This Nanoparticle Could Be the Key to a Universal Covid Vaccine

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Ending the covid pandemic might well require a vaccine that protects against any new strains. Researchers may have found a strategy that will work.

Long before Alexander Cohen—or anyone else—had heard of the alpha, delta, or omicron variants of covid-19, he and his graduate school advisor Pamela Bjorkman were doing the research that might soon make it possible for a single vaccine to defeat the rapidly evolving virus—along with any other covid-19 variant that might arise in the future.

Before the pandemic, Cohen had been a PhD student in Bjorkman's structural biology lab at the California Institute of Technology, attempting to engineer a new kind of "universal" flu vaccine. It was designed to train the body's immune system to recognize portions of the influenza virus that the pathogen wouldn't be able to change or disguise even as it evolved.

So in early 2020, when covid-19 hit and he was soon to receive his degree, Cohen, Bjorkman, and other members of the lab set to engineering a universal covid vaccine—one that would provide protection not just against all its variants, but also against future illnesses caused by entirely new types of coronaviruses.

"We're definitely going to need something like this to fight covid-19 as new variants emerge," Cohen says. "But beyond that, the potential for new global outbreaks and pandemics caused by other coronaviruses is clear. We need something that can prevent new covid-19-like scenarios from happening again. And we need it as soon as possible."

Public health officials and scientists had long complained about a lack of funding—or a sense of urgency—to develop vaccines that would protect us against future pandemics. Prompted by covid-19, however, the US National Institutes of Health began doling out tens of millions of

dollars to research groups pursuing universal coronavirus vaccines.

The stakes couldn't be higher. In January, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, called the development of universal coronavirus vaccines an "urgent need," noting that the emergence of covid-19 variants over the last two years hints at far larger long-term threats. He has since argued that even more resources are needed to continue the fight, and he has been publicly lobbying lawmakers to allocate them.

"Scientific evidence and ecologic reality suggest that coronaviruses will emerge again in the future, potentially posing an existential threat," Fauci wrote in an article coauthored with two other infectious disease experts for the New England Journal of Medicine.

The key to meeting the challenge, groups like Bjorkman's are showing, may lie in our ability to use the tools of synthetic biology to trick the microscopic weapons of the immune system—weapons that already exist in the human body. The researchers are finding ways to supercharge these immune cells to provide remarkably general protection against invading microbes. If these approaches succeed, they could not only provide much more effective protection against covid but possibly revolutionize how we create new vaccines for complex viruses in general.

Having helped lead the way in developing these techniques, Cohen, Bjorkman, and their collaborators are now tantalizingly close to achieving their goal of manufacturing a vaccine that broadly triggers an immune response not just to covid and its variants but to a wider variety of coronaviruses.

Their vaccine consists of a spherical protein core, studded in a soccer-ball-like pattern with the tips of "spike" proteins taken from the surface of eight varieties of coronaviruses—what the scientists call a mosaic nanoparticle. Remarkably, initial results showed that in a test tube, antibodies produced by this synthetic vaccine were able to identify and stick to not just all eight coronaviruses represented on the nanoparticle, but four additional coronaviruses not used in the vaccine. In March, the group reported that the vaccine appeared to protect mice and monkeys that had been exposed to an array of coronaviruses.

In July, they published results in Science, showing that their mosaic nanoparticle vaccine protected mice and nonhuman primates against the delta and beta covid-19 variants as well as the human viruses that caused the first SARS outbreak in 2003. The results are perhaps the most promising evidence yet that this new kind of custom-designed, bioengineered vaccine could be the answer we so desperately need to avoid future coronavirus pandemics.

The next step is to test the vaccine in humans. The Coalition for Epidemic Preparedness Innovations will provide as much as $30 million to begin human trials. Edinburgh-based biotech company Ingenza will manufacture the medicine.

Since this approach is novel, it could take as long as two years to begin the trial. But if it's successful, it could protect us against ever having to endure another covid-related lockdown again.

Soccer-ball vaccine

Covid-19, like many viruses, has shown itself to be a master of disguise. It relies upon natural selection's most potent tool—random mutations—to change its shape in ways that, at least in the case of the omicron variant, often allow it to outwit the most ubiquitous tool the body uses to stop viruses: antibodies.

