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.

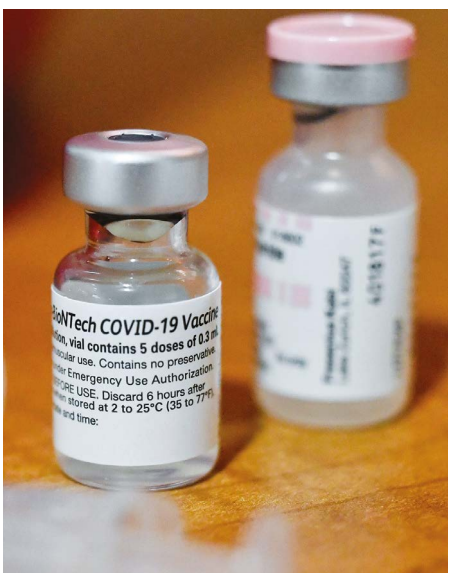
By Heidi Ledford

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

made by Novavax in Gaithersburg, Maryland. Protein vaccines provoke immune responses in a similar way to RNA vaccines, he says, and Novavax's vaccine might be easier to make and distribute than the RNA vaccines.

Unlike the RNA vaccines, Sputnik V works by combining two vaccines that each tuck the DNA encoding a crucial coronavirus protein, called spike, into a harmless virus. The virus enters human cells, where the DNA is expressed. The immune system then mounts a response to the spike protein.

But if the same virus is used in subsequent shots, an immune response against the harmless virus itself could dampen the response to spike. Sputnik V addresses this problem by using two different shuttling viruses, one in each shot. AstraZeneca's vaccine uses only one, making the heterologous prime–boost studies with Pfizer's vaccine and Sputnik V particularly attractive.

If all goes well, the results from the trial arm testing the four-week regimen should be available by June, in time to inform the United Kingdom's ongoing vaccination campaign, says Matthew Snape, a paediatrician at Oxford and the trial's chief investigator.

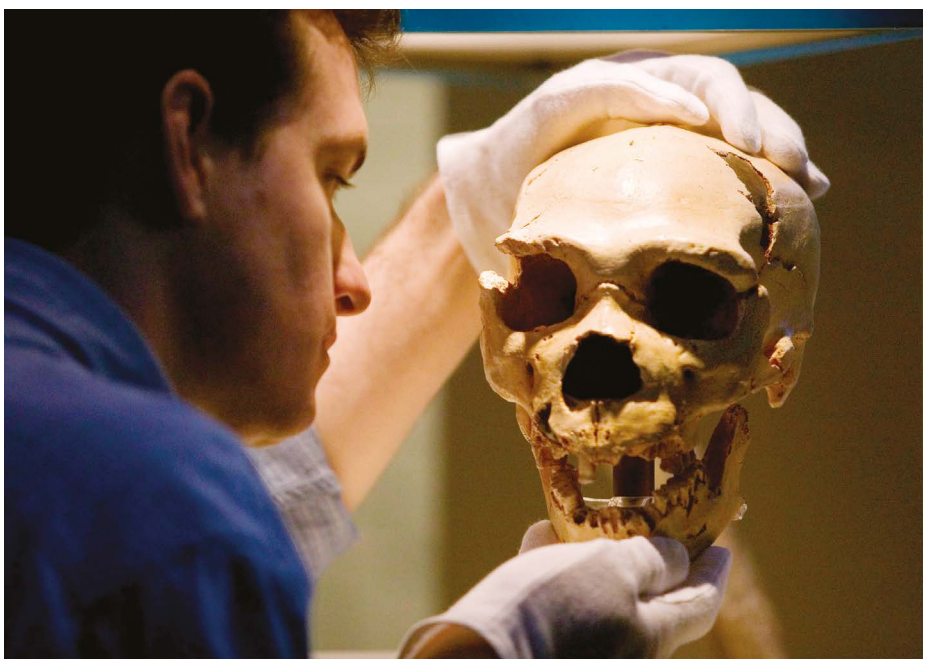
Snape says the team hopes to add further vaccines to its study as they become available. Combination studies are possible thanks to the rapid development of multiple vaccine options against the coronavirus, says Xing. "We are in a strong position to go after the best immunologically considered strategies," he says.

NEANDERTHAL-LIKE 'MINI-BRAINS' CREATED IN THE LAB WITH CRISPR

Organoids with an ancient gene variant are smaller and bumpier than those with human genes.

By Ariana Remmel

Researchers have created tiny, brain-like 'organoids' that contain a gene variant harboured by two extinct human relatives, Neanderthals and Denisovans. The tissues, made by engineering human stem cells, are far from being true representations of these species' brains — but they show distinct differences from human organoids, including their size, shape and texture. The findings, published in *Science* on 11 February, could help scientists to understand the genetic pathways that allowed human brains to evolve (C. A. Trujillo *et al. Science* **371**, eaax2537; 2021).



Most research on Neanderthal brains looks at the size and shape of fossilized skulls.

NATURAL HISTORY MUSEUM, LONDON/SPL

"It's an extraordinary paper with some extraordinary claims," says Gray Camp, a developmental biologist at the University of Basel in Switzerland, whose laboratory last year reported growing brain organoids that contained a gene common to Neanderthals and humans (M. Dannemann *et al. Stem Cell Rep*. **15**, 214–225; 2020). The latest work takes the research further by looking at gene variants that humans lost in evolution. But Camp remains sceptical about the implications of the results, and says the work opens more questions that will require investigation.

Humans are more closely related to Neanderthals and Denisovans than to any living primate, and some 40% of the Neanderthal genome can still be found spread throughout living humans. But researchers have limited means of studying these ancient species' brains — soft tissue is not well preserved, and most studies rely on inspecting the size and shape of fossilized skulls. Knowing how the species' genes differ from humans' is important because it helps researchers to understand what makes humans unique — especially in our brains.

The researchers, led by Alysson Muotri, a neuroscientist at the University of California, San Diego, used the genome-editing technique CRISPR–Cas9 to introduce the Neanderthal and Denisovan form of a gene called *NOVA1* into human pluripotent stem cells, which can develop into any cell type in the body. They cultured these to form organoids, clumps of brain-like tissue, up to 5 millimetres across, alongside normal human brain organoids for comparison.

It was immediately clear that the organoids expressing the archaic variant of *NOVA1* were different. "As soon as we saw the shape of the organoids, we knew that we were on to something," says Muotri. Human brain organoids are typically smooth and spherical, whereas the ancient-gene organoids had rough, complex surfaces and were smaller. This is probably because of differences in how the cells grow and multiply, say the authors.

Genome comparison

To determine which archaic gene to express in the organoids, the researchers compared a library of human genome sequences with near-complete genomes of two Neanderthals and one Denisovan. They found 61 genes for which the human version is consistently different from that in the ancient species. Of these, *NOVA1* is involved in forming the brain's synapses, or nerve junctions, and is associated with neurological disorders when its activity is altered.

The human *NOVA1* gene differs from the