Researchers reveal a strategy for next-generation COVID-19 vaccines

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Dr Deborah Burnett, first author of the paper and Conjoint Senior Lecturer at UNSW's St Vincent's Clinical School. Credit: Garvan Institute of Medical Research

Medical researchers have outlined a strategy to generate future-proofed COVID-19 vaccines that can resist emergent new viral strains.

A study led by the Garvan Institute of Medical Research and involving UNSW Sydney academics has revealed a guide to developing COVID-19 vaccines that both prevent the coronavirus from infecting human cells and that are more resistant to evolving viral strains.

The team's key criteria for antibodies generated by future vaccines are to target regions of the SARS-CoV-2 viral surface that are unlikely to mutate and share key features that the researchers found could block the virus from infecting human cells.

Remarkably, the researchers found in experimental models that immunizing with surface proteins from related viruses, such as SARS-CoV-1, the virus responsible for the original 2003 SARS epidemic, generated antibodies that met these criteria. The findings, published this week in the journal *Immunity*, provide a new direction for vaccine development.

"Current COVID-19 vaccines, which target the SARS-CoV-2 spike protein, are highly effective at reducing disease severity and reducing transmission. Future variant strains, which will emerge due to the virus's mass spread, may escape the current strategy," says co-senior author Professor Chris Goodnow, Director of UNSW's Cellular Genomics Futures Institute and Executive Director of the Garvan Institute.

"Research into next-generation vaccines with increased resistance to future variants is therefore warranted. Our work provides a guide for developing such future-proofed vaccines," says co-senior author Professor Daniel Christ, Professor at UNSW's St Vincent's Clinical School and Director of the Centre of Targeted Therapy at Garvan.

Strategy to reduce future virus threat

Existing variants of coronavirus, such as the Delta strain, have already

partially reduced the efficacy of antibodies generated by current vaccines to prevent COVID-19 infection, although they remain highly effective at preventing death and hospitalisations.

"Our research aimed to identify a vaccination strategy that would target a key site of vulnerability on the virus surface that is unlikely to change over time. This site is unchanged in different coronavirus strains, meaning that the virus may be less likely to mutate to escape from an antibody immune response targeting this site," says Dr. Deborah Burnett, first author of the paper and Conjoint Senior Lecturer at UNSW's St Vincent's Clinical School.

The team tested different immunisations in mice that had been specialized to produce human antibody responses. Specifically, the researchers aimed to generate antibodies that target the 'class 4 epitope' region, which is conserved among coronaviruses (does not genetically vary between different strains) and may therefore be less likely to mutate in the future.

"Surprisingly, when we immunized with a protein from SARS-CoV-1, 80 percent of antibodies that were formed bound to the class 4 epitope. In contrast, when we used the SARS-CoV-2 protein, the mice generated antibodies that targeted regions of the coronavirus spike protein that are prone to mutations that allow the virus to easily escape," Dr. Burnett says.

"What this leads us to propose is that targeting SARS-CoV-2 may not be the most effective vaccination strategy moving forward, and that immunizing against a related virus may produce an antibody response that has greater resistance against emerging strains."

A path towards a next-generation COVID-19 vaccine

The researchers next set out to identify antibodies that not only bind to the SARS-CoV-2 class 4 epitope but can also block its entry into human cells. They analyzed thousands of individual antibody-producing B cells and pinpointed a rare subset of these 'class 4' antibodies that were able to neutralize the virus.

"When we analyzed the 3D structure of these antibodies, they all had several features in common," says co-senior author Professor Christ.

"They bound to the same section of the class 4 epitope and oriented the rest of the antibody to physically block access to the ACE2 binding site. ACE2 is the receptor on human cells that the virus needs to dock to before it can infect. We confirmed antibodies capable of blocking this interaction were able to neutralize the SARS-CoV-2 virus in laboratory assays, performed at the Kirby Institute, which traced the ability of the virus to enter human cells."

As part of this work, the researchers isolated a subset of antibodies effective at neutralizing SARS-CoV-2, which they hope to advance to clinical trials as an antibody therapy.

"To progress our proposed vaccine approach, we are now aiming to test next-generation vaccines in our preclinical models, to determine if they can generate these antibodies, which can protect against different strains of the virus," says Professor Goodnow.

"We now know what to look for in an antibody response. Our goal for this research is to help develop a vaccine that that would need no updating and that could ultimately lead to better control of COVID-19."

More information: Deborah L. Burnett et al, Immunizations with diverse sarbecovirus receptor binding domains elicit SARS-CoV-2 neutralizing antibodies against a conserved site of vulnerability,

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