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Rare, dangerous side effects of some COVID-19 vaccines explained

"Groundbreaking" study uncovers why adenovirus-based shots caused life-threatening blood clots and bleeding in some people

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A woman receives a dose of AstraZeneca's COVID-19 vaccine in Sarajevo, Bosnia-Herzegovina, in September 2021. Most European countries restricted use of the vaccine or dropped it completely after severe side effects emerged in February 2021. NEDIM GRABOVICA/XINHUA

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In February 2021, soon after the first COVID-19 vaccines were rolled out in Europe, hematologist Sabine Eichinger of the Medical University of Vienna was confronted with a disturbing case: a 49-year-old nurse who had unusual blood clots and uncontrollable bleeding after receiving AstraZeneca's vaccine. The woman died, and Eichinger could not get the case out of her head. The vaccine seemed to be the only plausible explanation for her symptoms, and Eichinger worried what that might mean for its future. "I could barely sleep," she says. Eichinger even attended the patient's autopsy, hoping it would turn up some other explanation.

When it didn't, she turned to hematologist Andreas Greinacher of the University of Greifswald, who had spent decades studying a rare, strikingly similar phenomenon in patients who received the blood thinner heparin. That disorder is caused by antibodies against PF4, a protein involved in blood clotting. Within days, Greinacher's lab confirmed that Eichinger's patient had those antibodies as well.

More cases of vaccine-induced immune thrombocytopenia and thrombosis (VITT), as the syndrome became known, soon emerged in Europe among AstraZeneca recipients and also in people in the United States who had received a similar COVID-19 vaccine produced by Johnson & Johnson (J&J). They, too, had PF4 antibodies. The condition turned out to be rare—occurring in roughly one in 200,000 people who received the vaccines—but Eichinger's worries were borne out. Many European countries restricted the use of AstraZeneca's vaccine to older people, who were most at risk of dying from COVID-19, or dropped it completely. In the U.S., where AstraZeneca was never approved, the J&J vaccine was ultimately abandoned.

Now, after years of detective work, Greinacher's team and two other groups have identified what causes VITT. Both vaccines used an adenovirus to ferry a gene for the COVID-19 virus' spike protein into human cells, and in a paper today in *The New England Journal of Medicine*, the scientists show how an adenovirus protein triggers "rogue" antibodies in people with an unlucky combination of genetic background and a particular mutation in their antibody-producing B cells. Instead of targeting a viral protein, the rogue antibodies bind to PF4, setting off a dangerous cascade.

"This is a beautiful piece of work," says Stanley Plotkin, a veteran vaccine developer and professor emeritus at the University of Pennsylvania. "It's groundbreaking stuff," says Gowthamai Arepally, a hematologist at Duke University. And although both COVID-19 vaccines are out of the picture, leaving the field to vaccines based on other technologies, an adenovirus-based Ebola shot is on the market, and similar vaccines against many other diseases are in development. The new data suggest they, too, could cause VITT, but they might be made safer by tinkering with the adenovirus.

Several clues over the past few years helped researchers solve the riddle. One came from immunologists Jing Jing Wang and Tom Gordon at Flinders University and their colleagues, who in 2022 found all VITT patients had nearly identical anti-PF4 antibodies. Another came from hematologist Theodore Warkentin at McMaster University and his colleagues, who found a handful of cases in which a natural adenovirus infection caused VITT-like symptoms. Those patients, too, had the characteristic antibody. That pointed to something in the adenovirus as the culprit, Greinacher says.

