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Scientists map structure of potent antibody against coronavirus

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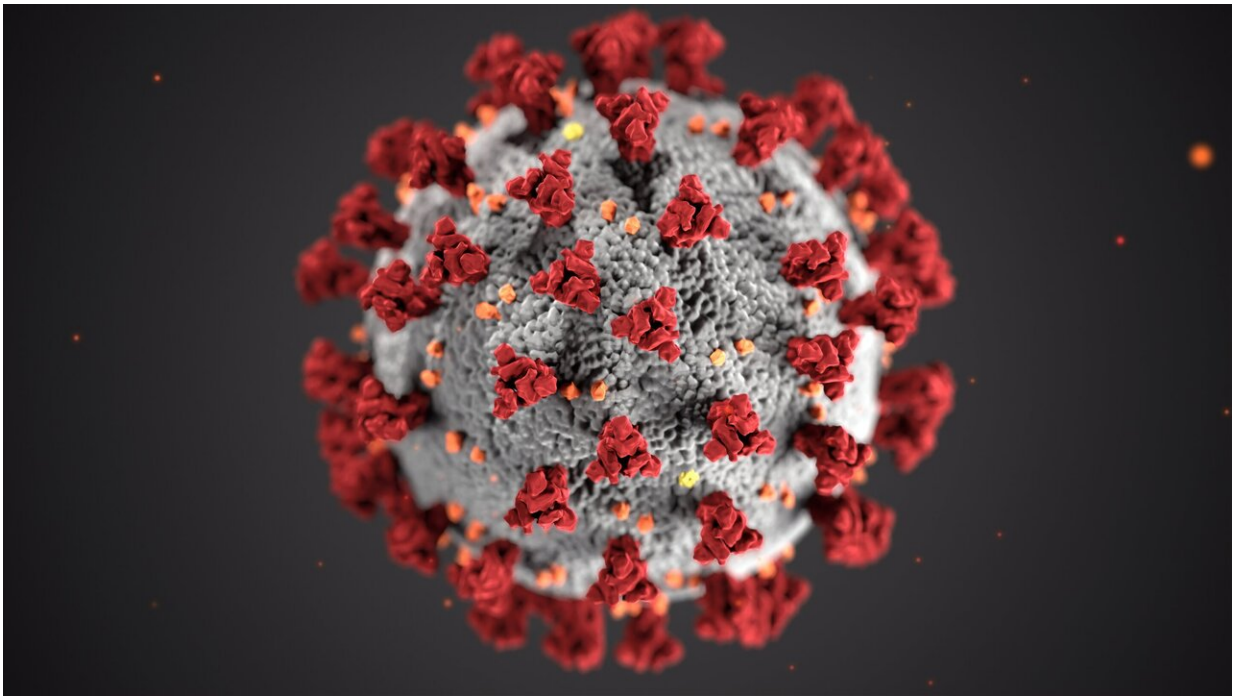

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Scientists at Fred Hutchinson Cancer Research Center in Seattle have shown that a potent antibody from a COVID-19 survivor interferes with a key feature on the surface of the coronavirus's distinctive spikes and induces critical pieces of those spikes to break off in the process.

The antibody—a tiny, Y-shaped protein that is one of the body's premier

weapons against pathogens including viruses—was isolated by the Fred Hutch team from a blood sample received from a Washington state patient in the early days of the pandemic.

The team led by Drs. Leo Stamatatos, Andrew McGuire and Marie Pancera previously reported that, among dozens of different antibodies generated naturally by the patient, this one—dubbed CV30—was 530 times more potent than any of its competitors.

Using tools derived from high-energy physics, Hutch structural biologist Pancera and her postdoctoral fellow Dr. Nicholas Hurlburt have now mapped the molecular structure of CV30. They and their colleagues published their results online today in the journal *Nature Communications.*

The product of their research is a set of computer-generated 3-D images that look to the untrained eye as an unruly mass of noodles. But to scientists they show the precise shapes of proteins comprising critical surface structures of antibodies, the coronavirus spike and the spike's binding site on human cells. The models depict how these structures can fit together like pieces of a 3-D puzzle.

"Our study shows that this antibody neutralizes the virus with two mechanisms. One is that it overlaps the virus's target site on human cells, the other is that it induces shedding or dissociation of part of the spike from the rest," Pancera said.

