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Engineered llama antibodies neutralise COVID-19 virus

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Antibodies taken from llamas have been shown to neutralise the SARS-CoV-2 virus in lab tests.

In a paper published in *Nature Structural & Molecular Biology*, a team of UK scientists have shown that engineered nanobodies taken from a library of llama blood cells bind tightly to the spike protein of the SARS-CoV-2 virus, blocking it from entering human cells and stopping infection.

They are now screening antibodies from Fifi, one of the 'Franklin llamas' based at the University of Reading, taken after she was immunised with harmless purified virus proteins. The team are investigating preliminary results which show that Fifi's immune system has produced different antibodies from those already identified, which will enable cocktails of nanobodies to be tested against the virus.

Prof Gary Stephens, who leads the work at the University of Reading producing llama nanobodies said:

"The search is on for effective treatments to combat the unprecedented COVID-19 pandemic. Given the lengthy development process for vaccines, one major immediate priority is the development of selective antibodies that can neutralise the SARS-CoV-2 virus responsible for COVID-19. A particularly exciting new advance is the recent development of "nanobody" technology.

"Nanobodies are smaller, more stable types of antibody taken from the immune systems of camelid species—such as llamas, alpacas and camels. Due to their smaller size, they are more able to target relevant proteins and stop the virus from attaching to a host and spreading.

"At the University of Reading, we are currently working with the Rosalind Franklin Institute, Oxford to generate llama nanobodies that bind to proteins in the SARS-CoV-2 virus including the "spike" glycoprotein that enables the virus to enter human cells. These nanobodies may provide additional capacity to bind SARS-CoV-2 proteins at different sites and neutralise the virus even more effectively."

Nanobodies bind to the spike

The team, involving researchers from the Rosalind Franklin Institute, Oxford University, Diamond Light Source and Public Health England, started with a lab-based library of llama antibodies.

Using advanced imaging with X-rays and electrons at Diamond Light Source and Oxford University, the team also identified that the nanobodies bind to the spike protein in a new and different way to other antibodies already discovered.

Professor James Naismith, Director of The Rosalind Franklin Institute and Professor of Structural Biology at Oxford University said:

"These nanobodies have the potential to be used in a similar way to convalescent serum, effectively stopping progression of the virus in patients who are ill. We were able to combine one of the nanobodies with a human antibody and show the combination was even more powerful than either alone. Combinations are particularly useful since the virus has to change multiple things at the same time to escape; this is very hard for the virus to do. The nanobodies also have potential as a

powerful diagnostic."

Professor Ray Owens from Oxford University, who leads the nanobody program at the Rosalind Franklin Institute said:

"This research is a great example of team work in science, as we have created, analysed and tested the nanobodies in 12 weeks. This has seen the team carry out experiments in just a few days, that would typically take months to complete. We are hopeful that we can push this breakthrough on into pre-clinical trials."

Professor David Stuart, from Diamond Light Source and Oxford University said, "The electron microscopy structures showed us that the three nanobodies can bind to the virus spike, essentially covering up the portions that the virus uses to enter human cells."

More information: Jiangdong Huo et al. Neutralizing nanobodies bind SARS-CoV-2 spike RBD and block interaction with ACE2, *Nature Structural & Molecular Biology* (2020). DOI: 10.1038/s41594-020-0469-6

Provided by University of Reading