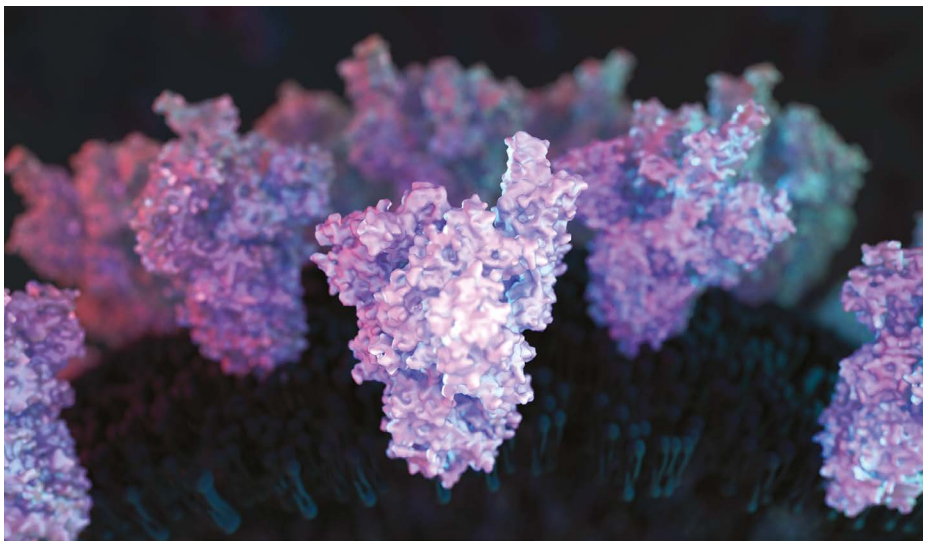

DESIGN CELLS/SPL

An illustration of the spike proteins that SARS-CoV-2 uses to break into human cells.

RARE REACTIONS MIGHT HOLD KEY TO VARIANT-PROOF COVID VACCINES

Some people mount an immune response that can fend off a menagerie of SARS-CoV-2 variants.

By Ewen Callaway

Penny Moore was one of the first scientists to show that a coronavirus variant identified in South Africa could dodge the immune system. So the virologist was expecting more grim news when she tested the responses of people who had been infected with that variant, named B.1.351.

Instead, her team found a ray of hope: B.1.351 infection triggered antibodies that fended off variants old and new. "That was a surprise," says Moore, who is based at the National Institute for Communicable Diseases and the University of the Witwatersrand in Johannesburg.

The discovery, posted on bioRxiv last month[1], joins a slew of recent research suggesting that vaccines for COVID-19 might cope with existing variants — and maybe even future ones.

"Getting vaccines that will tackle the variants that are currently circulating is an eminently solvable problem," says Paul Bieniasz, a virologist at the Rockefeller University in New York City, whose laboratory is studying variants. "It might be that we already have that solution."

Researchers in South Africa identified B.1.351 in late 2020. It now accounts for the majority of the country's cases and has spread around the world. The variant attracted scientists' attention because it was linked to outbreaks in places that had already been hit hard by South Africa's first wave, earlier in the year, and because it carried changes that blunted the potency of some antibodies that ordinarily disable SARS-CoV-2.

Research led by Moore and Alex Sigal at the Africa Health Research Institute in Durban stoked early worries over B.1.351 in January[2,3]. It showed that the variant evaded virus-blocking antibodies produced by a large number of people who had been infected with first-wave strains. Weeks later, clinical-trial results showed that the variant diminished the efficacy of vaccines developed by Novavax[4] and Johnson & Johnson, and potentially wiped out much of the protection conferred by AstraZeneca's jab[5].

'Pseudovirus' surprise

Moore hoped that B.1.351 infection would trigger strong immune responses, but she was open to the possibility that this variant might be less visible to the immune system than are other strains. To find out, her team analysed antibodies from 89 people who had been hospitalized with B.1.351 infections. The researchers used a 'pseudovirus' — a modified form of HIV that infects cells using the SARS-CoV-2 spike protein — to measure the capacity of the antibodies to block infection.

Reassuringly, people who recovered from B.1.351 infection made as many antibodies as did those infected with earlier circulating variants. Those antibodies did a good job of blocking pseudoviruses with B.1.351 mutations. To Moore's surprise, the antibodies also blocked other strains, including a variant called P.1, identified in Brazil, that shares several mutations with B.1.351. Sigal's team reported similar results in February[3].

Moore does not know why B.1.351 infection results in a such a broad immune response, but she is working to find out. "It's about the only thing I think about these days," she says. It's possible that the antibodies are recognizing features of the viral spike protein that do not differ between those variants.

The results are a boost to nascent efforts to develop vaccines that can cope with variants such as B.1.351. In mid-March, updated versions of Moderna's vaccine, based on the genetic sequence of the B.1.351 variant, were given to trial participants for the first time. Other developers, including Pfizer–BioNTech, also plan to test vaccines based on B.1.351.

Different coronavirus variants can trigger different immune responses, and researchers are only beginning to map their full diversity. Infection with a fast-spreading variant identified in the United Kingdom, known as B.1.1.7, seems to provoke antibodies that do a poor job against B.1.351 and earlier variants[6], according to work led by immunologist George Kassiotis at the Francis Crick Institute in London and virologist Eleni Nastouli at University College London.

Again, it's not clear why B.1.1.7 seems to generate a narrow immune response. The variant is handled by existing vaccines — which are based on the virus that emerged in Wuhan, China, in late 2019 — but researchers urgently need to determine whether vaccines based on B.1.351 can also cope with B.1.1.7, says Kassiotis. If not, future vaccines might need to immunize simultaneously against multiple variants, in a similar way to seasonal influenza jabs.

