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Health

These laboratory-made antibodies are a best bet for a coronavirus treatment, but there won't be enough

Coronavirus treatments will be key to getting back to normal, even with a vaccine.

Biotech production specialists work at the Regeneron Pharmaceuticals facility in Rensselaer, N.Y. The large vats are full of cells that churn out a potential coronavirus treatment called monoclonal antibodies. (John Halpern/Regeneron)

By Carolyn Y. Johnson

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In two-story-high stainless steel vats, a drug is brewing in trillions of hamster ovary cells. Many experts think this could be the best bet to defang the novel coronavirus and transform it from a potentially lethal infection into a treatable illness.

Current treatments for the coronavirus aim to help the sickest patients survive. But this drug, called a monoclonal antibody cocktail, aims to keep people out of the hospital altogether. The experimental shot of lab-generated antibodies imitates the body's own disease-fighting force. The goal is to boost a person's immune defense, instead of waiting for human biology to muster its own response — and possibly lose to the virus.

Predictions about coronavirus vaccines have become almost deafening in recent weeks, but whether or not the first doses of a vaccine arrive this year, some people will continue to get sick. A medication that could prevent people from progressing to the point that they need a hospital bed or ventilator could be a bridge to a vaccine, or it could be the lifeline that could give people confidence to return to normal life even once vaccines are developed.

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In the search for such a countermeasure, monoclonal antibodies, a Nobel Prize-winning biotechnology developed in the 1970s, have become the first line of attack, pursued by at least 50 companies and academic teams. That includes the two-antibody cocktail churned out by Regeneron Pharmaceuticals' hamster cells in Rensselaer, N.Y.

Promising but preliminary data has bolstered the chorus of hope around monoclonals from top health officials.

They are "a real best chance of being a game changer," according to Francis S. Collins, director of the National Institutes of Health.

"We're looking for big impacts on disease, not the small incremental impacts we often see in ordinary drug development," said Janet Woodcock, who is leading therapeutics development for Operation Warp Speed, the Trump administration's initiative to provide treatments and vaccines for covid-19, the disease caused by the coronavirus.

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One thing is certain about monoclonal antibodies: If the pandemic keeps raging, there won't be enough. Unlike conventional pills, these are expensive, injectable drugs synthesized by living organisms in specialized reactors, at a biological cadence that can't be rushed. A worldwide scramble to find capacity to make the drugs is afoot, with companies striking deals with competitors to increase their manufacturing capabilities.

Even then, to create enough antibody medication to treat all the people diagnosed with covid-19 so far, the entire global capacity for making monoclonals would have to be switched over for a year, according to an analysis conducted for The Washington Post by the BioProcess Technology Group at global accounting firm BDO, which advises the pharmaceutical industry. Now, the reactors that make monoclonal antibodies are mostly occupied, making essential drugs for people with cancer and autoimmune diseases.

"I pray to God these therapies work," said Howard Levine, national leader of BDO's BioProcess Technology Group. "But in the short term, there is going to be a problem, I think, in making enough to treat every single patient."

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Creating a drug recipe

When a deadly pneumonia was identified in China in January, scientists at Regeneron Pharmaceuticals knew the drill. As with Zika, Ebola and the new coronavirus's close cousin, Middle East respiratory syndrome, scientists started

calls "magical mice." These rodents, genetically engineered to have humanized immune systems, can muster human antibodies that serve as the template for a new drug.

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On Jan. 21, a week after the scientific work began, Christos Kyratsous, vice president of research, made an unusual call, asking his colleagues to get ready to manufacture a drug that didn't exist yet.

"It's probably going to move fast," he told Hanne Bak, senior vice president of preclinical manufacturing, who develops the initial recipes to turn science experiments into a repeatable process. "How fast can you move?"

Bak's colleague Daniel Van Plew, who oversees industrial operations and product supply — including a global team of 4,000 people and a massive facility filled with giant tanks connected by steel arteries of pipes — happened to be visiting Bak that day. Together, they sketched out the first timelines for scaling up production of a drug.

Many of the steps had a natural speed limit — scientists had to expose the mice to a form of the virus, wait for their immune systems to respond and then study the antibodies. Scientists also examined antibodies from people who recovered from the virus. They needed to test which ones were most potent, and then engineer hamster ovary cells to produce those antibodies. They would have to feed and nourish those cells for a month — with scientists seeking the laboratory equivalent of Goldilocks.

