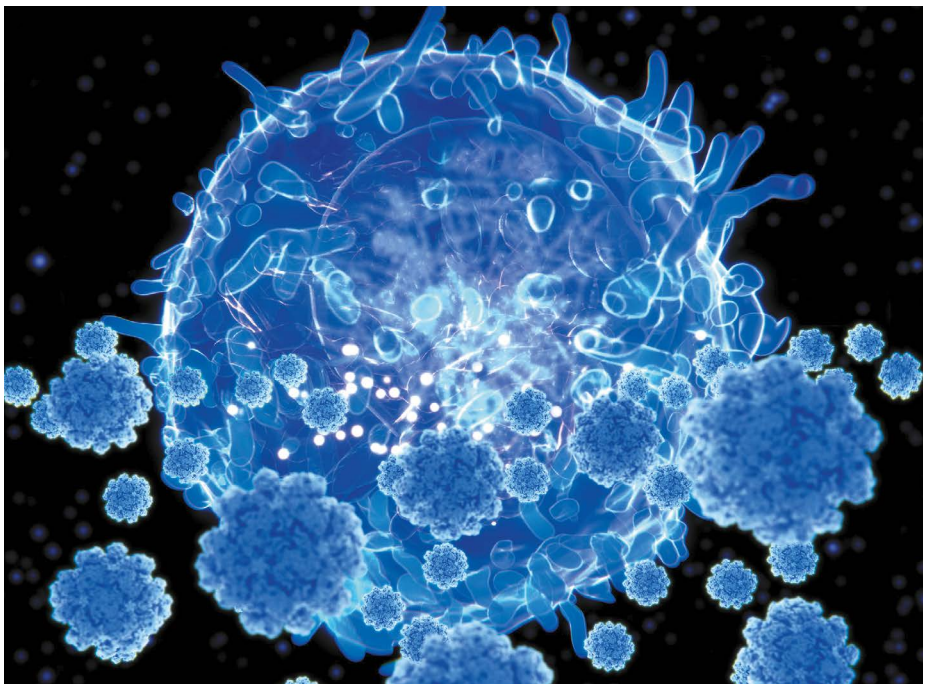


JUAN GAERTNER/SPL

A T cell targets coronavirus particles (illustration).

'KILLER' T CELLS COULD BOOST COVID IMMUNITY AMID NEW VARIANTS

Researchers are looking beyond antibodies for clues to lasting protection from COVID-19.

By Heidi Ledford

Concerns about coronavirus variants that might be partially resistant to antibody defences have spurred renewed interest in other immune responses that protect against viruses. In particular, scientists are hopeful that T cells — a group of immune cells that can target and destroy virus-infected cells — could provide some immunity to COVID-19, even if antibodies become less effective at fighting the disease.

Researchers are now picking apart the available data, looking for signs that T cells could help to maintain lasting immunity.

"We know the antibodies are likely less effective, but maybe the T cells can save us," says Daina Graybosch, a biotechnology analyst at investment bank SVB Leerink in New York City. "It makes sense biologically. We don't have the data, but we can hope."

Coronavirus vaccine development has focused largely on antibodies, and for good reason, says immunologist Alessandro Sette at the La Jolla Institute for Immunology in California. Antibodies — particularly those that bind to crucial viral proteins and block infection — can hold the key to 'sterilizing immunity', which not only reduces the severity of an illness, but prevents infection altogether.

That level of protection is considered the gold standard, but typically it requires large numbers of antibodies, says Sette. "That is great if that can be achieved, but it's not necessarily always the case," he says.

"We know the antibodies are likely less effective, but maybe T cells can save us. It makes sense biologically."

Alongside antibodies, the immune system produces a battalion of cells that can target viruses. Some of these, known as killer T cells, seek out and destroy cells that are infected with the virus. Others, called helper T cells, are important for various immune functions, including stimulating the production of antibodies and killer T cells.

