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First Antibody Trial Launched in COVID-19 Patients

In record time, scientists have gone from harvesting antibodies against SARS-CoV-2 from survivo of coronavirus infections to testing the antibodies' safety as a drug in humans.

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Thanks to a remarkable feat of natural molecular engineering that allows our bodies to generate countless different kinds of antibodies against pathogens, COVID-19 survivors typically have scads of SARS-CoV-2–specific antibodies cruising through their bloodstreams. Only a few of those antibodies stick to the virus at the right spot, blocking a protein the virus needs to break into cells, while oth antibodies bind to it without stopping infection. By the time a human body has generated these diverse antibodie in sufficient quantities, the original infection is usually nearly over, but the antibodies remain, leaving the immun system braced for a second infection.

For the past few months, scientists have been eager to find the most effective antibodies the human body produce and turn them into drugs. In contrast to convalescent plasma therapies—whereby a hodgepodge of antibodies fro recovered patients is given to people battling COVID-19—such "monoclonal antibody" treatments would be standardized, manufactured at scale, and potentially more effective. The treatments could be given to people in t early stages of COVID-19, or used prophylactically to give instant, short-term immunity to vulnerable people suc as healthcare workers or those in which vaccines may be ineffective. Technological advances have allowed scientis to find promising antibodies at a record pace. Just this week (June 1), the pharma giant Eli Lilly announced the launch of the world's first human safety trial with a monoclonal antibody against SARS-CoV-2.

"Before there's a vaccine, there could be great use for the antibodies in prevention. And even when there is a vacc they could be used in therapy," says Dennis Burton, chair of immunology and microbiology at the Scripps Resear Institute in California. But first, "all of these things need to be tested in humans."

Choosing the best fighters

Vanderbilt University immunologist James Crowe was already working on a long-term project to develop monoclonal antibodies against potential epidemic-causing viruses in late January when it became clear that SARS CoV-2 was spreading into the US. His team rushed to track down people who had recovered from the infection—ones who had been infected in China who then traveled to the US—and procured blood samples. Using several commercial technologies, Crowe and colleagues screened millions of white blood cells to pick out plasma B cells that carry SARS-CoV-2–specific antibodies by teasing out the cells with viral antigen.

His team then extracted antibody-encoding DNA from those cells and used that as a blueprint to synthesize them into antibodies. Through experiments testing whether the antibodies could prevent SARS-CoV-2 from entering a human cell in vitro, they identified around 400 kinds of antibody that recognized the virus's spike protein, 50 of

which could neutralize the virus in vitro. Several companies Crowe has partnered with—including AstraZeneca, t Nashville-based biotech company IDBiologics, and Ology, a company contracted by the US government to devel and manufacture monoclonal antibodies for COVID-19—are planning clinical trials for some of the candidates in July or August, he says. "[We] literally handed them off to manufacturers within the first few months of an outbre That's what's different now, is that these technologies have matured to the point where we can compress the time down to weeks—this type of thing used to take years."

The antibody that Eli Lilly is currently administering to COVID-19 patients, LY-CoV555, was also discovered in sc of the first COVID-19 patients in North America, explains Carl Hansen, CEO of the Vancouver-based biotech company AbCellera, which has partnered with Eli Lilly to develop its candidate. "It would normally take anywher from two and a half years to five years for a program like this to move forward," Hansen says. But thanks to a rapi antibody identification platform AbCellera scientists have refined as part of the Pandemic Preparedness Program funded by the Defense Advanced Research Projects Agency over the past several years, the researchers were able go from a blood sample to a clinical trial in just three months.