Antibodies are Y-shaped proteins that float around in the blood, bind to the surface of specific pathogens, and wrap them in an immobilizing bear hug until they can be killed. To protect us from anything nature might throw our way, the human body is equipped with the capacity to manufacture a seemingly infinite variety of antibodies—each one shaped a little differently. The interwoven amino acids that come together to form an antibody's two arms form distinct shapes that are designed to snap like Lego blocks into complimentary-shaped proteins found on the surface of a specific invading pathogen.

The viruses that give us the most trouble are those that can stay one step ahead of the human immune system (and our best efforts to stimulate it using vaccines)—by changing the shape of their surface proteins fast enough, or by evolving into shapes that make it harder for

an antibody to bind to them. The proteins on the surface of HIV, for instance, are spaced so far apart that only one arm of the antibody's Y can attach. Those on the influenza virus mutate and evolve into new shapes so frequently that the antibodies we produce no longer snap snugly into place and lose the ability to hold on to them. That's why we need a new vaccine every year to keep up.

But what if we could identify a shape so important to the integrity of a virus's structure that it can never mutate or change—what biologists call a "conserved" feature—and then engineer a microscopic particle to latch onto that shape?

"There are parts of many viruses that don't change," Cohen explains. "But unfortunately, our body does a much poorer job of recognizing these conserved sites. There seems to be a preference for your antibody response to recognize the highly variable sites. And viruses are good at changing the parts the immune system most easily recognizes."

By 2019, Cohen was deep into a project attempting to develop a universal flu vaccine that coaxed the immune system into targeting conserved areas found on the surface of most flu viruses. He was working with a technology pioneered by Mark Howarth, a protein biologist at the University of Oxford: a self-assembling nanoparticle with 60 open spots on its surface, each one engineered to have Velcro-like qualities. These spots are designed to attract and bind with molecules that have a lab-engineered patch of complimentary Velcro on their surfaces.

Biologists like Cohen can affix these complimentary Velcro-like tags to any protein, and that protein will attach itself to the nanoparticle. In its final form, this particle self-assembles into a spiky soccer-ball-like structure studded with a mosaic of proteins of different shapes, kept in place with the equivalent of protein superglue.

The technology, which Howarth has made available to research groups worldwide, makes it possible to selectively engineer vaccines. Cohen and his colleagues began experimenting with proteins taken from variations of the influenza virus, measuring the ability of different combinations to prevent new strains of flu from infecting mice. He had just finished putting

the finishing touches on his PhD and was getting ready to begin a new series of experiments.

Then covid-19 happened.

Common targets

Cohen first learned of the mysterious new virus emanating from Wuhan, China while scanning his favorite website—an online infectious disease tracker that monitors new outbreaks in humans and animals across the globe. When he found out that his efforts to engineer a universal influenza vaccine would have to temporarily shut down, he immediately suggested to Bjorkman that they launch a project applying the same approach to covid—trying to identify conserved parts of the covid-19 virus, SARS-CoV-2, that might also be present in other SARS-like viruses and make a vaccine targeting them.

By April 2020, Cohen was back in the lab. To find the shapes on the viral surface that were likely to be conserved, he and Bjorkman drew upon a wide body of scientific literature characterizing and comparing the genetic sequences of coronaviruses.

Most coronaviruses, including the one that causes covid-19, consist of a piece of genetic material wrapped in a protein and encased in a protective soap-bubble-like membrane, which is difficult for the immune system to distinguish from the outer membrane surrounding human cells. But there is an Achilles' heel: grappling-hook-like proteins that protrude through the membrane so that the virus can grip vulnerable host cells long enough to inject its genetic materials and commandeer the cell's protein-making machinery to make copies of itself. These spikes have distinct shapes that, in the case of covid-19, are designed to snap into proteins called ACE2 receptors, which are found on the surface of many human cells.

The spikes are attractive targets for antibodies. But they readily mutate to form new shapes that allow them to escape detection. Of the 53 new mutations identified in the omicron variant, for example, 30 involve the gene for the spike protein. Thirteen of them form three distinct clusters, two of which change the spike near its tip while the third group alters the area closer to the base. Together, these mutations change the shape of the spike enough to

let it evade antibodies that would bind tightly to other versions of the covid-19 virus.
The key to the universal vaccine is the mosaic nanoparticle with so many different viral fragments clustered in close proximity on its surface. The immune system's B cells, which generate specific antibodies, are likely to find and bind to at least some of these conserved pieces of the virus, which remain unchanged on new variants. Thus, the B cells will make antibodies effective against even previously unseen variants.