T cells do not prevent infection, because they kick into action only after a virus has infiltrated the body. But they are important for clearing an ongoing infection. In the case of COVID-19, killer T cells could mean the difference between a mild infection and a severe one that requires hospital treatment, says Annika Karlsson, an immunologist at the Karolinska Institute in Stockholm. "If they are able to kill the virus-infected cells before they spread from the upper respiratory tract, it will influence how sick you feel," she says. They could also reduce transmission by restricting the amount of virus circulating in the body, meaning that an infected person sheds fewer virus particles into the community.

T cells could also be more resistant than antibodies to threats posed by emerging variants. Studies by Sette and his colleagues have shown that people who have been infected with SARS-CoV-2 typically generate T cells that target at least 15 different fragments of coronavirus proteins (A. Tarke *et al. Cell Rep. Med*. https://doi.org/fvqm; 2021). But which protein snippets are used as targets can vary widely from person to person, meaning that a population will generate a large variety of T cells that could snare a virus. "That makes it very hard for the virus to mutate to escape cell recognition," says Sette, "unlike the situation for antibodies."

So when laboratory tests showed that the 501Y.V2 variant identified in South Africa (also called B.1.351) is partially resistant to antibodies raised against previous coronavirus variants, researchers wondered whether T cells could be less vulnerable to its mutations.

Early results suggest that this might be the case. In a preprint published on 9 February, researchers found that most T-cell responses to coronavirus vaccination or previous infection do not target regions that were mutated in two recently discovered variants, including 501Y.V2 (D. T. Skelly *et al*. Preprint at https://researchsquare.com/article/rs-226857/v1; 2021).

If T cells remain active against the 501Y.V2 variant, they might protect against severe disease, says immunologist John Wherry at the University of Pennsylvania in Philadelphia. But it is hard to know from the data available thus far, he cautions. "We're trying to infer a lot of scientific and mechanistic information from data that doesn't really have it to give," he says.

Updating vaccines

Researchers have been analysing clinical-trial data for several coronavirus vaccines, to look for clues as to whether their effectiveness fades in the face of the 501Y.V2 variant. So far, at least three vaccines — a protein vaccine made by Novavax in Gaithersburg, Maryland, a single-shot vaccine made by Johnson & Johnson in New Brunswick, New Jersey, and a vaccine made by AstraZeneca in Cambridge, UK, and the University of Oxford, UK — were less effective at protecting against mild

COVID-19 in South Africa, where the 501Y.V2 variant dominates, than in countries where that variant is less common.

Some developers are already looking at ways to create next-generation coronavirus vaccines that stimulate T cells more effectively. Antibodies detect only proteins outside cells, and many coronavirus vaccines target a protein called spike that decorates the surface of the virus. But the spike protein is "quite variable", suggesting that it might be prone to mutating, says Karlsson, increasing the risk that emerging variants will be able to evade antibody detection.

T cells, by contrast, can target viral proteins expressed inside infected cells, and some of those proteins are very stable, she says. This raises the possibility of designing vaccines against proteins that mutate less frequently than spike, and incorporating targets from multiple proteins into one vaccine.

Biotechnology firm Gritstone Oncology in Emeryville, California, is designing an experimental vaccine that incorporates the genetic code for fragments of several coronavirus proteins known to elicit T-cell responses, as well as for the full spike protein, to ensure that antibody responses are robust. Clinical trials are due to start in the next few months.

But Gritstone president Andrew Allen hopes that current vaccines will be effective against new variants, and that his company's vaccine will never be needed. "We developed this absolutely to prepare for bad scenarios," he says. "We're half hoping that everything we did was a waste of time. But it's good to be ready."

COULD MIXING COVID VACCINES BOLSTER IMMUNE RESPONSE?

Combining different coronavirus shots has potential to speed up immunization campaigns.

