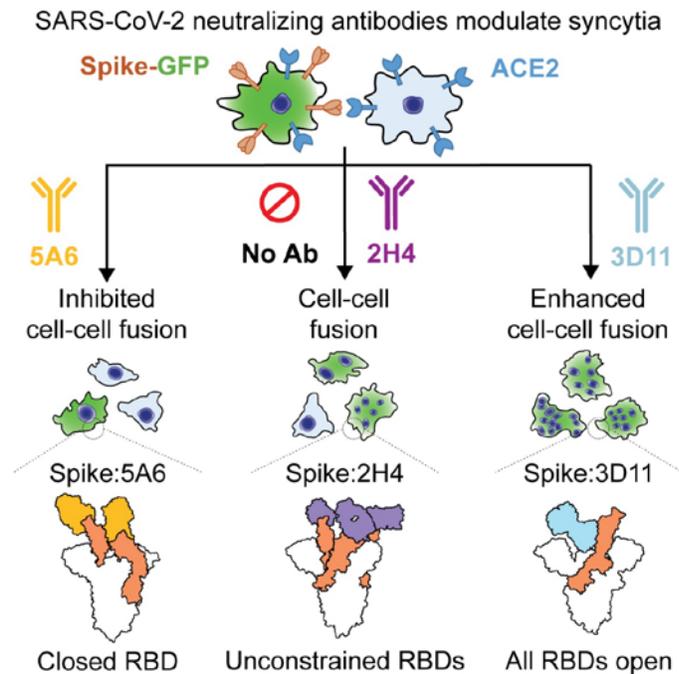


SOME COVID-19 NEUTRALISING ANTIBODIES MAY WORSEN THE DISEASE

A series of neutralising antibodies against SARS-CoV-2 that potently block binding to the host receptor ACE2 are found to either enhance or inhibit virus spike-mediated membrane fusion and the formation of syncytia, a sign of tissue damage in COVID-19 patients.



Caption: How the SARS-CoV-2 neutralising antibodies interact with the viral Spike proteins determine the fate of the infected cells.

21 May 2021, Singapore - SARS-CoV-2 infection results in syncytia in airway tissues, a cell-cell fusion event that has been linked to severe tissue damage. Infection by SARS-CoV-2 is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. While some antibodies that block this interaction are in emergency use as early COVID-19 therapies, precise determinants of neutralisation potency remain unknown.

A team of researchers from the Agency of Science, Technology and Research (A*STAR), in collaboration with the QBI Coronavirus Research Group (QCRG) at University of California San Francisco (UCSF), University of Lyon, and DSO National Laboratories discovered that while some neutralising antibodies inhibit syncytia, some drastically enhance it.

The researchers discovered a series of human antibodies that all potentially block ACE2 binding yet exhibit divergent neutralisation efficacy against live virus. Strikingly, these neutralising antibodies can either inhibit or enhance spike-mediated membrane fusion and formation of syncytia, which are associated with chronic tissue damage in COVID-19 patients.

Cryogenic electron microscopy reveals differential antibody-viral spike binding modes leading to different biological consequences. The distinct binding modes not only block ACE2 binding, but also alter the spike protein conformational cycle triggered by ACE2 binding.

The study shows that stabilisation of different spike conformations leads to modulation of spike-mediated membrane fusion, with profound implications in COVID-19 pathology and immunity.

Dr Wang Cheng-I, senior principal investigator at A*STAR's Singapore Immunology Network and last author of the study said, "This is the first time that a neutralising antibody can either inhibit or enhance syncytia is discovered and described. The discovery has a profound implication in how the therapeutic antibodies against COVID-19 should be designed. Better understanding of the mechanism of neutralising is critical for better treatment design, given the ever-mutating nature of the COVID-19 virus."

"The project was made possible by the remarkable progress that has been made in cryo EM in ways that could not be imagined before," said Yifan Cheng, Ph.D., professor of biochemistry and biophysics at University of California, San Francisco.

Charles Craik, Ph.D., professor of pharmaceutical chemistry at University of California San Francisco added, "The collaboration among the different groups with complementary technologies and expertise was such that the sun never set on the project. Someone from one of the groups was working on it 24 hours of the day in some part of the world."

More information on the study, "Structural insight into SARS-CoV-2 neutralizing antibodies and modulation of syncytia", can be found via the team's published paper in Cell.

DOI: <https://doi.org/10.1016/j.cell.2021.04.033>.

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