Vaccine resilience

Redesigning vaccines is not necessarily the only way to cope with emerging coronavirus variants. Researchers are identifying other factors that could make existing vaccines more resilient, such as mimicking how natural immunity caused by infection can sometimes offer broad protection. For instance, Bieniasz's team found that some people who recover from COVID-19 make antibodies that, over time, become more capable of blocking diverse coronavirus variants[7].

Antibody-producing B cells can evolve through natural selection to make antibodies that bind more tightly to their target, a process known as maturation. Bieniasz's team isolated B cells, at intervals of several months, from people who had recovered from infection, and looked at how the potency of individual antibodies changed as the B-cell lineages that made them matured.

In some instances, 'matured' antibodies recognized variants, including B.1.351, that

earlier versions of these antibodies failed to recognize; one matured type even neutralized some other coronaviruses.

It's not obvious how to make vaccines trigger such antibodies. Maturation occurs when viral molecules called antigens, which are recognized by antibodies, persist in the body. "Really, the way to drive the process is to have the antigen be as persistent as possible," says Bieniasz. Formulating vaccines with adjuvants — foreign molecules that increase their potency — might be one way to achieve this.

Some of the existing vaccines might already be triggering variant-resilient immune responses. In another March preprint, a long-running COVID-19 study in Seattle, Washington, reported that after receiving a single dose of an mRNA vaccine, participants who had previously been infected with SARS-CoV-2 produced heaps of antibodies that can neutralize B.1.351, as well as an earlier circulating variant[8].

Leonidas Stamatatos, an immunologist at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle who co-led the study, suspects that a single vaccine dose boosted the levels of pre-existing antibodies that were capable of recognizing diverse variants. It's not clear how to mimic this response in people who haven't had COVID-19. One possibility is that a lag of several months between infection and vaccination was responsible, and that its effect could be replicated with another vaccine dose, given six months or a year after the first two, says Andy McGuire, an FHCRC immunologist who co-led the study.

By showing such a broad immune response to variants, the latest data make researchers cautiously optimistic that vaccines will be able to protect against a breadth of variants. "I think it's very good news in terms of a path towards better vaccines," says Morgane Rolland, a virologist who works at the Walter Reed Army Institute of Research in Silver Spring, Maryland.

And the fact that the virus is repeatedly developing the same immune-evading mutations could mean that its spike protein has limited capacity for change, Rolland adds.

Moore isn't so sure. Given enough time, "I have infinite faith in the ability of a virus to escape an immune response", she says. "We've got to lower the global number of infections to the point where the virus doesn't have as many opportunities to escape."

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Q&A

We need a non-political way to track viruses

Rick Bright put his career on the line last year, when he blew the whistle on how then-US president Donald Trump's administration was mishandling the coronavirus pandemic. Bright, who was director of the US Biomedical Advanced Research and Development Authority — which is responsible for countermeasures against pandemics, bioterrorism and other health emergencies — was abruptly removed from the agency. Now, he is trying his hand at curbing outbreaks from outside the government. On 8 March, the Rockefeller Foundation, a philanthropic organization based in New York City that funds science, announced that Bright would become the senior vice-president of its pandemic-prevention activities. His first move will be to spearhead a plan to use genomic sequencing and analysis to track the coronavirus SARS-CoV-2 in the United States. *Nature* spoke to Bright about this project, and protecting integrity in science.

Will Rockefeller give scientists grants to sequence SARS-CoV-2?
Sequencing is important, but it's not our only emphasis. We're hoping that the CDC [US Centers for Disease Control and Prevention] will follow through with its strategy of funding more sequencing across the country. But we need more than sequences to make decisions. So, we are trying to build the capacity to analyse those data quickly, and to create impactful analyses that will better inform public-health officials or government officials about the actions they need to take to get in front of outbreaks.

Why build this early-warning system outside the government?
We want to partner with the CDC and other national and international health entities. But there are advantages to having a neutral, non-political organization manage this type of information.

One is that a non-governmental platform would be less susceptible to politics, internationally and domestically. I've worked under four presidents, and I've seen various levels of political influence, collaboration and cooperation with science. The last administration certainly had a way of suppressing and revising science-based messages, and that got us where we are today with the pandemic in the United States. So, a non-governmental, non-political entity would have the ability to seal and protect those data, and to make sure that the world has access to all the same information at the same time.

Why didn't more government researchers speak out about the Trump administration's political meddling?
We need more protections in place for government employees and scientists who speak out or come forward. It was a very difficult administration to work under as a scientist. My scientific colleagues in the government were afraid of losing their jobs, but were also working really hard to do the right thing and push for the best decisions with the right data.

I could only take so much. When the administration clearly, in my opinion, showed a disregard for the general population in a subject area that I know a lot about — pandemic response — and pushed an unproven drug [hydroxychloroquine] to the general public without close clinical oversight, that was a line that I could not cross. I had to speak out.

I felt my life would probably change for the worse, and that I'd go through a lot of pain and frustration and retaliation from the administration. But it came on strong — I had to go into hiding for quite some time.

But, you know, it was worth it. And I hope that no other scientist ever has to find themselves in that position again.

Does a warning system help if a country has a leader who doesn't listen to science?
Well, you have to have strong leadership, and the leadership has to respect science. But I think this system helps. Early last year, there was the narrative that COVID-19 was low risk and that it was not spreading in our country. But if we had an early-warning system that was neutral, and non-political, and was just like the weather report, individuals wouldn't need to rely on someone in the White House to tell them what was happening.

Interview by Amy Maxmen
This interview has been edited for length and clarity.

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