In government, industry, and university laboratories, scientists are striving to outwit enemies that don’t yet exist: the next coronavirus to threaten human health, and the one after that.

They’re working on vaccines that would not only protect against any variant SARS-CoV-2 could throw at them but also against any of its cousins that might arise in the future. Most of these vaccines haven’t yet moved out of preclinical testing, but human trials of one began in April.

“What’s to say we’re not going to have another coronavirus in the next 5 to 10 years?” said Kayvon Modjarrad, MD, PhD, director of the Emerging Infectious Diseases Branch at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland, and coinventor of the first universal—or pancoronavirus—vaccine to be tested in people. “The point is not that we’re claiming to be clairvoyant. This is just a pattern that we’re seeing, and it’s a pattern that’s not going away.”

After all, there was the first SARS-CoV in late 2002 to 2003. Then Middle East respiratory syndrome coronavirus (MERS-CoV) appeared in Saudi Arabia in 2012. And then, of course, SARS-CoV-2 in December 2019 launched a global pandemic. All 3 are betacoronaviruses, a genus that also includes 2 common cold viruses.

Before establishing his branch at WRAIR a few years ago, Modjarrad had worked on vaccines against influenza, MERS, and Zika virus disease at the National Institutes of Health (NIH) and as part of the World Health Organization’s Ebola response.

“What I found was that we were just constantly in this reactive mode and always behind the curve, meaning the epidemiological curve,” Modjarrad, an infectious disease physician whose PhD is in epidemiology, said in an interview.

With SARS-CoV-2, it could have been worse. If the NIH had “not had this incipient program on coronaviruses, we would be in a very different situation in regards to the vaccine,” Modjarrad said. Getting 2 messenger RNA (mRNA) vaccines into people’s arms only a year after SARS-CoV-2 was sequenced was an astounding scientific achievement, experts generally agree.

But it could have been better. “We had warnings,” said Matthew Memoli, MD, citing SARS and MERS. “We didn’t heed these warnings.”

SARS vaccines reached early phase 2 clinical trials after that epidemic, but then interest “kind of dried up,” Memoli, director of the Clinical Studies Unit at the National Institute of Allergy and Infectious Diseases (NIAID) Laboratory of Infectious Diseases, told JAMA. SARS and SARS-CoV-2 are 95% the same, he noted. “Imagine if we had a SARS vaccine last March [2020] or even February.”

Early in the pandemic, Memoli and other vaccine researchers recognized the need to take a long view. In March 2020, Memoli coauthored an article headlined “Universal coronavirus vaccines: the time to start is now.”

All in the Family

Studies using blood samples from people who’d recovered from either SARS or SARS-CoV-2 have provided tantalizing evidence supporting the feasibility of a pancoronavirus vaccine.

Serum from people who’d been infected with SARS-CoV during the 2003 SARS outbreak demonstrated cross-reactive neutralizing activity against the SARS-CoV-2 spike protein, while serum from people recovered from COVID-19 showed cross-reactive neutralizing activity against both SARS-CoV and MERS.

Why individuals who’d been infected with 1 coronavirus could produce neutralizing antibodies against other coronaviruses relates to the evolutionary biology principle of conservation: the presence of similar genes or gene parts in different members of, in this case, virus families. The stability of these family heirlooms, so to speak, makes them attractive pancoronavirus vaccine targets.

“These are going to be conserved aspects of the biology of these different pathogens,” including conserved epitopes, the portion of an antigen that stimulates an immune response, explained Modjarrad, who developed WRAIR’s pancoronavirus vaccine with colleague M. Gordon Joyce, PhD, his branch’s structural biology chief.
First-in-Human Trial
Like other potential pancoronavirus vaccines, Modjarrad and Joyce's prototype capitalizes on conserved parts of betacoronavirus spike proteins.

Their candidate is a spike ferritin nanoparticle vaccine. Ferritin is a naturally occurring iron storage protein, and ferritin nanoparticles are used in drug delivery, bioassays, molecular imaging, and experimental universal influenza vaccines.

The WRAIR vaccine consists of a ferritin nanoparticle studded with multiple triplets of the SARS-CoV-2 Wuhan-Hu-1 spike protein and WRAIR's proprietary adjuvant. "When you have a repetitive array of an antigen presented, it augments the immune response in terms of the quantity and quality of antibodies," Modjarrad explained.