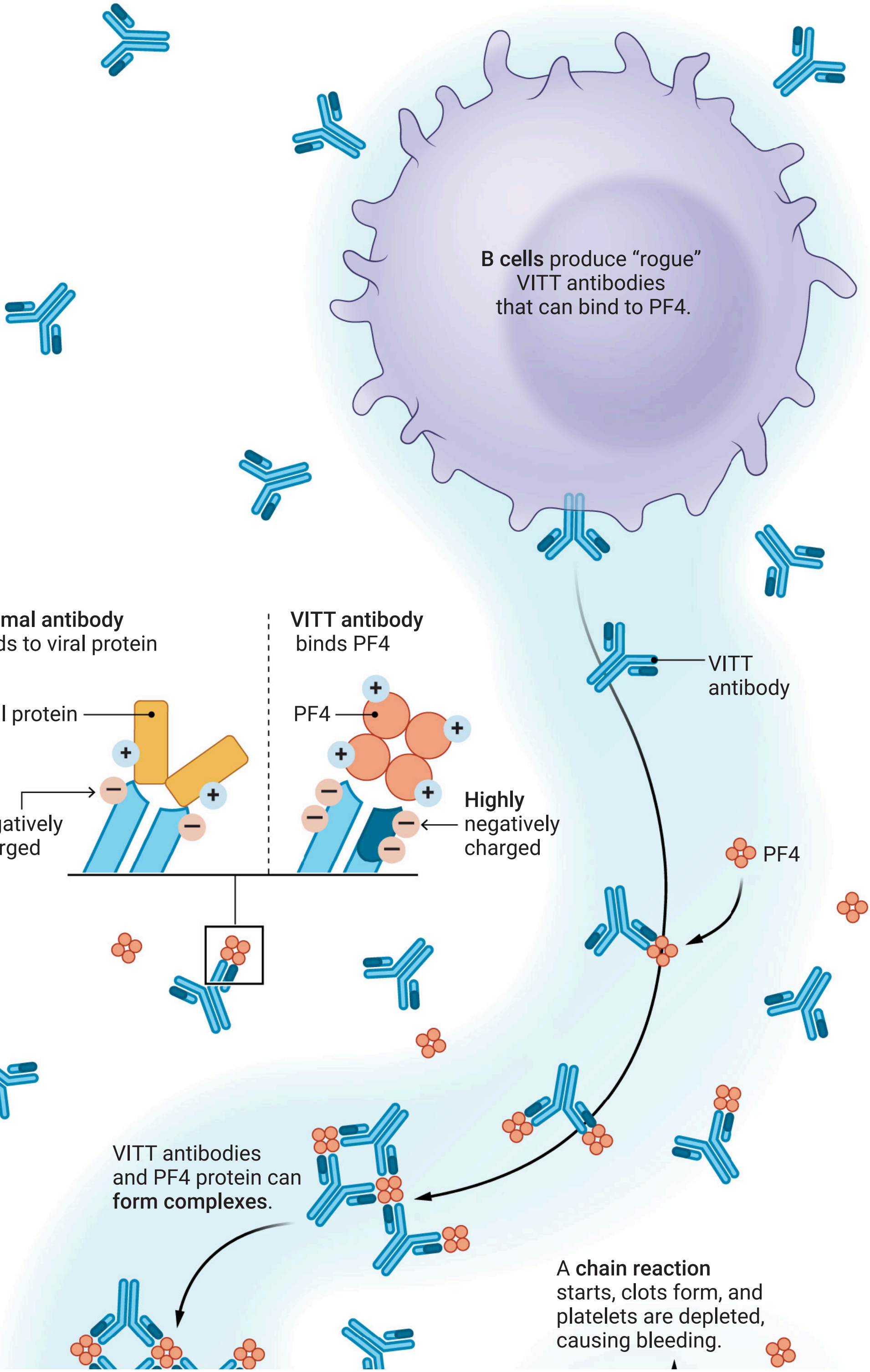
Using mass spectroscopy, the researchers took a close look at the sequence of amino acids in the anti-PF4 antibodies from 21 VITT patients. All contained a key similarity: At position 31 in the antibody's so-called light chain, they carried either the amino acid glutamic acid or aspartic acid, both of which are negatively charged. But the gene sequence in other cells from the patients showed there should be a lysine, which has a positive charge, at that position. The researchers concluded the switch had occurred only in the particular B cells that make the rogue antibodies.

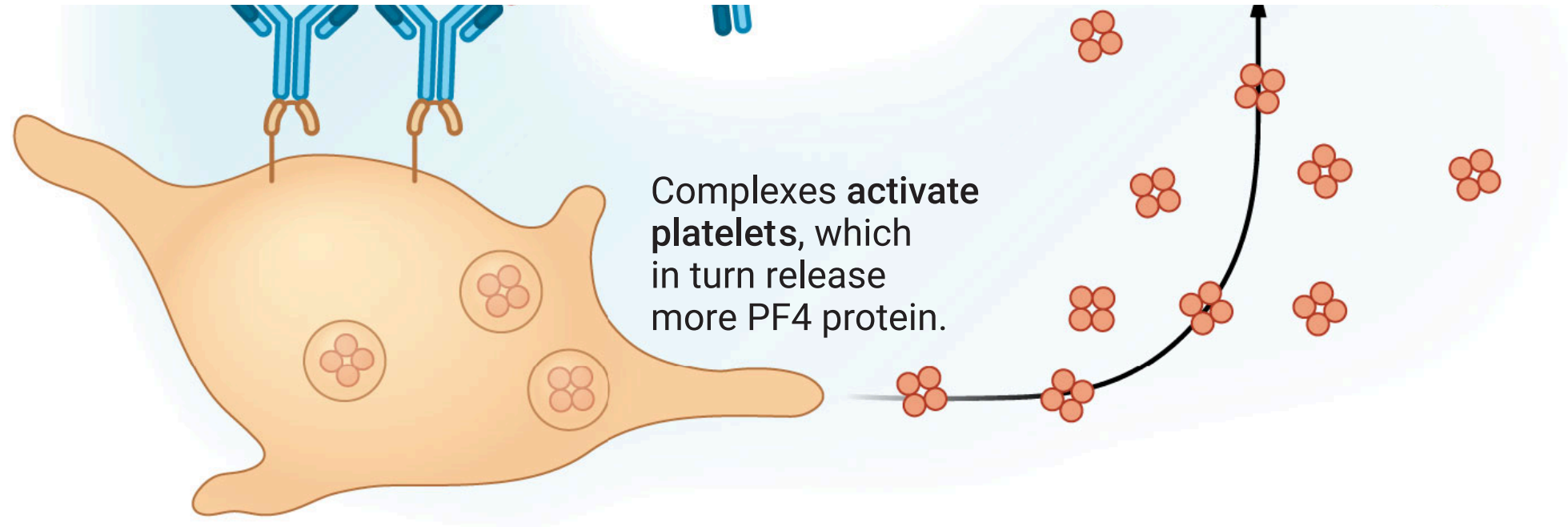
All VITT patients also happened to have variants of the light chain gene that already included a negatively charged amino acid at position 50. Together with the change at position 31, this led to antibodies with a very strong negative charge that bind readily to the PF4 protein, which has a strong positive charge. The resulting complex between multiple antibodies and proteins activates platelets, cell fragments key to blood clotting. They release more PF4, starting a chain reaction that leads to the dangerous clots (see graphic, below). The process also uses up the body's store of platelets, which leads to uncontrollable bleeding.