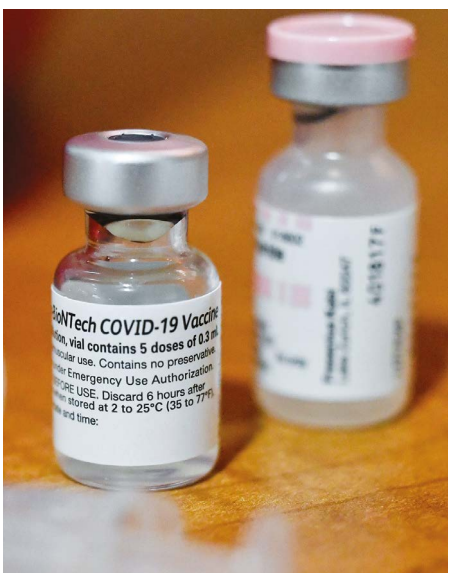
By Heidi Ledford

Researchers in the United Kingdom have launched a study that will mix and match two COVID-19 vaccines in a bid to ease the daunting logistics of immunizing millions of people — and potentially boost immune responses in the process.

Most coronavirus vaccines are given as two injections: an initial 'prime' dose followed by a 'boost' to stimulate the immune system's memory cells and amplify the immune response. The clinical trial will test participants' immune responses to receiving one shot of a coronavirus vaccine produced by the University of Oxford, UK, and drug firm AstraZeneca — which uses a harmless virus to carry a key coronavirus gene into cells — and one shot of the vaccine produced by drug company Pfizer, which uses RNA instructions to trigger an immune response. The trial, which is being run by Oxford investigators, began enrolment this month.

Vaccine developers often combine two vaccines to combat the same pathogen, and researchers are keen to deploy the strategy — known as a heterologous prime–boost — against the coronavirus. A heterologous prime–boost combination was approved last year by European regulators to protect against Ebola, and experimental HIV vaccines often rely on the strategy, says Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston, Massachusetts. But it has yet to be tested for vaccines against COVID-19.

The ability to mix and match vaccines could make vaccination programmes more flexible:



A trial will test a two-shot regimen that uses two types of COVID vaccine.

BEN HASTY/MEDIANEWS GROUP/READING EAGLE/GETTY

it would speed up the process and reduce the impact of any supply-chain disruptions. "It really makes the implementation much more simple," said Mary Ramsay, head of immunization at Public Health England, at a press briefing on 3 February.

AstraZeneca has said that it will also trial combinations of its COVID-19 vaccine with the Russian coronavirus vaccine, Sputnik V, which uses harmless viruses to shuttle components of the coronavirus into cells. Sputnik V, which has greater than 90% efficacy against COVID-19 (D. Y. Logunov *et al. Lancet* https://doi.org/ghxj4g; 2021), is itself a heterologous prime–boost vaccine, consisting of different viral components in the first and second doses.

T-cell focus

Some researchers also think that combining two vaccines could strengthen immune responses by harnessing the best features of each. That would be particularly desirable now that vaccine developers are combating coronavirus variants that seem to be partially resistant to certain immune responses, says Barouch. "It's possible that responses might be better than what either vaccine can achieve on its own," Barouch says. "But that remains to be proven experimentally for COVID-19."

The Oxford trial aims to enrol 820 people, and it will test two dosing schedules: one with 4 weeks between the two injections, and another with a 12-week interval. The trial will not look directly at how well the combination protects against COVID-19 — such a study would need to be much larger and would take a long time to complete. Instead, the team will take regular blood samples to measure levels of antibodies and immune cells called T cells that participants produce against the coronavirus. It will also monitor for safety concerns.

T cells could be key to boosting immune response (see page 374). RNA vaccines have generated powerful antibody responses to the SARS-CoV-2 coronavirus. But they have not proved to be as good as the AstraZeneca and Oxford vaccine at stimulating a class of T cells called $CD8^+$ T cells, says Zhou Xing, an immunologist at McMaster University in Hamilton, Canada. These cells can strengthen an immune response by identifying and destroying cells infected with the virus.

Animal studies suggest that a strengthened immune response is possible: in a preprint published on 29 January, researchers reported that a combination of an RNA coronavirus vaccine and the AstraZeneca vaccine roused $CD8^+$ T cells in mice better than did either vaccine alone (A. J. Spencer *et al.* Preprint at bioRxiv https://doi.org/fvd8; 2021).

Other combinations could yield similar results. Immunologist Jae-Hwan Nam at the Catholic University of Korea in Bucheon is particularly keen to see trials of AstraZeneca's vaccine together with a protein-based vaccine