boy's muscles correlated with better muscle function. In the end, however, the advisory committee voted eight to six in favor of the therapy, which under an accelerated approval could be sold until a larger trial already underway is completed. If that study fails to definitively show benefits, the treatment could be pulled from the market. An FDA decision was expected by 29 May.

Even if the treatment proves to work, researchers now expect its effects to wear off. The AAV does not integrate the replacement gene into a cell's genome, instead delivering it into the nucleus as a loop of DNA. As damaged muscle fiber cells are being repaired by dividing muscle stem cells, some will not inherit the loop, and the benefits will fade as the modified cells become outnumbered.

Jessica Curran says this appears to be happening to Conner: Last fall, the sixth grader began using an electric scooter to conserve his strength in long school hallways. UCLA neurologist Perry Shieh, who is seeing declines in DMD patients he's treated in the Sarepta, Pfizer, and Solid trials, says, "The parents are asking: 'What is next for my child?'"

"This approval is going to help the field move forward."

Melissa Spencer, University of California, Los Angeles

For now, the answer is nothing because the boys make antibodies to AAV that would block any effort to retreat them the same way. But companies and academic researchers are trying to remove these antibodies with blood-filtering machines and drugs. They are also testing using other drugs to suppress immune cells that recognize AAVs or that make antibodies targeting the viruses.

"There are many overlapping, complementary strategies" that would allow AAV redosing, Byrne says. His group will soon launch a small study to see whether AAV antibodies can be lowered enough in Conner Curran and other DMD gene therapy patients to potentially allow them to be retreated. Although these immunosuppressive approaches carry their own risks, "compared to the consequences of disease … we feel it's justified," Byrne says.

Preventing a patient's immune system from making antibodies to an initial dose of AAV gene therapy might also make it possible to exchange a single large dose for smaller, repeat doses. An analysis of the October 2022 death of Terry Horgan, a 27-year-old DMD patient who received a custom-made CRISPR treatment designed to switch on a gene, underscored the need to reduce risks. Last week, a team of researchers, funded by the nonprofit his family had established to treat DMD and other diseases, posted a preprint on medRxiv absolving the gene editor and instead suggesting that the AAV he was given was toxic to his lungs and atrophied heart.

There's hope that CRISPR-based DMD gene therapies can eventually sidestep the AAV issue. Some teams are trying to use the same lipid nanoparticles, or fat bubbles, employed in the messenger RNA COVID-19 vaccines as a delivery vehicle for RNA encoding the gene editor's molecular components. But until researchers figure out how to steer the fat bubbles to muscle cells, AAV remains the only proven option for targeting the tissue.

Even if delivered by AAVs, CRISPR could still prove a better solution than current approaches that introduce a new dystrophin gene. For example, the gene editor could be used in some patients to "repair" the existing dystrophin gene in muscle cells by snipping out a sequence that causes cells to misread it. The gene would then produce nearly full-length dystrophin driven by natural promoters so it's made "at the right time, in the right place," notes molecular biologist Eric Olson of the University of Texas Southwestern Medical Center. And if the CRISPR therapy edits muscle stem cells, the changed gene should persist and its effects could be long-lasting.

Olson's approach, which his lab has demonstrated in mice and dogs, is under development by Vertex Pharmaceuticals. It hopes to start a clinical trial later this year. "The work is progressing well," Olson says.

CRISPR has its own downsides, however. The DNA-snipping Cas9 protein, one of its two components, comes from bacteria and can trigger an immune reaction against edited cells. As a result, "Your treated cells will be eliminated," says gene therapy researcher Dongsheng Duan of the University of Missouri School of Medicine, whose lab showed this phenomenon 2 years ago in dogs that got CRISPR for their DMD. Efforts are now underway to design Cas9 to be less immunogenic or to be quickly eliminated from cells after it makes the needed DNA cut.

For now, Spencer welcomes the expected approval of Sarepta's gene therapy. "We have to start somewhere. This approval is going to help move the field forward," she says. Eventually, we'll have improved therapies."

