SOUTH AFRICAN SCIENTISTS COPY MODERNA COVID VACCINE

Researchers complete first step in project to bring vaccine manufacturing to the global south.

By Amy Maxmen

Researchers at a South African biotechnology company say they have nearly completed the process of reproducing Moderna's mRNA vaccine against COVID-19, without Moderna's involvement.

The company, Afrigen Biologics and Vaccines in Cape Town, has made only microlitres of the vaccine, which is based on data that Moderna used to make its shot. But the achievement is a milestone for a major initiative launched by the World Health Organization (WHO) — a technology-transfer hub meant to build capacity for vaccine manufacturing in low- and middle-income countries.

During the COVID-19 pandemic, developers of mRNA vaccines — Moderna, based in Cambridge, Massachusetts, Pfizer in New York City and BioNTech in Mainz, Germany — have sent more than 70% of their doses to wealthy nations, according to vaccine-distribution analyses. Meanwhile, millions of doses purchased by or promised to low- and middle-income countries have been delayed. "Moderna and Pfizer–BioNTech's vaccines are mainly still going to just the richest countries," says Martin Friede, the WHO official coordinating the hub. "Our objective is to empower other countries to make their own."

Going it alone

Many steps remain before Afrigen's mRNA vaccine candidate can be distributed to people in Africa and beyond, and it definitely won't help to curb the pandemic this year. But the WHO hopes that the process of creating it will lay the foundation for a more globally distributed mRNA-vaccine industry.

Gerhardt Boukes, chief scientist at Afrigen — the firm at the core of the WHO's hub — is proud to have helped with the first phase of the plan, which included creating messenger RNA that encodes a modified portion of the coronavirus SARS-CoV-2 and encapsulating it in a lipid nanoparticle that delivers the vaccine to cells. "We didn't have help from the major COVID-vaccine producers," he says, "so we did it ourselves to show the world that it can be done, and be done here, on the African continent."

When the WHO launched its mRNA tech-transfer hub in South Africa last June, it asked Moderna, Pfizer and BioNTech to help teach researchers in low- and middle-income countries how to make their COVID-19 vaccines. But the companies did not respond, and the WHO decided to go ahead without their help. Friede says the WHO chose to replicate Moderna's shot because more information on its development is available publicly, compared with Pfizer–BioNTech's vaccine, and because Moderna has vowed not to enforce its patents during the pandemic. Moderna did not respond to requests from *Nature* to comment on the WHO's decision to copy its vaccine.

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With funds from countries including France, Germany and Belgium, South African researchers began chipping away at the project in late September. A team at the University of the Witwatersrand in Johannesburg took the lead on the first step: making a DNA molecule that would serve as a template to synthesize the mRNA. Although Moderna has controversially patented this sequence, researchers at Stanford University in California deposited it in the online database Virological.org in March last year.

Patrick Arbuthnot, director of gene-therapy research at the University of the Witwatersrand, says, "We were not intimidated, because mRNA synthesis is a fairly generic procedure." Despite delays in the shipment of raw materials, the team completed this process in ten weeks and sent vials of mRNA to Afrigen in early December.

An empowerment process

During this period, having heard about plans to mimic Moderna's shot, scientists from around the world e-mailed Afrigen researchers to offer assistance. Some of them were at the US National Institutes of Health, and had conducted foundational work on mRNA vaccines. "It was extraordinary," says Petro Terblanche, Afrigen's managing director. "I think a lot of scientists were disillusioned with what had happened with vaccine distribution, and they wanted to help get the world out of this dilemma."

On 5 January, Afrigen's researchers accomplished another tricky part of the process: they encapsulated the mRNA in a fatty nanoparticle made of a mixture of lipids. Boukes says they haven't yet used Moderna's specific lipid mixture, but rather one that was immediately available from the manufacturer of the machine that the laboratory uses to create lipid nanoparticles. The researchers plan to use Moderna's lipid mixture as soon as one last analytical instrument arrives. After that, the team will analyse the formulation to ensure that it is truly a near copy of Moderna's vaccine.

The next set of challenges will be to make

AFRIGEN BIOLOGICS

Researchers at Afrigen Biologics and Vaccines are attempting to replicate Moderna's vaccine.

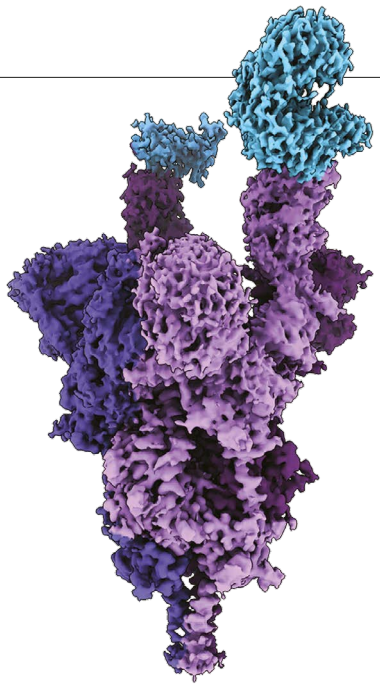
a lot more of the vaccine. Jason McLellan, a structural biologist at the University of Texas at Austin whose work was foundational to the development of several COVID-19 vaccines, says he is not surprised that South African researchers seem to have copied Moderna's vaccine, but he adds that scaling up production of that original shot required a lot of extra innovation by manufacturers.