In a recent article that had not been peer reviewed, Modjarrad, Joyce, and their coauthors reported that their vaccine elicited broad neutralizing antibody responses against the SARS-CoV-2 Wuhan-Hu-1 isolate as well as SARS-CoV-2 variants of concern and SARS-CoV in macaques. The vaccine rapidly protected against respiratory infection and disease in the monkeys' upper and lower airways and lung tissue.

"It exceeded our expectations," Modjarrad said. "What we have now may be a pan-SARS vaccine." He and his collaborators are now adding spike proteins from other betacoronaviruses, such as MERS-CoV, to their vaccine with the aim of eliciting an even broader immune response, he said.

Why the WRAIR vaccine containing only the SARS-CoV-2 spike protein stimulated such a broad response isn't yet clear, he said, but possible explanations include the spike ferritin nanoparticle and WRAIR's adjuvant, which, in a study that had not been peer reviewed, was found to generate a better immune response in mice than a spike ferritin nanoparticle vaccine with aluminum hydroxide, the most commonly used adjuvant.

First-in-human trials of the WRAIR vaccine began April 7. Twenty-four participants have received the vaccine, and the researchers are now injecting 24 more participants. The plan is to enroll a total of 72 volunteers who have never been infected with SARS-CoV-2 or vaccinated against it. "We are running up against the clock here in terms of finding those individuals," Modjarrad acknowledged.

Different Approaches, Same Goal
Other laboratories have taken different tack.

Duke University scientists have also created a ferritin nanoparticle vaccine, but theirs displays multiple copies of a highly conserved site on coronaviruses' receptor binding domain (RBD)—their Achilles heel, as Kevin Saunders, PhD, director of research at the Duke Human Vaccine Institute, calls it. The vaccine also contains an adjuvant to boost the immune response.

The RBD, located on the spike protein, enables coronaviruses to dock with angiotensin-converting enzyme 2 (ACE2) receptors on the surface of cells, leading to infection. Neutralization of the RBD should shut the door on coronaviruses' ability to enter cells.

The Duke vaccine elicited neutralizing antibodies against a large panel of coronavirus variants in macaques, Saunders and his coauthors reported in May. "Overall, it was well tolerated" by the macaques, Saunders told JAMA. He and his collaborators are seeking funding to manufacture the vaccine for clinical trials.

Memoli and his collaborator, Jeffrey Taubenberger, PhD, chief of the Viral Pathogenesis and Evolution Section at NIAID's Laboratory of Infectious Diseases, want to develop a vaccine that would not only be broadly protective against coronaviruses but would also be broadly protective across the population.

Factors such as age, genetics, and comorbidities appear to reduce the effectiveness of vaccines, including those against influenza, in certain individuals, Memoli said. "What I think is the problem is that every person is unique, and their immune system is unique."

The solution, Memoli said, is to stimulate multiple aspects of the immune system, which could be done using inactivated whole virus or multiple antigens from a variety of viruses or combining different vaccine strategies. He and Taubenberger have decided to pursue the killed whole virus approach, using a cocktail of several killed whole coronaviruses.

They'd like to be able to deliver a pancoronavirus vaccine via a nasal spray. "All of these viruses, they get in through your mucosal system," Memoli said. "The big problem is we don't understand enough about mucosal immunity for respiratory viruses. This is a big unexplored area."

Rather than killed whole viruses, biopharmaceutical company VBI Vaccines uses synthetic virus-like particles (VLPs) in its candidate pancoronavirus vaccine.

VBI, headquartered in Cambridge, Massachusetts, with research operations in Ottawa, Ontario, Canada, has created a proprietary enveloped VLP (eVLP) platform technology for the development of prophylactic as well as therapeutic vaccines. Like coronaviruses, VBI's VLPs are enveloped in a double layer of natural lipids.

VLPs are like sheep in wolf's clothing: The nanoparticles mimic viruses, eliciting an immune response at least as robust as natural infection, but they're not infectious themselves because they contain no viral genetic material, only a protein core. Currently licensed VLP vaccines target human papillomavirus and hepatitis B virus.

"Conceptually, we know that VLPs are very effective vaccines," VBI Vaccines Chief Scientific Officer David Anderson, PhD, said in an interview. "They're just really great ways to educate the immune system, because they look so much like the virus."