Jessica Curran hopes those improvements will come soon, and make it possible for her son to get another gene boost. "We have to figure out this antibody issue," she says. "Because these kids are all going to need [gene therapy] again." ■

COVID-19

New antibodies that the coronavirus can't elude

Researchers aim to make monoclonal antibodies that mutations in SARS-CoV-2 won't thwart

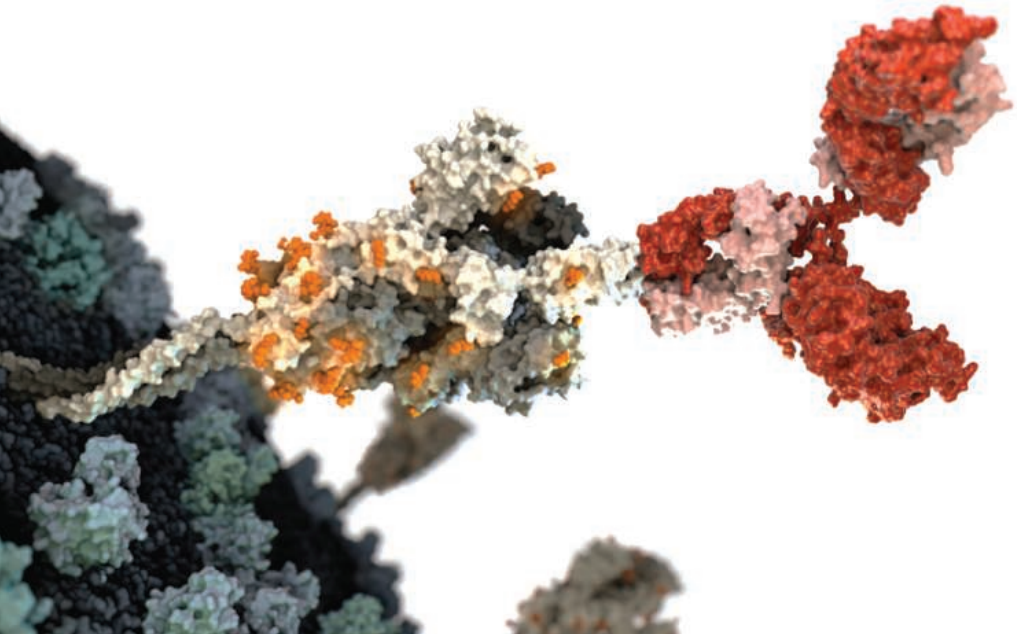
By **Robert F. Service**

In 2020, as the COVID-19 pandemic raged and other effective drugs were elusive, monoclonal antibodies (mAbs) emerged as a lifesaving treatment. But now, 3 years later, all the approvals for COVID-19–fighting antibodies have been rescinded in the United States, as mutations of the SARS-CoV-2 virus have left the drugs—which target parts of the original virus—ineffective.

Researchers around the globe are now trying to revive antibody treatments by redesigning them to take aim at targets that are less prone to mutation. "There are new approaches that present a much more challenging task for the virus to evade," says Paul Bieniasz, a virologist at Rockefeller University. Just this week, for example, researchers in Canada reported that they've created antibodylike compounds able to grab dozens of sites on viral proteins at the same time, acting as a sort of molecular Velcro to restrain the virus even if some of the sites have mutated to elude the drug candidate. Other researchers have taken less radical approaches to producing mutation-resistant antibodies.

All, however, worry that the work may be slow to reach the clinic. With the pandemic emergency declared over in the U.S. and other countries, governments and industry may have less incentive to develop promising new COVID-19 treatments. "There is no business model for this anymore," says Michael Osterholm, a public health expert at the University of Minnesota.

The antibodies that initially saved lives all glommed on to the tip of spike, the protein SARS-CoV-2 uses to attach to angiotensin-converting enzyme 2 (ACE2), a receptor on the surface of human cells. For the first 2 years of the pandemic, spike changed mod-



An antibody (right) bound to the surface spike protein of SARS-CoV-2 can block infection.

estly enough for the mAbs to continue to work. But as the virus encountered more people with antibodies from previous infections and vaccination, new variants emerged with extensive mutations in the ACE2-binding region, known as the receptor-binding domain (RBD). The variants dodged treatment and left pharma companies scrambling. "By the time you've isolated a good [mAb] the virus has moved on," says Laura Walker, who heads infectious disease biotherapeutics discovery and engineering for Moderna.

Now, researchers are seeking antibodies targeting segments of spike that the virus can't mutate without losing its ability to infect cells. "People are fishing for that hidden gem that targets something so conserved that the virus cannot mutate away from it," says Jean-Philippe Julien, an immunologist at the University of Toronto.