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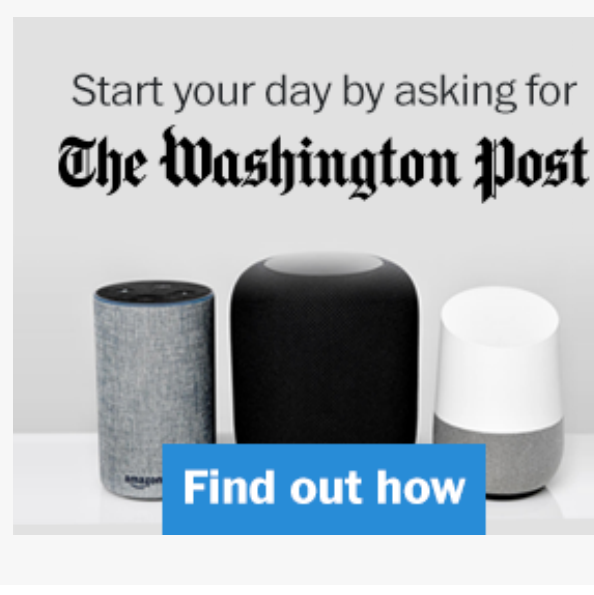
"You're dealing with a living system. ...The amount of oxygen, the food, the way [cells are] agitated [in the vat], little things can disrupt it," Van Plew said. "For all intents and purposes, it has a memory — if you do something bad to it at the beginning of production, it might not produce as well at the end."

The scientists tried to move everything else forward as fast as possible, pretending there were no evenings and no weekends. Regeneron split its employees into pods in March, so that if one person got sick, it wouldn't take out the whole team on a two-week quarantine.

That meant upending how people usually worked. Instead of one person owning a project from beginning to end, pods on tap to come in on Monday would do all the science they could and then hand off their work to the pod that came in on Tuesday, which would pick up where they left off.

Taylor Houghtaling, an associate manager at Regeneron, uses specialized chemistry techniques to purify the monoclonal antibody drug during 12-hour shifts. (Regeneron Pharmaceuticals)

Once the cocktail — a combination of two antibodies — had been selected, Bak's group began to brew the cells in early April. Normally, her team would meticulously develop a complete recipe for creating a batch of the drug and then hand it off to Van Plew's team, which would bring it up to the large scale needed to supply clinical trials and, eventually, patients.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It's the difference between cooking dinner for two people and preparing that same meal for a giant banquet, when suddenly what worked on a small scale may go awry — the vegetables don't heat evenly, the cake doesn't rise or the sauce doesn't reduce the same way.

But the pandemic meant Van Plew's team started just two weeks after Bak's team, when the recipe they were following was still full of blank spaces. Bak's team would, with two weeks lead time, have to figure out the steps and then send it to Van Plew's team, which would translate it for an industrial scale.

"It was almost like a relay race — you've got to stick that handoff of the baton and have nobody drop it," Bak said.

Once the cells had been growing for about a month, the scientists had to separate out the antibodies. The process takes four days, according to Taylor Houghtaling, an associate manager who dons protective gear for the clean room conditions and uses specialized techniques to purify the drug during 12-hour shifts.

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Houghtaling recalled that the day the first harvest of antibodies finished, she arrived in the morning and stayed until after midnight. She had done the same thing many times for other drugs during her six years working at Regeneron, but no moment proved more exhilarating. Many members of teams that worked on the drug remained on the floor that night to see the first harvest go into a special bag of medicine that could be given to patients.

"At that last stage, we don't necessarily know how well this treatment is going to work yet, but we could be making history right in this moment," Houghtaling said. "The excitement in the room — we were wearing face masks so you can't see anyone's mouth. But everyone was beaming."

Scaling it up

To turn that moment of triumph into a viable treatment, ongoing clinical trials will have to show that monoclonal antibodies are safe and effective, and determine the best dose. The drugs are being tested on three fronts: to see whether they can prevent disease in people who have been exposed to the virus, help people early in the illness get better sooner or treat patients who are hospitalized.

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A dose for treatment will require much more drug than a prevention dose, so the capacity to treat people will depend largely on what the trials show. Many experts are hopeful the drugs could prevent disease, providing crucial protection to elderly people whose immune systems may not respond robustly to vaccines.

Data is beginning to trickle out. Regeneron announced Tuesday that its drug appeared to knock back the virus, reducing virus levels and relieving symptoms when given to people recently diagnosed with covid-19 who weren't in the hospital — particularly in people whose bodies had not mounted a robust immune response.

Eli Lilly announced in September "proof of concept" interim data that its monoclonal antibody shows signs of reducing hospitalizations when given to people in outpatient settings. The data are preliminary and not yet peer-reviewed, and both trials are ongoing.

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To prepare for making the drug at scale, Regeneron transferred its other products to its facility in Ireland. It recently struck a deal with a competitor, Roche, to rapidly increase production.

"This is quite unusual, because we're giving a competitor a lot of our know-how, our technology," said Schleifer, the Regeneron CEO. "They're going to get to drive our cars, so to speak."

With the partnership, the companies can manufacture between 650,000 and 2 million treatment doses in a year, or 4 million to 8 million prevention doses. The United States has placed an order for $450 million worth of medicine — enough for 70,000 to 300,000 treatments, depending on how much of the drug is in each dose. But with the Centers for Disease Control and Prevention forecasting 1,500 to 5,000 hospitalized patients a day by late October, that supply could be rapidly consumed.

