

nanoparticle induced much higher levels of antibodies against SARS-CoV-2 than did the Pfizer vaccine. It also induced cross-reactive antibodies against the original SARS virus and bat and pangolin sarbecoviruses.

Martinez and his colleagues have induced these widely reactive antibodies in mice, using a vaccine made from a combination of spike proteins from different coronaviruses³. But Martinez says the latest study suggests that this spike chimaera might not be necessary; a similar response could be induced simply by

the original SARS virus's spike protein.

Wang says he is already working on potential vaccines that target multiple sarbecoviruses, and he now hopes to find further survivors of the 2002–04 SARS outbreak to conduct a much larger study, including testing their responses to other COVID-19 vaccines.

1. Tan, C.-W. et al. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2108453> (2021).
2. Saunders, K. O. et al. *Nature* **594**, 553–559 (2021).
3. Martinez, D. R. et al. *Science* <https://doi.org/10.1126/science.abi4506> (2021).

THE MUTATION THAT HELPS DELTA SPREAD LIKE WILDFIRE

A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.

By Ewen Callaway

As the world grapples with the hyper-infectious Delta coronavirus variant, scientists are racing to understand the biological basis for its behaviour. A slew of studies has highlighted an amino-acid change present in Delta that might contribute to its swift spread. Delta is at least 40% more transmissible than is the Alpha

variant identified in the United Kingdom in late 2020, epidemiological studies suggest.

“The key hallmark of Delta is that transmissibility seems to be ramping up to the next notch,” says Pei-Yong Shi, a virologist at the University of Texas Medical Branch in Galveston. “We thought Alpha was pretty bad, very good at spreading. This one seems to be even more.”

Shi's team and other groups have zeroed in

on a mutation that alters a single amino acid in the SARS-CoV-2 spike protein – the viral molecule responsible for recognizing and invading cells. The change, which is called P681R and transforms a proline residue into an arginine, falls within an intensely studied region of the spike protein called the furin cleavage site.

The presence of this short string of amino acids set off alarm bells when SARS-CoV-2 was first identified in China, because it is associated with heightened infectivity in other viruses such as influenza, but had not previously been found in sarbecoviruses, the family of coronaviruses to which SARS-CoV-2 belongs. “This little insert sticks out and hits you in the face,” says Gary Whittaker, a virologist at Cornell University in Ithaca, New York.

Pre-activated virus

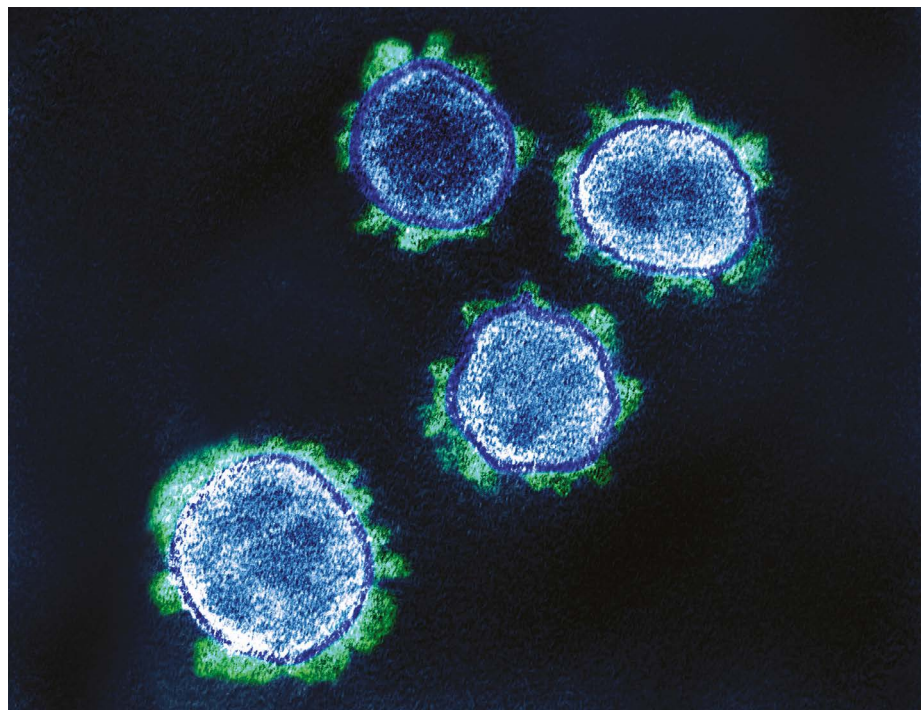
To penetrate cells, the SARS-CoV-2 spike protein must be cut twice by host proteins. In the SARS-CoV-1 virus that causes severe acute respiratory syndrome (SARS), both incisions occur after the virus has locked on to a cell. But with SARS-CoV-2, the presence of the furin cleavage site means that host enzymes (including one called furin) can make the first cut as newly formed viral particles emerge from an infected cell. These pre-activated viral particles can then go on to infect cells more efficiently than do particles requiring two cuts, says Whittaker.