In March, for example, an international team led by researchers at the University of Italian Switzerland reported that it had isolated several human antibodies aimed at conserved targets on spike, unchanged across multiple viral variants. One binds to a site known as the fusion peptide, preventing the virus from merging with human cells. In cell-based assays, the antibody bound to four separate families of coronaviruses, including SARS-CoV-2. Another antibody, which targets a spike site known as the stem helix, blocked all SARS-CoV-2 variants from fusing with human cell membranes. The group, reporting in the 10 March issue of *Science Immunology*, also found that a "bispecific" antibody that binds to both the RBD and a separate region called subdomain 1 (SD1) that's involved in cell fusion protected mice against ancestral and Omicron SARS-CoV-2 variants.

Other groups are pursuing the same strategy. Researchers at the Fred Hutchinson Cancer Center (FHCC) reported in a March bioRxiv preprint that they, too, have isolated an SD1-targeting antibody that protects mice against all the recent variants of concern. And in January, a group led by antibody biologist Joshua Tan at the National Institute of Allergy and Infectious Diseases reported in *Cell Host & Microbe* that other fusion peptide and helix-binding antibodies can neutralize a broad array of SARS-CoV-2 variants in animals. "There are more and more antibodies that act more broadly because they are targeting spike in different areas," says Julie Overbaugh, a virologist at FHCC who led the SD1 work.

A separate approach takes aim at the human protein, ACE2, that SARS-CoV-2 and its relatives bind to on the cell surface. Last week, Bieniasz and his colleagues reported encouraging results in *Nature Microbiology*. They injected mice with copies of a soluble version of the human ACE2 receptor. Thirty-five days later, they screened the animals' blood serum for antibodies that targeted ACE2 and blocked SARS-CoV-2 from binding to it. They selected the most potent and injected it into mice that had been infected with a SARS-CoV-2 variant or a variety of other sarbecovirusus, the group of human and animal viruses that includes SARS-CoV-2. The antibody "was equally effective against all of them," Bieniasz says.

"This looks quite promising," Overbaugh says. But she and others are concerned that targeting human proteins could prompt side effects. They worry about interfering with ACE2's normal function, as it helps regulate blood pressure among other duties. Recent reports have added to the concern by suggesting that people with Long Covid may be producing antibodies against their own proteins, including ACE2 (*Science*, 28 January 2022, p. 364). Bieniasz agrees that more animal and human trials of the strategy will be needed, but he notes that in the initial cell culture studies, his group's antibody does not seem to keep ACE2 from working properly.

A third strategy looks to modify the structure of antibodies themselves in hopes of making them more potent. Antibodies are usually Y-shaped, with two arms that can attach to two separate targets. Julien and his colleagues have designed a family of spherical "multibodies," each with 24 attachment sites. In its most recent study, published this week in *Science Translational Medicine*, the Toronto team designed two different multibodies, one in which all 24 binding sites targeted the same site on SARS-CoV-2's spike protein, the other that targeted three different sites. When they injected their multibodies into infected mice, they found that both designs neutralized the virus at doses well below those needed for conventional antibodies. The three-target multibody also neutralized all recent subvariants and a wide array of viruses more distantly related to SARS-CoV-2.

Walker, who was impressed by these results, cautions that because the multibody strategy is new, it faces a longer road to the clinic. Researchers must verify that the multibodies remain in circulation for days—if not months—after infusion, and developers must show that the drugs can be manufactured reliably and cheaply. "It's not enough to have [mAbs] that will work, but [it's also] whether they will be available," Osterholm says.

But the momentum needed to turn the new antibodies into approved drugs may be waning. In March, President Joe Biden's administration launched Project Next Gen to help commercialize vaccines, mAbs, and other therapeutics. But the $5 billion for the effort could soon evaporate, a likely victim of ongoing negotiations between the administration and Congress over the U.S. debt ceiling. With little government help, pharma companies may be loath to pour hundreds of millions of dollars into commercializing new treatments. "It's going to take long-term investment," Osterholm says. "That is something we are missing."

At the same time, Tan notes, "There are at least some companies that remain interested." At least one sizable market remains—people who are immunocompromised, some 3% of the U.S. population. Still, pushing for new treatments is "definitely more challenging than it was a year or two ago," he says. ■

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New antibodies that the coronavirus can't elude

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