For the next phase of the project, several companies in the global south will learn from Afrigen and attempt to create batches of vaccine themselves, in preparation for testing the shots in rodents. The WHO expects a Moderna mimic to be ready for phase I trials in people by the end of November.

What will happen next year remains uncertain. Charles Gore, director of the Medicines Patent Pool in Geneva, Switzerland — an organization working with the hub that is devoted to expanding drug and vaccine access around the world — says that the initiative has no intention of infringing Moderna's patents. Laboratory research is generally not subject to patent rules, Gore explains.

And he hopes that once the vaccine is ready for use, Moderna might then license its patents — or that by then, there might be alternatives that companies could produce without fear of a lawsuit. Scientists at several universities are currently developing next-generation mRNA vaccines that might be cheaper to make or not require the ultracold storage needed for Moderna and Pfizer–BioNTech's vaccines.

Although the pace of this effort will not meet the urgent need for vaccines across Africa, many researchers from the continent are enthusiastic. A reliance on vaccines from wealthy countries and companies has proved dangerous during the pandemic — only about 10% of people in Africa have been fully vaccinated — and this initiative aims to help nations to protect themselves. "Global health's dysfunction derives from power imbalances," explains Olusoji Adeyi, president of the organization Resilient Health Systems in Washington DC. "Addressing that will come from countries in the global south developing their own capabilities and taking responsibility for their own health."



SRIRAM SUBRAMANIAM/UNIV. BRITISH COLUMBIA

Researchers have found that despite myriad mutations, Omicron's spike protein binds tightly to the ACE2 receptor (blue) on cells.

OMICRON'S STRUCTURE COULD HELP EXPLAIN ITS GLOBAL TAKEOVER

Studies hint at why the SARS-CoV-2 variant spreads fast, yet seems to cause milder disease than earlier versions.

By Diana Kwon

After it was first detected in South Africa last November, Omicron spread around the globe faster than any previous variant of the coronavirus SARS-CoV-2, readily infecting even those who had been vaccinated or had had COVID-19 before. To learn how it was able to do this, scientists have turned to techniques such as cryo-electron microscopy, to visualize Omicron's molecular structure at near-atomic resolution.

By comparing Omicron's structure with that of the original version of SARS-CoV-2 and its other variants, they have begun to shed light[1] on which features of the highly mutated virus have enabled it to evade the body's immune defences, while also maintaining its ability to attack a person's cells. And they've begun to unpick why Omicron seems to cause milder disease than previous variants.

"Omicron is very different structurally than all the other variants we have known so far," says Priyamvada Acharya, a structural biologist at the Duke Human Vaccine Institute in Durham, North Carolina.

Omicron has dozens of mutations not seen in the original SARS-CoV-2 strain that researchers first detected in Wuhan, China. More than 30 of those mutations are in the spike protein on the coronavirus's surface, which helps the virus to latch on to and infect host cells. No previous SARS-CoV-2 variant seems to have accumulated so many genetic changes.

Fifteen of Omicron's spike mutations are found in the protein's receptor binding domain (RBD), a region that binds to a receptor called ACE2 on a person's cells to gain entry. A research team including David Veesler, a structural biologist at the University of Washington in Seattle, has shown[2] that these changes, along with 11 mutations in a region of the spike called the N-terminal domain, have completely remodelled the areas of the protein that are recognized by 'neutralizing' antibodies. These antibodies are generated after a person receives a vaccine against SARS-CoV-2 or is infected; they later recognize the pathogen and prevent it from entering cells. The remodelling severely hinders the ability of most neutralizing antibodies to recognize the virus.

With such a big shift in shape, there's a huge question over how Omicron can still bind strongly to ACE2. "Normally, when you have so many mutations all over, you expect that you will also have compromised the ability to bind the receptor," says Sriram Subramaniam, a structural biologist at the University of British Columbia in Vancouver, Canada.

A net effect

Subramaniam and his colleagues answered the question by demonstrating that although some of the mutations in Omicron's RBD hinder its ability to bind to ACE2, others strengthen it[3]. For example, the K417N mutation disrupts a key salt bridge — a bond between oppositely charged bits of protein — that helps to link the spike protein to ACE2. A combination of other mutations, however, helps to form new salt bridges and hydrogen bonds that strengthen the link to ACE2. The net effect is that Omicron binds to ACE2 more strongly than does the original version of SARS-CoV-2, and as strongly as does the Delta variant.

Veesler and his colleagues have also found[2] enhanced interactions between Omicron's RBD and ACE2. Omicron has adopted a "very elegant molecular solution, where the mutations are mediating immune evasion while enhancing receptor binding", Veesler says.

Martin Hällberg, a structural biologist at the Karolinska Institute in Stockholm, applauds the work by these groups, but points out that it's an open question how some neutralizing antibodies can still detect Omicron. If researchers can understand the structural