Delta wasn't the first SARS-CoV-2 variant to gain a mutation that alters the furin cleavage site. The Alpha variant has a different amino-acid change at the same location as Delta. But the available evidence suggests that the mutation's effect has been especially profound in Delta.

In a study reported as a preprint on 13 August¹, Shi's team found that the spike protein is cut much more efficiently in Delta-variant particles than in Alpha particles, echoing results reported in May by virologist Wendy Barclay at Imperial College London and her team, who compared Delta with an earlier strain². Follow-up experiments by both groups showed that the P681R change was largely responsible for spike being clipped so much more efficiently. “This really nailed it, in terms of the mechanism,” says Shi.

Researchers are also beginning to join the dots between P681R and Delta's ferocious infectivity. Shi's team found that, in cultured human-airway epithelial cells infected with equal numbers of Delta and Alpha viral particles, Delta rapidly outcompeted the Alpha variant, mimicking epidemiological patterns that have played out globally. But Delta's advantage disappeared when the researchers eliminated the P681R change.

The mutation might also speed up the spread of SARS-CoV-2 from cell to cell. A team led by Kei Sato, a virologist at the University



SARS-CoV-2 coronavirus particles isolated from a person with COVID-19.

of Tokyo, found that spike proteins bearing the P681R change fuse with the plasma membranes of uninfected cells – a key step in infection – almost three times faster than do spike proteins lacking the change³.

“I think the virus is succeeding on volume and speed,” says Whittaker. “It’s become a much more efficient virus. It’s going through people and going through cells a lot quicker.”

More than one mutation

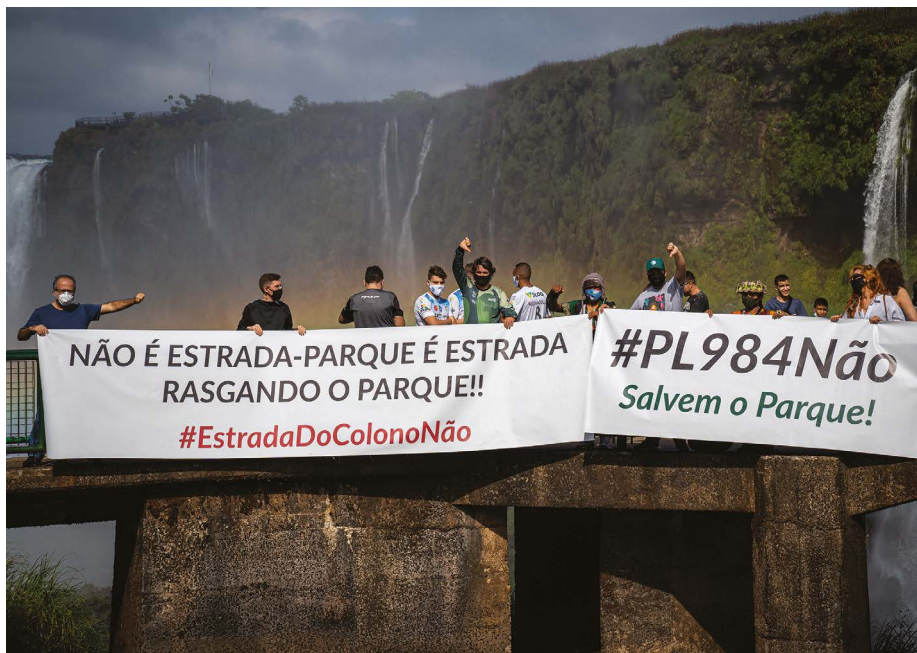
Although evidence is building that the P681R change is a crucial feature of Delta, researchers emphasize that it is unlikely to be the only mutation responsible for the variant’s fast spread. Delta carries numerous other mutations to the spike protein, as well as to other, less well-studied proteins, that might be important. “It’s very simplistic to say it’s just this 681 change. I think it’s a sum of everything,” says Teresa Aydillo-Gomez, a virologist at Icahn School of Medicine at Mount Sinai in New York City.

