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.

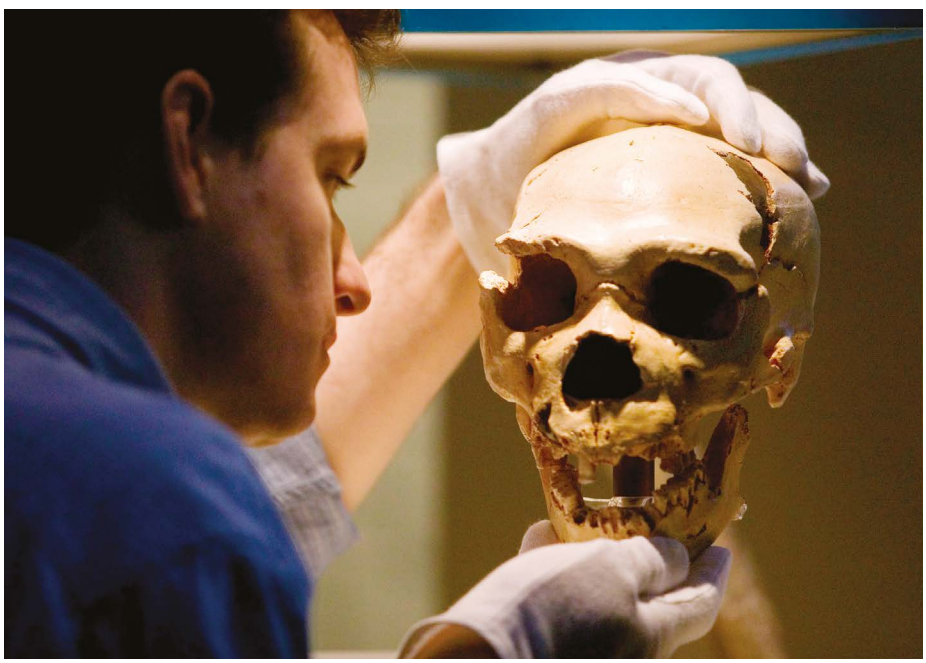
Snape says the team hopes to add further vaccines to its study as they become available. Combination studies are possible thanks to the rapid development of multiple vaccine options against the coronavirus, says Xing. "We are in a strong position to go after the best immunologically considered strategies,"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

TIMOTHY NWACHUKWU/NYT/REDUX/EYEVINE

archaic variant — which is still present in other living primates — by a single base, which the researchers edited into the stem cells using CRISPR–Cas9. That difference swaps a single amino acid in the *NOVA1* protein made by the archaic organoids. "The fact that all humans, or nearly all humans, now have this version and not the old one means it gave us a tremendous advantage at certain points during evolution. So the question we have now is, what are these advantages?" says Muotri.

The differences between the resulting organoids continued at the molecular level. The team found 277 genes that had different activity between the ancient-gene and human organoids; some of those genes are known to affect neuronal development and connectivity. As a result, the archaic organoids contained different levels of synapse proteins, and their neurons fired in less orderly patterns than did those in the control tissues. There is also evidence that they matured more quickly.

> **"As soon as we saw the shape of the organoids, we knew that we were on to something."**

Big difference

"The most significant finding is that you revert [the gene] to an ancestral state, and you see an effect in the organoid," says Wolfgang Enard, an evolutionary geneticist at Ludwig Maximilian University of Munich in Germany. He's amazed that such a small genetic difference causes such obvious changes, but he is sceptical that the organoids' odd appearance tells us much about Neanderthal brains.

Camp also cautions that it's unlikely that these ancient-gene organoids fully represent true Neanderthal tissue. Instead, the characteristics observed could be the result of changing an important protein that is present in humans because of compounding effects of many mutations stacked on top of each other over time. "It's like Jenga," he says, "you pull out that amino acid and the brain doesn't function."

Still, the edited-organoid approach could be useful for studying brain evolution across primates, says Suzana Herculano-Houzel, an evolutionary neuroscientist at Vanderbilt University in Nashville, Tennessee. Muotri's team plans to make organoids edited to contain other reverted genes that could offer insights into the human brain. If researchers can understand the evolutionary pathway that brought humans to our current state, he says, they might improve understanding of diseases specific to the human brain.

Q&A

Tackling vaccine hesitancy — in churches and on Twitter

Kizzmekia Corbett, an immunologist at the US National Institutes of Health (NIH), is one of the scientists who in early 2020 helped to develop an mRNA-based vaccine for COVID-19. Developed in collaboration with biotech firm Moderna of Cambridge, Massachusetts, the vaccine, which delivers a piece of genetic code to a person's cells to create immune-stimulating virus proteins, is now being distributed across the United States and elsewhere. And Corbett is taking on another challenge: tempering vaccine hesitancy (see page 369) by talking and tweeting about COVID-19 science with people of colour. Corbett is one of many Black scientists and doctors doing this work. In the United States, COVID-19 has affected Black, Native American and Latin American people at higher rates than white people. At the same time, people in these groups are more wary of COVID-19 vaccines, partly because of past medical exploitation. In a survey by the US Centers for Disease Control and Prevention last December, 46% of Black adults said they probably would not get vaccinated against the coronavirus SARS-CoV-2, compared with 30% of white respondents (K. H. Nguyen *et al. MMWR Morb. Mortal. Wkly Rep.* 70, 217–222; 2021).

What was your role in designing a vaccine for SARS-CoV-2, and what was that like?
My contribution was helping to design the vaccine, leading the preclinical studies that informed the Phase I clinical trial, and designing assays used for testing of clinical-trial samples.

The quest in early January 2020 was to gear up. We started ordering all the things that we needed around animal experiments. We mapped out a plan. I started assigning roles to team members.

You began giving science talks to the public at age 20. What did you talk about?
I would do it really around the thing that the people need to know. Girl Scouts need to know about puberty and sexually transmitted diseases and sex. And churches often need to have something scientifically broken down for them by someone who also believes in God. It's not about what you're saying, it's about how you relate to the people you're saying it to.

During the pandemic, you've spoken at many events, often with communities of colour. What are some ways you build trust?
Always invite questions at the end. Scientists are notorious for running over time. If you short people on their questions, you lose all the trust you just gained, because it looks like you're avoiding them. I generally try to double my question time.

My role is to deliver science in a digestible fashion. When I present a bar chart, I say, "This is the axis, and this is what you're seeing, and this is how it was tested." So, the goal is that eventually people see enough of this, and we get to a point where we don't have to do that any more.

Why is it important for you to tweet about vaccines?
I do it to communicate science to people who aren't scientists. I am learning more and more that people have not been exposed to all the things that we do from a research perspective. We publish these articles and we think we're getting data out — but, like, who to?

For a long time, we left the general public on the outside of vaccine development, until it was time to give them their shot. And that's just unacceptable. I can't even blame anyone for being sceptical about this, because they don't have any idea what went into it. So, our goal is to inform people. It's very helpful for people to feel like they're part of something.

Why is this outreach important for you now?
I have studied health disparities since I was in college. I'm a double major in sociology. I understand the intricate interlacing of science and health, particularly for disparities, and particularly for people of colour. So it's near and dear to my heart. It's actually the reason vaccine development is important to me, and is where I chose to take my viral-immunology career.

Vaccines have the potential to be the equalizer of health disparities, especially around infectious diseases. I could never sleep at night if I developed anything — if any product of my science came out — and it did not equally benefit the people who look like me. Period.

Interview by Nidhi Subbaraman
This interview has been edited for length and clarity.