On the surface of the complex structure of the antibody is a spot on the tips of each of its floppy, Y-shaped arms. This infinitesimally small patch of molecules can neatly stretch across a spot on the coronavirus spike, a site that otherwise works like a grappling hook to grab onto a docking site on human cells.

The target for those hooks is the ACE2 receptor, a protein found on the surfaces of cells that line human lung tissues and blood vessels. But if CV30 antibodies cover those hooks, the coronavirus cannot dock easily with the ACE2 receptor. Its ability to infect cells is blunted.

This very effective antibody not only jams the business end of the coronavirus spike, it apparently causes a section of that spike, known as S1, to shear off. Hutch researcher McGuire and his laboratory team performed an experiment showing that, in the presence of this antibody, there is reduction of antibody binding over time, suggesting the S1 section was shed from the spike surface.

The S1 protein plays a crucial role in helping the coronavirus to enter cells. Research indicates that after the spike makes initial contact with the ACE2 receptor, the S1 protein swings like a gate to help the virus fuse with the captured cell surface and slip inside. Once within a cell, the virus hijacks components of its gene and protein-making machinery to make multiple copies of itself that are ultimately released to infect other target cells.

The incredibly small size of antibodies is difficult to comprehend. These proteins are so small they would appear to swarm like mosquitos around a virus whose structure can only be seen using the most powerful of microscopes. The tiny molecular features Pancera's team focused on the tips of the antibody protein are measured in nanometers—billionths of a meter.

Yet structural biologists equipped with the right tools can now build accurate 3-D images of these proteins, deduce how parts of these structures fit like puzzle pieces, and even animate their interactions.

Key to building models of these nanoscale proteins is the use of X-ray crystallography. Structural biologists determine the shapes of proteins by

illuminating frozen, crystalized samples of these molecules with extremely powerful X-rays. The most powerful X-rays come from a gigantic instrument known as a synchrotron light source. Born from atom-smashing experiments dating back to the 1930s, a synchrotron is a ring of massively powerful magnets that are used to accelerate a stream of electrons around a circular track at close to the speed of light. Synchrotrons are so costly that only governments can build and operate them. There are only 40 of them in the world.

Pancera's work used the Advanced Photon Source, a synchrotron at Argonne National Laboratory near Chicago, which is run by the University of Chicago and the U.S. Department of Energy. Argonne's ring is 1,200 feet in diameter and sits on an 80-acre site.

As the electrons whiz around the synchrotron ring, they give off enormously powerful X-rays—far brighter than the sun but delivered in flashes of beams smaller than a pinpoint.

Structural biologists from around the world rely on these brilliant X-ray beamlines to illuminate frozen crystals of proteins. They reveal their structure in the way these bright beams are bent as they pass though the molecules. It takes powerful computers to translate the data readout from these synchrotron experiments into the images of proteins that are eventually completed by structural biologists.

The Fred Hutch team's work on CV30 builds on that of other structural biologists who are studying a growing family of potent neutralizing antibodies against the coronavirus. The goal of most coronavirus vaccine candidates is to stimulate and train the immune system to make similar neutralizing antibodies, which can recognize the virus as an invader and stop COVID-19 infections before they can take hold.

Neutralizing antibodies from the blood of recovered COVID-19 patients

may also be infused into infected patients—an experimental approach known as convalescent plasma therapy. The donated plasma contains a wide variety of different antibodies of varying potency. Although once thought promising, recent studies have cast doubt on its effectiveness.

However, pharmaceutical companies are experimenting with combinations of potent neutralizing antibodies that can be grown in a laboratory. These "monoclonal antibody cocktails" can be produced at industrial scale for delivery by infusion to infected patients or given as prophylactic drugs to prevent infection. After coming down with COVID-19, President Trump received an experimental monoclonal antibody drug being tested in clinical trials by the biotech company Regeneron, and he attributes his apparently quick recovery to the advanced medical treatment he received.

The Fred Hutch research team holds out hope that the protein they discovered, CV30, may prove to be useful in the prevention or treatment of COVID-19. To find out, this antibody, along with other candidate proteins their team is studying, need to be tested preclinically and then in human trials.

"It is too early to tell how good they might be," Pancera said.

More information: Nicholas K. Hurlburt et al, Structural basis for potent neutralization of SARS-CoV-2 and role of antibody affinity maturation, *Nature Communications* (2020). DOI: 10.1038/s41467-020-19231-9

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