To firm up the link, the scientists showed that labmade versions of the anti-PF4 antibodies from two patients can cause VITT-like symptoms in mice. To test whether the substitution at position 31 was really key to the disorder, they made a "corrected" version with lysine instead of glutamic acid. The resulting antibodies still bound to PF4, but at a much lower rate, and they caused far fewer clots in mice.

Molecular mimicry

Adenovirus-based vaccines against COVID-19 can cause B cells to produce antibodies carrying an excess of negative charge that miss their target, a viral protein, and instead bind to PF4, a human clotting factor. That sets off a potentially fatal chain reaction called vaccine-induced immune thrombocytopenia and thrombosis (VITT).


B cells produce “rogue” VITT antibodies that can bind to PF4.
Normal antibody binds to viral protein
VITT antibody binds PF4
Viral protein
Negatively charged
PF4
Highly negatively charged
VITT antibody
PF4
VITT antibodies and PF4 protein can form complexes.
A chain reaction starts, clots form, and platelets are depleted, causing bleeding.



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The researchers also identified the trigger for the misdirected immune response. They discovered that the recombinant VITT antibodies attached to an adenovirus protein named protein VII (pVII). Further studies identified the key piece of the protein, 15 amino acids long, to which the antibody clings. The segment forms a shape called an alpha helix—an echo of a structure in PF4.

Putting all the pieces together, the researchers hypothesize that patients who developed VITT had previously been infected with an adenovirus, which primed their B cells to recognize pVII. The vaccine then kicked those cells into action, starting a mutation-generating process that produces new variants of the antibodies. In a few people, this process generated an unlucky variant with the negatively charged amino acid—and that ultimately led to VITT.

“I’m convinced,” says Demin Wang, an immunologist at the Medical College of Wisconsin. “It’s very elegant work.”

According to the European Medicines Agency, about 900 VITT cases have been reported after immunization with the AstraZeneca or J&J vaccines in Europe, including 200 deaths. Few data are available about the rest of the world, even though more than 3 billion doses of the AstraZeneca vaccine were administered globally. (They’re estimated to have saved millions of lives.) Two VITT cases were reported in Argentina after immunization with Sputnik V, Russia’s COVID-19 vaccine, which also contains adenoviruses. No cases have been tied to an adenovirus-based vaccine made by the Chinese company CanSino.

It’s not clear whether the syndrome was rarer outside Europe or whether cases were missed. In most parts of the world, between 40% and 60% of the population has the genetic background that makes people more prone to VITT, but in East Asia the prevalence is only 20%. Other factors, too, might contribute to the rare cases when they happen.

The new findings may help address concerns about the possible risk of VITT in adenovirus-based vaccines for other diseases. For instance, one of the two approved vaccines against Ebola uses the same adenovirus as J&J’s COVID-19 vaccine. Adenoviral vaccines—which are inexpensive to make and easy to distribute because they don’t need to be stored at very low temperatures—are also being developed against influenza, malaria, meningitis, tuberculosis, and emerging diseases such as Nipah.

“Adenoviral vectors have a major role to play in producing new vaccines against outbreak pathogens, and also for diseases with low potential for vaccine profits,” says University of Oxford vaccinologist Sarah Gilbert, who helped develop AstraZeneca’s vaccine. The new study could help make these new shots safer, she says. It is unlikely that pVII can simply be removed from the virus, but scientists might be able to design versions that don’t resemble PF4 as closely, Gilbert says. “There’s still a lot of work to do to verify the approach, but the way forward appears clearer.”

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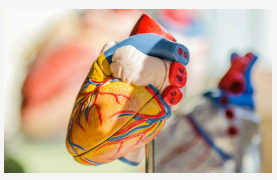

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