

Powerful new antibody neutralizes all known SARS-CoV-2 variants

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As SARS-CoV-2 has evolved and mutated, therapeutic antibodies that worked early in the pandemic have become less effective, and newer variants, especially omicron, have developed ways to evade the

antibodies we make in response to vaccines. A new, broadly neutralizing antibody developed at Boston Children's Hospital could potentially improve our ability to defend against future variants. In tests, it neutralized all currently known SARS-CoV-2 variants of concern, including all omicron variants.

"We hope that this humanized antibody will prove to be as effective at neutralizing SARS-CoV-2 in patients as it has proven to be thus far in preclinical evaluations," says Frederick Alt, Ph.D., of the Program in Cellular and Molecular Medicine at Boston Children's Hospital, who co-led the research.

As described in *Science Immunology* on August 11, Alt and Sai Luo, Ph.D., in his lab turned to a modified version of a humanized [mouse model](#) that the lab has used to search for broadly neutralizing antibodies to HIV, another virus that frequently mutates. The mice essentially have built-in human immune systems, and the model mimics the trial-and-error process our immune system uses to create increasingly effective antibodies.

The researchers first inserted two human gene segments into the mice, pushing their B cells to rapidly produce a diverse repertoire of humanized antibodies. They then exposed the mice to the SARS-CoV-2 spike protein, the main protein targeted by our antibodies and current vaccines, from the original Wuhan-Hu-1 strain of the virus. In response, the modified mice produced nine lineages or "families" of humanized antibodies that bound to the spike.

Alt and Luo then vetted these antibodies for efficacy in collaboration with the group of Barton Haynes, MD at Duke University. Antibodies in three of the nine lineages were potent neutralizers of the original Wuhan-Hu-1 virus. In particular, the SP1-77 antibody and other members of its lineage showed very broad activity, neutralizing alpha, beta, gamma,

delta, and all previous and current omicron strains.

A novel approach to virus neutralization

What made the SP1-77 antibody so broadly neutralizing? Structural studies by a collaborating team led by Bing Chen, Ph.D. and Jun Zhang, Ph.D. at Boston Children's Hospital and the Haynes group at Duke, showed that SP1-77 works differently from current antibodies (either [therapeutic antibodies](#) or those we make in response to current vaccines).

Many of the existing antibodies function by binding to the spike's receptor-binding domain (RBD) in specific locations that prevent SARS-CoV-2 from binding to our cells' ACE2 receptors, the first step in initiating infection. The SP1-77 antibody also binds to the RBD, but in a totally different manner that does not block the virus from binding to ACE2 receptors.

Using a novel live-cell imaging platform [described in a preprint](#), collaborators Alex Kreutzberger, Ph.D. and Tomas Kirchhausen, Ph.D., of Boston Children's Hospital showed that SP1-77 prevents the [virus](#) from fusing its outer membrane with the membrane of the target cell. This thwarts the final necessary step that throws the door open to infection.

These features may inform design of new SARS-CoV-2 vaccines. "SP1-77 binds the spike protein at a site that so far has not been mutated in any SARS-CoV-2 [variant](#), broadly neutralizing current variants by a novel mechanism," says Kirchhausen.

More information: An Antibody from Single Human VH-rearranging Mouse Neutralizes All SARS-CoV-2 Variants Through BA.5 by Inhibiting Membrane Fusion, *Science Immunology* (2022). [DOI: 10.1126/sciimmunol.add5446](#)

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