Enveloped VLPs can express antigens from multiple coronavirus spike proteins, he explained. "We simply choose at any time what we want to express on the surface." VBI's pancoronavirus eVLP vaccine, a collaboration with the National Research Council of Canada, expresses the spike proteins of the SARS-CoV-2 Wuhan-Hu-1 isolate, SARS-CoV, and MERS. Clinical trials of the vaccine are expected to begin later this year.

At least 2 pancoronavirus vaccine prototypes use plasmids, small circular DNA strands, typically in the cytoplasm of a bacterium or protozoan, to deliver viral antigens to cells.

One such vaccine was developed by Inovio, a Plymouth Meeting, Pennsylvania-based biotech company that uses a proprietary computer algorithm to identify and optimize the DNA sequences of target antigens. The company is conducting preclinical testing of a pan-SARS-CoV-2 vaccine to protect against current and future variants. SARS-CoV-2 variant sequences from around the world were collected for 4 months beginning in October 2020. Spike protein mutations were aggregated for each geographic region, and a common set of overlapping mutations from the variants were used to generate the vaccine.
"We’ve essentially taken the genetic sequence from all of the sequences and made a mosaic of them," Kate Broderick, PhD, Inovio senior vice president for research and development, explained in an interview.

In an article posted in May that hadn’t been peer reviewed, Broderick and her co-authors reported that their vaccine induced broad immunity against SARS-CoV-2 variants in mouse and hamster models.

The other prototype pancoronavirus vaccine that uses plasmids was developed by Steven Zeichner, MD, PhD, a University of Virginia pediatric infectious disease specialist, and Virginia Tech virologist Xiang-Jin Meng, MD, PhD. Their vaccine uses a new production platform that Zeichner invented.

Authorized COVID-19 vaccines include the entire spike protein, part of which is the viral fusion peptide (VFP) that, Zeichner said, is essentially the same across coronaviruses and plays an important role in helping them fuse with host cells. But, as far as the immune system is concerned, the highly conserved VFP kind of gets lost in the crowd of all the spike protein’s components, Zeichner said.

Zeichner and Meng synthesized VFPs for SARS-CoV-2 and porcine epidemic diarrhea virus (PEDV)—a coronavirus that sickens pigs—and inserted the peptides into plasmids. They then inserted the plasmids into Escherichia coli bacteria that had been stripped of nearly a third of their genes, finalizing distractions that could divert the immune system’s attention from the VFPs expressed on the bacteria’s surface.

The scientists injected pigs with either the SARS-CoV-2 vaccine or the PEDV vaccine or a placebo. They chose pigs, Zeichner said, because they wanted to study their vaccines in the natural host of a coronavirus, not a transgenic animal model.

They recently reported that, compared with a placebo vaccine, their PEDV vaccine produced significant protection against severe illness in pigs that had been challenged with that virus. Unexpectedly, their SARS-CoV-2 vaccine also protected pigs against severe PEDV, suggesting the VFP could be a target for a broadly protective coronavirus vaccine, Zeichner, Meng, and their coauthors concluded.

"It’s a long way to having something to go into a phase 1 trial in people," Zeichner noted. "Right now, we have a vaccine that keeps pigs from getting sick."

Impossible Dream?

For years, many of the researchers now working on pancoronavirus vaccines had been focused on developing universal vaccines for influenza and for HIV, both of which are RNA viruses, as are SARS-CoV-2 and its cousins.

No universal flu or HIV vaccine has made it to market yet. However, the scientists say, betacoronaviruses aren’t as much of a moving target as influenza viruses and HIV, so they’re hopeful that a pancoronavirus vaccine will prove to be less challenging.

"Overall, flu is a more difficult problem simply because of the nature of the virus," Memoli noted. Influenza viruses are segmented. They develop mutations in each segment, and then the segments recombine, he explained. "That makes it change more drastically."

HIV is not only genetically diverse, because of its high rate of mutations and recombination, but it’s stealthy and can lie dormant inside cells. "It’s a really daunting virus," Saunders said.

The main goal of a pancoronavirus vaccine is to prevent infected individuals from dying, Memoli said. Even better, such a vaccine could keep them out of the hospital and shorten the period during which they could infect others.

"We’re not trying to create a vaccine that stops you from getting infected with every coronavirus on earth forever," Memoli said. "We’re trying to help your immune system. We’re trying to give you time to recover. There’s a heck of a lot we don’t know about coronaviruses. These viruses are predictably unpredictable."

Note: Source references are available through embedded hyperlinks in the article text online.