Lilly's LY3819253 Antibody, the BLAZE-2 Study

BLAZE-2 is testing the LY3819253 antibody. It will be enrolling staff and residents in skilled nursing and assisted living facilities with a high risk of exposure to SARS-CoV-2. The study questions are:

- Does the antibody prevent the acquisition of SARS-CoV-2?
- Does the antibody help to prevent the development of more severe COVID-19, or does it reduce the symptoms?

The study will be conducted in the United States with up to 2,400 participants. LY3819253 is designed to bind to SARS-CoV-2 and prevent the virus from entering healthy cells. LY3819253 was developed in a lab by the pharmaceutical company Eli Lilly. LY3819253 cannot give you SARS-CoV-2, nor will it make you sick with COVID-19.

Visit blaze2study.com or ClinicalTrials.gov - NCT04497987

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**COVID-19 Prevention Network**
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# Monoclonal Antibodies for SARS-CoV-2

The monoclonal antibodies for SARS-CoV-2 that are now in trials have been isolated from the blood of recovered Covid-19 patients. They have been shown to neutralize the virus under laboratory conditions, and in animals, by stopping it from infecting healthy cells.

In contrast, convalescent plasma from recovered COVID-19 patients has many different antibodies produced in response to the virus with varying affinity to different parts of the virus, and various efficacy neutralizing the virus.

# Monoclonal Antibodies for SARS-CoV-2

Monoclonal antibodies can be given as a treatment for sick patients, particularly in early stages of the disease, or as a preventive measure for people with high risk of exposure.

However, if a T cell immune response turns out to be critical in fighting off SARS-CoV-2 infection, monoclonal antibodies may play a diminished role. It is also possible that a large variety of antibodies — not just one or two — are required to decapitate the virus. This is something a vaccine could provide but that monoclonal antibody therapies likely cannot.

# Hybridoma Technique

The 1984 Nobel Prize in Physiology or Medicine was awarded jointly to Georges J.F. Köhler and César Milstein *“for the discovery of the principle for production of monoclonal antibodies.”*

B cells cannot survive for long outside the body, a few weeks at best when incubated in cell-culture broth.

Köhler and Milstein’s devised a technique to keep B cells alive.

# Hybridoma Technique

They fused the B cells with myeloma tumor cells creating new cells, called hybridomas. Hybridomas retain the growth traits of a tumor with the antibody-producing abilities of the original B cell. This creates immortal versions of the B cells.

The process used for creating monoclonal antibodies can be used to create a protein shaped to lock onto any molecule. As well as being used as medicines, antibodies are used in all kinds of scientific experiments.

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## JAMA Network Channel

*https://www.youtube.com/channel/UC4p6bEngiRCN7TyTxZVJ3OQ*

# Monoclonal Antibodies for SARS-CoV-2