To make their mosaic nanoparticle, Cohen, Bjorkman, and their collaborators chose proteins from the surfaces of 12 coronaviruses identified by other research groups and detailed in the scientific literature. These included the viruses that caused the first SARS outbreak and the one that causes covid-19, but also non-human viruses found in bats in China, Bulgaria, and Kenya. For good measure, they also threw in a coronavirus found in a scaly anteater known as a pangolin. All the strains had already been genetically sequenced by other groups and share 68 to 95% of the same genomic material. Thus, Cohen and Bjorkman could be relatively sure that at least some portions of each distinct spike protein they chose to place on the exterior of their nanoparticle would be shared by some of the other viruses.

Then they made three vaccines. One, for comparison purposes, had all 60 slots occupied by particles taken from a single strain of SARS-CoV-2, the virus that causes covid-19. The other two were mosaics, each one displaying a mix of protein fragments taken from eight of the 12 bat, human, and pangolin coronavirus strains. The remaining four strains were left off the vaccine so the researchers could test whether it would protect against them anyway.

In mouse studies, all three vaccines bound equally well to the covid-19 virus. But when Cohen sat down to look at his results, he was shocked at how much more powerfully the mosaic nanoparticles performed when exposed to different strains of coronavirus not represented on the spikes they had been exposed to.

The vaccine was triggering the production of armies of antibodies to attack the parts of the proteins that changed least among the different strains of coronavirus—the parts, in other words, that are conserved.

New era

In recent months, Bjorkman, Cohen, and their collaborators have been testing out the vaccine in monkeys as well as rodents. So far, it seems to be working. Some of the experiments proceeded slowly because they had to be done by overseas collaborators in special high-security biosafety labs designed to ensure that highly contagious viruses do not escape. But when the results finally appeared in Science, the paper received widespread attention.

Other promising efforts are moving in parallel. At the University of Washington's Institute of Protein Design, biochemist Neil King has custom-designed hundreds of new types of nanoparticles, "sculpting them atom by atom," he says, in such a way that the atoms self-assemble, attracted to the correct positions by other pieces engineered to carry complimentary geometric and chemical charges. In 2019, King's collaborator Barney Graham at NIH was the first to successfully demonstrate that mosaic nanoparticles could be effective against different flu strains. King, Graham, and collaborators formed a company to modify and develop the technique, and they have a nanoparticle influenza vaccine in phase 1 clinical trials. They are now deploying the new technology against a variety of different viruses, including SARS-CoV-2.

Despite the recent promising developments, Bjorkman warns that her vaccine likely won't protect us from all coronaviruses. There are four families of coronaviruses, each a little different from the next, and some target entirely different receptors in human cells. Thus, there are fewer sites conserved across coronavirus families. The vaccine from her lab focuses on a universal vaccine for the sarbecovirus, the subfamily that contains SARS coronaviruses and SARS-coV-2.

"I'm not sure it would ever be possible to make a single pan-coronavirus vaccine," Bjorkman says. "So we're just trying to do relatively low-hanging fruit, which would be a pan-sarbecovirus vaccine. But I think that's important, since that is the family from which many of the recent spillover events have happened."

Moreover, the research in Bjorkman's lab and others is opening a new frontier in vaccine

design that has implications far beyond her efforts. The work can perhaps be adapted to target coronaviruses in other families, and even entirely different viruses altogether. It might also presage a new era in vaccine development in which vaccines against a wide array of challenging pathogens can be more easily created and customized.

But the regulatory hurdles they must overcome are significant. A new vaccine produced through a conventional approach would be required to demonstrate “correlates of protection” to existing vaccines—evidence that the immune system is responding to the vaccine to the way it does to existing vaccines. But since mosaic nanoparticle vaccines are new, the researchers need to show that the vaccine prevents individuals from getting sick, which takes far longer and requires more money.

Cohen suggests it could take a couple of years just to begin the trials, since the vaccine will need to undergo rigorous toxicology testing and meet strict manufacturing standards to pass regulatory muster. But with initial money secured, a manufacturer identified, and papers in the world’s top scientific journal demonstrating its promise, there is finally reason for optimism.

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