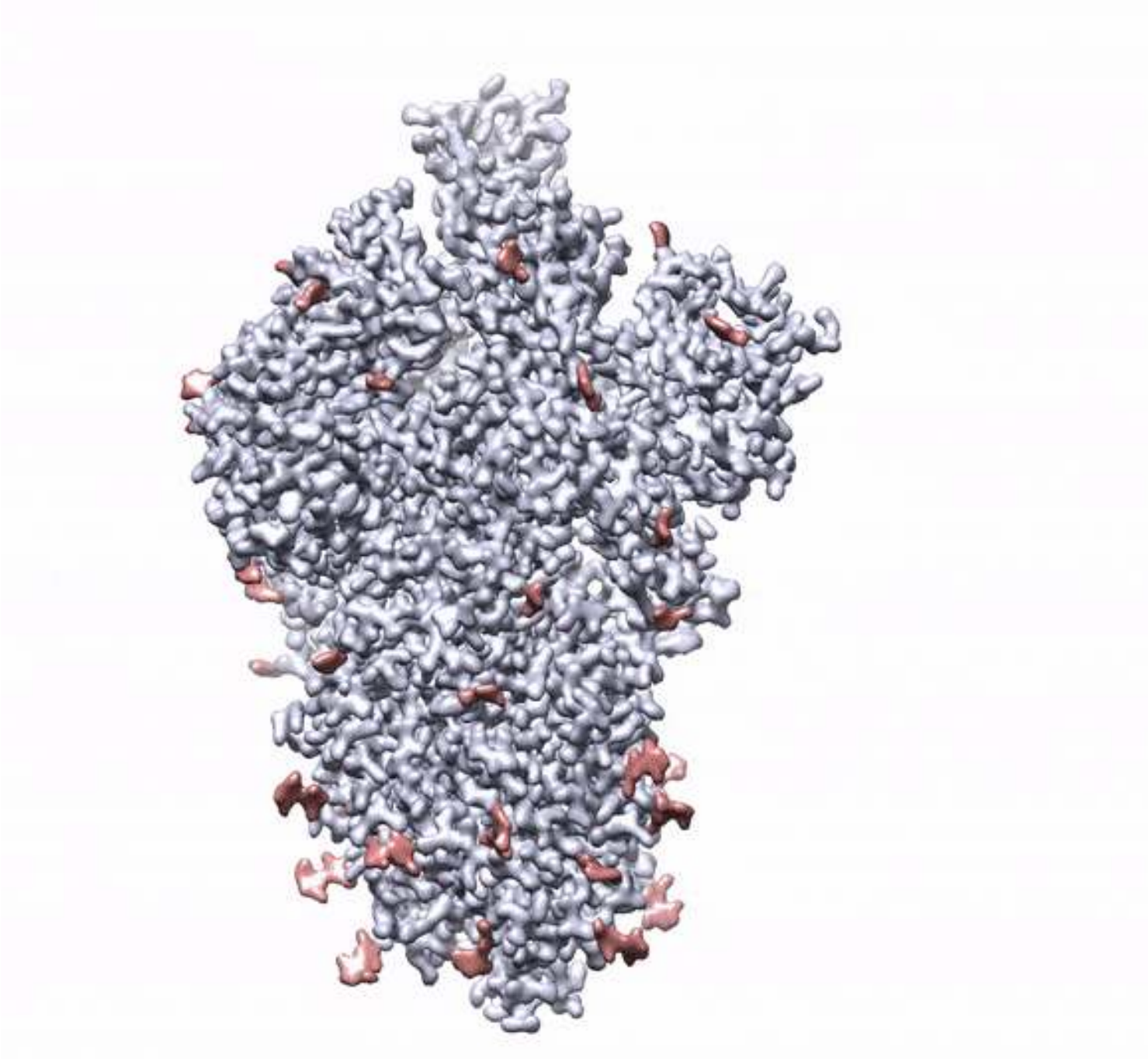
Others are pursuing different strategies. One group of scientists at San Francisco–based Vir Biotechnology turne antibodies isolated years ago from the blood of people who had recovered from the original SARS coronavirus. They recently found one such antibody that also neutralized SARS-CoV-2 in vitro, they reported in *Nature*. San Francisco–based biotech startup Distributed Bio used computational methods to tweak anti-SARS-CoV antibodie "so they're adapted to the novel coronavirus," among other methods, explains the company's CEO, Jake Glanville, who is working with several academic labs and a Department of Defense laboratory to test his top candidate in hamsters.

The German biotech company Yumab used a library of antibody protein-encoding genes generated from hundr of healthy people and shuffled the genes in different combinations to create a diverse range of antibodies—essentially mimicking the human body's own strategy. The team then used a technique known as phage display t screen which antibodies would bind most strongly to SARS-CoV-2 protein. Combined with studies of COVID-19 patients' blood, the group found several antibodies that looked promising, and are currently testing their efficacy vitro, explains André Frenzel, the chief scientific officer at Yumab.

Despite being in different stages of development and using different methods to find them, these groups' antibod candidates are similar: the ones that are most effective in neutralizing SARS-CoV-2 block the receptor binding **domain** (RBD), a dongle-shape protein at the end of the virus's spikes that it uses to dock onto the ACE2 receptor human cells. Eli Lilly's antibody candidate also binds to the spike protein. "Our prior studies have suggested that blocking receptor binding is a surefire **way** to neutralize the virus and come up with a protective antibody," says Erica Ollmann Saphire, an immunologist at the La Jolla Institute for Immunology.

Saphire recently launched a consortium of 50 different startups, corporations, and academic labs that have agree send their best antibodies to her lab. Her team will then line up the antibodies side by side and identify the very b ones. The goal is to find antibodies that neutralize the virus at the lowest concentrations, which will help reduce t typically sky-high costs for such treatments and make them financially accessible for low- and middle-income countries. "If it's more potent, you could deliver ten milligrams instead of a hundred milligrams, and so you can reach ten times more people."

Aiding her team's investigations is an 11-foot tall cryogenic electron microscope, which can visualize, at the resolution of a couple of angstroms, the precise molecular interactions between antibodies and SARS-CoV-2. Suc



A cryogenic electron microscope-based visualization of SARS-CoV-2 spike protein is helping researchers understand precise molecular interact with antibodies.
VISUALIZATION BY RUBEN DIAZ, BASED ON WORK BY DAVID VEESLER, UNIVERSITY OF WASHINGTON

studies will help scientists identify what exactly makes winning antibodies effective, examining, for instance, the angles from which they approach the viral surface, and which antibodies enhance each other's efficacy, Saphire sa "You can actually look at what a successful antibody is and how it works."

