

Llama nanobodies could be a powerful weapon against COVID-19

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Wally the Llama. Credit: Sonya Paske, Capralogics Ltd.

Today in *Science*, researchers at the University of Pittsburgh School of Medicine describe a new method to extract tiny but extremely powerful SARS-CoV-2 antibody fragments from llamas, which could be fashioned into inhalable therapeutics with the potential to prevent and treat COVID-19.

These special llama antibodies, called "[nanobodies](#)," are much smaller than human antibodies and many times more effective at neutralizing the SARS-CoV-2 virus. They're also much more stable.

"Nature is our best inventor," said senior author Yi Shi, Ph.D., assistant professor of cell biology at Pitt. "The technology we developed surveys SARS-CoV-2 neutralizing nanobodies at an unprecedented scale, which allowed us to quickly discover thousands of nanobodies with unrivaled affinity and specificity."

To generate these nanobodies, Shi turned to a black llama named Wally—who resembles and therefore shares his moniker with Shi's black Labrador.

Shi and colleagues immunized the llama with a piece of the SARS-CoV-2 spike protein and, after about two months, the animal's immune system produced mature nanobodies against the virus.

Using a [mass spectrometry](#)-based technique that Shi has been perfecting for the past three years, lead author Yufei Xiang, a research assistant in Shi's lab, identified the nanobodies in Wally's blood that bind to SARS-

CoV-2 most strongly.

Then, with the help of Pitt's Center for Vaccine Research (CVR), the scientists exposed their nanobodies to live SARS-CoV-2 virus and found that just a fraction of a nanogram could neutralize enough virus to spare a million cells from being infected.

These nanobodies represent some of the most effective therapeutic antibody candidates for SARS-CoV-2, hundreds to thousands of times more effective than other llama nanobodies discovered through the same phage display methods used for decades to fish for [human monoclonal antibodies](#).

Shi's nanobodies can sit at [room temperature](#) for six weeks and tolerate being fashioned into an inhalable mist to deliver antiviral therapy directly into the lungs where they're most needed. Since SARS-CoV-2 is a respiratory virus, the nanobodies could find and latch onto it in the respiratory system, before it even has a chance to do damage.

In contrast, traditional SARS-CoV-2 [antibodies](#) require an IV, which dilutes the product throughout the body, necessitating a much larger dose and costing patients and insurers around \$100,000 per treatment course.

"Nanobodies could potentially cost much less," said Shi. "They're ideal for addressing the urgency and magnitude of the current crisis."

In collaboration with Cheng Zhang, Ph.D., at Pitt, and Dina Schneidman-Duhovny, Ph.D., at the Hebrew University of Jerusalem, the team found that their nanobodies use a variety of mechanisms to block SARS-CoV-2 infection. This makes nanobodies ripe for bioengineering. For instance, nanobodies that bind to different regions on the SARS-CoV-2 virus can be linked together, like a Swiss army knife, in case one part of the [virus](#) mutates and becomes drug-resistant.

"As a virologist, it's incredible to see how harnessing the quirks of [llama](#) antibody generation can be translated into the creation of a potent nanoweapon against clinical isolates of SARS-CoV-2," said study coauthor and CVR Director Paul Duprex, Ph.D.

More information: "Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2," *Science*, science.sciencemag.org/cgi/doi/10.1126/science.abe4747

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