The epidemiological and genetic context of the mutation is also important to Delta’s rise, say scientists. One of Delta’s siblings, a variant called Kappa that, like Delta, was first identified in India, carries many of the same mutations, including P681R, but its effects haven’t been as devastating as Delta’s. In a preprint posted on 17 August, a team led by structural biologist Bing Chen at Harvard Medical School in Boston, Massachusetts, reports that Kappa’s spike protein is cleaved less frequently and fuses to cell membranes much less efficiently than does Delta’s⁴. The researchers say this finding raises questions over the role of P681R.

Researchers in Uganda identified the P681R change in a variant that spread widely in the country in early 2021, but that never took off as Delta did, even though it displays many of the same properties in cell-based laboratory studies. Whittaker’s team inserted the P681R change into a spike protein from the coronavirus that was circulating in Wuhan, China, at the beginning of the pandemic, and found no increase in its infectivity⁵. “It takes more than one mutation to make a difference,” he says.

Regardless of its role in Delta’s dominance, Whittaker and other scientists say, the mutation has underscored the importance of understanding changes in the coronavirus’s furin cleavage site. Whittaker doesn’t expect P681R to be the last furin cleavage site mutation to cause concern. “I’m waiting to see what happens next.”

1. Liu, Y. et al. Preprint at bioRxiv <https://doi.org/10.1101/2021.08.12.456173> (2021).
2. Peacock, T. P. et al. Preprint at bioRxiv <https://doi.org/10.1101/2021.05.28.446163> (2021).
3. Saito, A. et al. Preprint at bioRxiv <https://doi.org/10.1101/2021.06.17.448820> (2021).
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5. Lubinski, B. et al. Preprint at bioRxiv <https://doi.org/10.1101/2021.06.30.450632> (2021).



Protesters oppose the Caminho do Colono at Iguazu Falls.

BRAZILIAN ROAD PROPOSAL THREATENS BIODIVERSITY HOTSPOT

Researchers say the road, slated to pass through Iguazu National Park, could harm ecosystems.

By Meghie Rodrigues

Brazil’s National Congress could soon vote on a bill proposing to construct a road through the country’s Iguazu National Park. If the proposal moves ahead, researchers fear that it will threaten the park’s lush forest, a biodiversity hotspot that is home to almost 1,600 animal species, including endangered animals such as the purple-winged ground dove.

Environmentalists and researchers have fought off construction of the 17.5-kilometre road for years, arguing that it will bring not only pollution to the park, but also poachers, who would threaten animals such as jaguars and tapirs. Even research in the park could be affected. In a portion of the park that dips into Argentina, for example, “poachers often steal our cameras”, says Julia Pardo, a mammal conservation and ecology researcher at the Institute of Subtropical Biology in Misiones, Argentina.

Under the leadership of President Jair Bolsonaro, Brazil’s government has weakened protection of the country’s forests in favour of industries such as mining, logging and ranching. The lower house of Brazil’s

Congress, the Chamber of Deputies, put the bill on a fast track in June, allowing it to skip regular debate among its committees and head straight for a vote – a move that has researchers worried.

If passed, the legislation would establish a dangerous precedent that could weaken environmental law in Brazil, says Sylvia Torrecilha, a biologist at the Secretariat of Environment, Economic Development, Production and Family Agriculture in the state of Mato Grosso do Sul. In addition to cutting Iguazu Park in two with a road that will connect towns to its north and south (see ‘Contested route’), the bill seeks to create a new type of protected area – the *estrada-parque*, or park road – in Brazil’s System of Natural Conservation Units, which regulates environmentally protected areas. Approving the construction of the ‘Caminho do Colono’ (the Settler’s Road) in Iguazu could literally pave the way for creating throughways in other parks and conservation areas in Brazil, says Torrecilha.

Normally, the idea of a park road is to preserve the green areas along an already-existing scenic route, she says, not to bring commercial or economic advancement to a state – the argument lawmakers have