That has put companies in the unusual position of hoping competitors succeed and thinking about how to make an effective drug and to increase the yield. Eli Lilly is initially testing a single monoclonal antibody, which could allow the company to make twice as much drug as a cocktail approach.

"In terms of efficiency of manufacturing, of generating as much as possible to help as many as possible, it's simpler and easier if you have one antibody," said Andrew Adams, vice president of new therapeutic modalities at Eli Lilly, which plans to make at least 1 million doses by the end of the year.

Scientists at the California company Vir Biotechnology are developing an antibody designed to be effective at very low doses, with the hope they could manufacture 10 million doses in a year.

"Vaccines can be mass-produced for billions of people. Antibodies will be for millions of people," said Phil Pang, chief medical officer for Vir.

Many experts think that although demand will outstrip supply, there won't be a single silver bullet to end the pandemic but a convergence of cutting-edge technologies and old-fashioned public health measures. Monoclonal antibodies — potentially from many companies — will start to make the disease less dangerous. First-generation vaccines will start to tamp down the spread of the virus.

"We can't treat the whole country," Schleifer said. "But I do think if something was out there, that if you know that if your wife got sick or your husband got sick, you'd get a shot that would prevent you from getting it — or if you did get sick [you could be treated], that would change a lot of people's attitudes."

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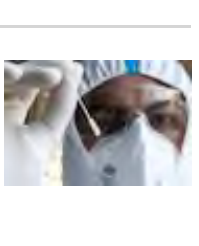

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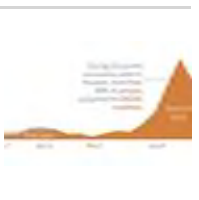

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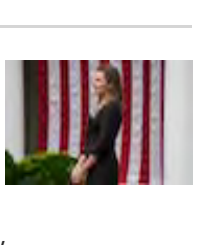

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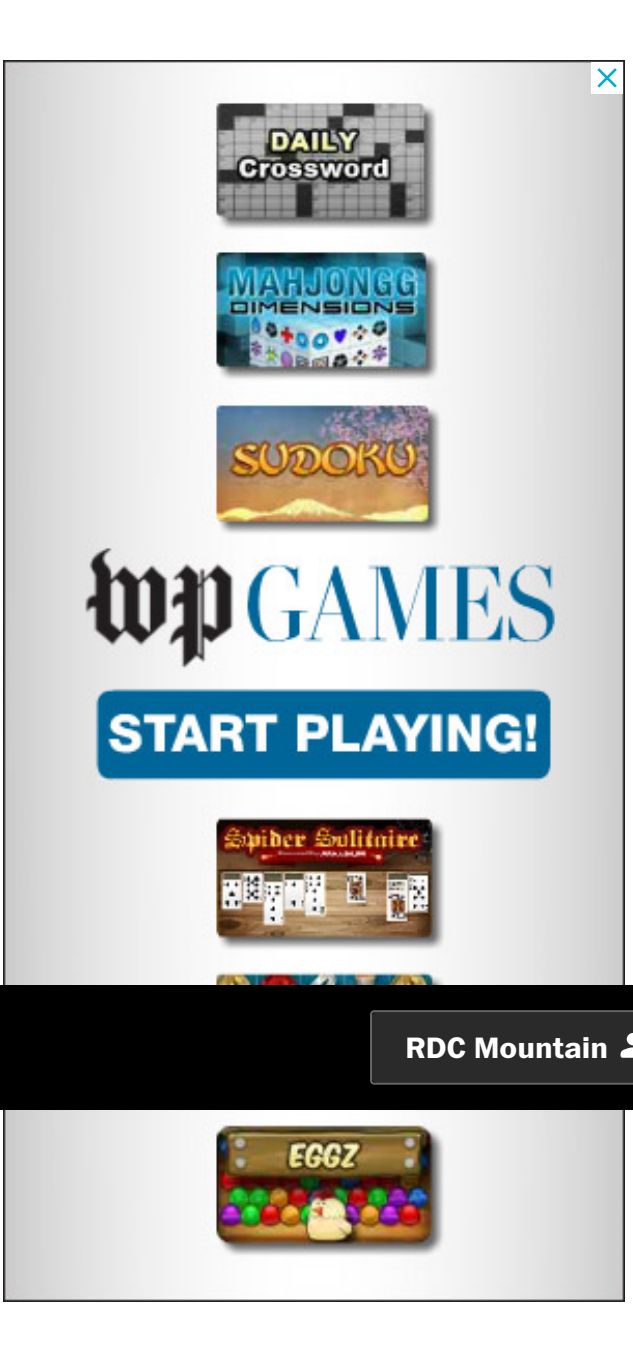
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