Antibodies for prevention or treatment

In Eli Lilly's Phase 1 trial, 32 COVID-19 patients in the US will receive varying doses of the antibody candidate, LY CoV555. The study only aims to assess side effects and tolerability, and results are expected by the end of June, according to the press release. This and upcoming trials may also shed light on the possibility of a rare and poorly understood phenomenon known as antibody-dependent enhancement, in which antibodies can worsen viral

infections, although there's no indication this happens with COVID-19 and prior coronavirus exposures or experimental vaccines.

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Should the study go well, the company plans to proceed to a Phase 2 trial to test whether the antibody is effective a treatment, and also to test whether the drug may be promising in preventing SARS-CoV-2 infections in vulnera groups. Some groups have tested that concept for SARS-CoV-2 in animal studies, notes Burton, who has experimented with one of his own candidate antibodies in hamsters. Untreated rodents lose around 10–15 percer their body weight when infected with SARS-CoV-2, "but if we gave them a neutralizing antibody before [infecting them], they were fine—they didn't lose any weight," he says. In people, "we would hope that they would stop the virus causing serious disease at least."

Using three different mouse models, Crowe's collaborators have also found that some of his antibody candidates "appear to work for prevention or treatments," he says.

While some companies are focusing on administering individual antibodies, others, such as the New York–based biotech Regeneron, are pursuing cocktail treatments. A single antibody may be easier to manufacture, Hansen nc but a combination could be important should SARS-CoV-2 mutate in a **way** that makes one antibody ineffective, although there's no evidence of that yet, he adds. Eli Lilly aims to test both single and multiple antibody therapie

Opting for a cocktail strategy would also be wise if it turns out that SARS-CoV-2 is capable of using multiple ports entry into a cell, Saphire says. "Viruses are crafty and many of them have more than one **way** into the cell." Researchers can't yet rule out that possibility for SARS-CoV-2.

The big challenge: making antibodies at scale, affordably

In the past, scientists made antibodies by fusing B cells with a cancer cell line to make them immortal so the cells will produce antibodies indefinitely. But modern, more-efficient methods have replaced that strategy. Some of Crowe's partners are using tobacco plants that are genetically modified to produce SARS-CoV-2 antibodies. By fa the most popular method is to make antibodies using a cell line derived from Chinese hamster ovary (**CHO**) cells which can be grown in giant bioreactors and the antibodies they produce can be sifted from the culture.

The average annual price of antibody therapies for cancer and autoimmune diseases between 1997 and 2016 was nearly

$97,000.

However, that manufacturing process is relatively slow—it can take many months to set up a productive CHO cel culture and scale it up in large bioreactors, although several groups are exploring ways to speed up that process, Frenzel notes. The ability to scale up treatments will depend on "just how much will we need and when will we n it," Hansen says. If the antibodies will only be used for treatment, it's unlikely there'll be shortages, but if there's n vaccine soon, and policymakers decide to give antibody therapies as preventive therapies for large numbers of th public, manufacturing capacity may reach its limits, he says. According to Eli Lilly, the company has begun manufacturing its antibody in bulk and aims to have several hundred thousand doses ready for COVID-19 patien by the end of the year.

In addition, the process of growing these cell cultures, as well as the research to identify and develop the most effective antibodies can make such therapies extremely expensive. The average annual price of antibody therapie for cancer and autoimmune diseases between 1997 and 2016 was nearly $97,000, according to a 2018 study. If cos for the first coronavirus antibody treatments push into the thousands or tens of thousands of dollars, it raises the question of who will pay for them. Perhaps some governments may be willing to cover, or at least subsidize, the costs of such therapy, favoring it over suffering through the economic disruption of another lockdown, Frenzel speculates.

During a global pandemic, the treatment has to be accessible for developing countries, too. "It is abundantly clear now that infectious disease anywhere in the world can become infectious disease everywhere in the world," Saphi says. "We are not safe until everyone has access to protection, and so one way or another, we're going to have to g there." One problem with antibody therapies developed against Ebola virus is that although they were effective enough to save patients if administered in time, "they were way too expensive to be able to treat a disease which happening in the developing world," says Glanville of Distributed Bio.

Eli Lilly did not provide details on the possible cost of such treatments, but Nicole Hebert, a spokesperson for the company, stressed that the priority is finding a treatment for COVID-19, rather than making a profit. "Regarding access, the industry is working with governments and insurers to ensure that when new treatments and vaccines a approved, they will be available and affordable for patients," Hebert writes to *The Scientist* in an email.

Glanville says he aims to charge no more than a few hundred dollars a dose—which should suffice as a treatment and provide protection for around two months, he says. "I don't know the exact number, but I'm not going to be charging eight thousand dollars a dose. I'm going to keep the number deliberately accessible so the whole world c gain access."

Keywords:

antibodies, coronavirus, COVID-19, Eli Lilly, immunology, monoclonal antibodies, news feature, pandemic, receptor binding sites, SARS-CoV-2, spike protein, virus