Scientists use ultrabright X-ray beams to characterize broadly neutralizing antibodies against a range of coronaviruses

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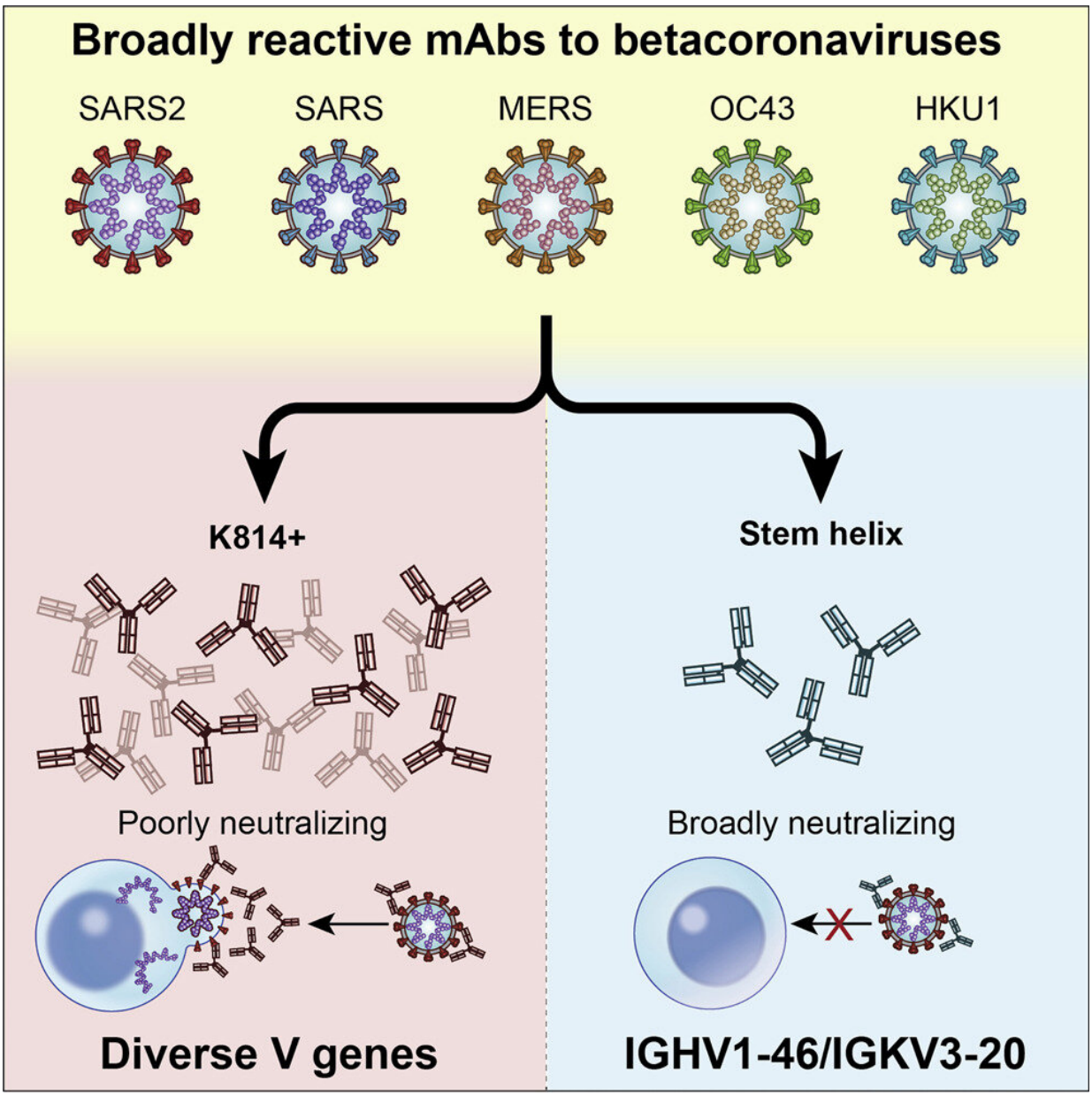

Graphical abstract. Credit: *Cell Host & Microbe* (2022). DOI: 10.1016/j.chom.2022.10.010

New variants of the coronavirus that caused the COVID-19 pandemic continue to emerge. To combat them, researchers are doing everything they can to find new therapies that can target a broad range of different coronavirus strains.

Thanks to new research conducted at the U.S. Department of Energy's (DOE) Argonne National Laboratory, scientists have identified a new class of injectable antibodies that can neutralize many different variants of coronavirus. This research gives scientists and pharmaceutical companies a potential leg up in designing a vaccine or antiviral medication that would be broadly effective over time.

All coronaviruses contain certain proteins, called spike proteins, that they use to infect human cells. The spike proteins themselves consist of two distinct components. Scientists call these connected spike protein components the S1 and S2 subunits.

After the virus binds to specific cells in the respiratory tract, the two subunits separate from each other and undergo a large structural reorganization in order to enter our cells. Scientists have been looking at ways to inhibit this process.

While vaccines developed by Moderna and Pfizer and others primarily bind to the S1 subunit, the advantage of focusing on the S2 subunit is that it is similar among different coronavirus strains. This allows researchers to target particular regions in that domain to build the

foundation for a more broadly active vaccine and other therapeutics.

In a recent study published in *Cell Host & Microbe*, scientists from the Scripps Research Institute in California and Joshua Tan's lab at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, identified 55 antibodies that bound a diverse set of coronavirus spike proteins. Many of these were found to be effective against the virus as well. Scientists call these antibodies "broadly neutralizing."

The broadly neutralizing antibodies bind to a region of the S2 subunit called the stem helix, which is found in a broad range of coronaviruses.

"The stem helix is the part of the coronavirus that is similar across many strains and implicated in how the coronavirus is able to infect our cells," said Argonne structural biologist Michael Becker. "This part of the virus enables cell membrane fusion, which allows the virus to do its damage. If these scientists and their collaborators can find a way to block the stem helix, researchers may have the roots of a new wide-ranging therapy."

"It's harder to introduce mutations into the stem helix than other parts of the coronavirus, so the antibodies that bind there are 'broad,' meaning they can bind to many different strains," said Ian Wilson, Hansen Professor of Structural Biology and chair of the department of Integrative Structural and Computational Biology at Scripps.

Researchers are looking to obtain or fashion a set of antibodies that are both neutralizing in addition to being broad. That means they need to find an antibody that binds really well to the viruses' vulnerable weak spots.

"The viral protein may need to go through a large change to its structure

to accommodate the antibody, and the antibody may in turn trigger a change of the viral protein," said Meng Yuan, a senior scientist at Scripps and an author of the study.

In addition to extracting antibodies that are found in patients recovering from coronavirus infection, Wilson and his colleagues have genetically engineered different antibodies in the lab in order to improve how well they bind. "After looking across the spectrum of patients to assess what antibodies can be discovered to put into our toolkit, we can also work with collaborators to go back to the lab to create improved antibodies or vaccines," Wilson said.

At Argonne, the researchers used the GM/CA beamline at the laboratory's Advanced Photon Source, a DOE Office of Science user facility to look at the crystal structures of some of the antibodies with the stem helices.

More information: Cherrelle Dacon et al, Rare, convergent antibodies targeting the stem helix broadly neutralize diverse betacoronaviruses, *Cell Host & Microbe* (2022). DOI: 10.1016/j.chom.2022.10.010

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