WHAT'S NEXT IN COVID VACCINE?

Research at University of Minnesota looks for new ways to fight the virus

BY LINDA PICONE

Two (and possibly three by the time this magazine comes out) vaccines to prevent infection with the novel coronavirus COVID-19 have been approved for emergency use in the United States and are being distributed across the country.

The development of vaccines with high efficacy rates in less than a year—and yet with all the required testing completed and safeguards in place—is remarkable. But the research doesn't end now. Scientists around the world continue to explore vaccines that could protect against COVID and potential future forms of virus. At the University of Minnesota, researchers are involved in several vaccine projects.

Phase 3 trial for Novavax

Recruitment in Minnesota for Phase 3 trial of Novavax, a potential vaccine for COVID-19, began in late December 2020 and closed on February 13. In seven weeks, about 30,000 participants were enrolled nationally with 319 at the U of M site, which included two clinical research units (CRUs): Delaware CRU in Minneapolis and St. Joseph's Hospital CRU in St. Paul.

Susan Kline, MD, MPH, a professor of medicine and infectious disease physician with the University of Minnesota Medical School and M Health Fairview, is the principal investigator for the trial at the U of M Medical School. She got involved with the vaccine trial through her work on a Phase 3 trial for remdesivir, the Adaptive COVID-19 Treatment Trial (ACTT). "Through that, I learned about the vaccine trial going on and reached out to one of the leads at NIH (National Institutes of Health) to see if they were looking for more sites," she says. She was connected with the COVID-19 Prevention Trials Network (COVPN) established by the National Institute of Allergy and Infectious Diseases (NIAID) and NIH last July to enroll volunteers in large-scale clinical trials to test vaccines and monoclonal antibodies.

"We were chosen to be a site for the Novavax testing," Kline says. "That study was launched at the end of December. There was one additional vaccine they were hoping to launch, but it has been pushed back."

Although Kline has been involved in a number of clinical trials in the past, including a vaccine trial, "this is different because it's part of a pandemic response, Operation Warp Speed," she says. "The timeline for enrollment is compressed. This study is trying to enroll 30,000 participants in two months or less; the Pfizer and Moderna trials did enrollment in two to three months."

By the time the Novavax study was seeking participants in Minnesota, the Pfizer and Moderna vaccines had already been approved for emergency use and were in distribution, albeit in limited quantities. That created a certain amount of difficulty in recruiting volunteers, although Kline says that as of mid-January, she was not concerned. "We thought we'd be starting recruitment last fall and the elderly were a priority group," she says. "But now, because hopefully they will have access to an emergency use vaccine in the near future, they're no longer a group to focus recruitment on."

Kline says the U of M Medical School reached out to communities that have been heavily affected by COVID, with minority communities a priority group.

Those who agreed to participate have been asked to stay with the trial for four to six months, not knowing whether they have received the vaccine or a placebo; about a third of the participants will be given the placebo. Participants are not supposed to receive any other vaccine during that time, although it is anticipated that,

if the early results show vaccine efficacy, those who got the placebo will have access to the vaccine in a blinded cross-over study, after the initial four to six months. This cross-over study plan still requires formal FDA approval. Altogether, participants are going to be followed for two years for long-term efficacy and safety.

Although the Pfizer-BioNTech and Moderna vaccines are already approved, with a Johnson & Johnson vaccine on the verge of approval and an AstraZeneca vaccine that may follow soon, Kline says it is important to continue research on other potential vaccines for three main reasons:

- "If we find several that work, we can end the pandemic sooner."
- "It will be helpful to have vaccines that work for many different kinds of people around the world. The first two vaccines require storage in deep freeze to maintain their potency, so that's difficult when you're talking about getting it out to areas that don't have access to those kinds of freezers. Others—including Novavax—require only refrigeration. Having more vaccines that require only refrigeration will help meet the demand in this country and around the world."
- "You need to scale up manufacturing. It takes a while to manufacture millions of doses, so having multiple manufacturers will allow releasing more vaccine quickly."

There is still a lot to learn about the vaccines now being distributed and any others likely to come into use, Kline says, so more data collection is helpful to answer questions like: How long does the vaccine effectiveness last? What are the long-term side effects, if any? How do different people react to vaccines?

Exploring different mechanisms for creating immunity

The Pfizer and Modern vaccines use lipid particles to deliver nucleoside-modified mRNA into host cells, which allows expression of the SARS-CoV-2 spike protein that creates an immune response that protects against COVID-19. The Novavax COVID-19 vaccine candidate, NVX-CoV2373, is a stable spike protein

produced by genetic engineering from the sequence of SARS-CoV-2, the virus that causes COVID-19 disease. NVX-CoV2373 was created using Novavax' recombinant nanoparticle technology to generate antigen derived from the coronavirus spike (S) protein and contains Novavax' patented saponin-based Matrix-M™ adjuvant to enhance the immune response and stimulate high levels of neutralizing antibodies. It does not contain viral material and cannot replicate.

Johnson & Johnson's vaccine uses an adenovirus that has been made unable to replicate. The adenovirus carries a gene from the coronavirus into human cells. This produces the coronavirus protein, which primes the immune system to fight off infection by COVID. The Oxford-AstraZeneca vaccine also works with an adenoviral vector.

But there are other potential ways to create immunity against the coronavirus and it just makes sense to keep researching, says Marc Jenkins, PhD, professor of Microbiology and Immunology and director of the Center for Immunology, U of M Medical School.

"If Pfizer and Moderna are really effective and provide long-lasting immunity, there's less of a need for additional vaccines," Jenkins says, "but we don't know everything about the virus, and it's early days for the vaccine."

The vaccines now available may not protect as well against variants of the

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COVID virus—there is already some evidence that the AstraZeneca vaccine is not as effective against the variant first seen in South Africa. The Novavax Phase 3 trial done in the United Kingdom and Phase 2b study in South Africa recently reported their preliminary results and demonstrated some efficacy against variant strains. The Novavax COVID-19 vaccine demonstrated 89.3 percent efficacy in the UK Phase 3 trial, in which less than 50 percent of the COVID-19 cases were attributable to the UK variant strain. In the South African Phase 2b trial, in which

about 90 percent of COVID-19 cases were attributed to the South African variant, 60 percent efficacy was seen for the prevention of mild, moderate and severe COVID-19 disease.

"The jury is still out whether the current vaccines are going to be like the polio vaccines, which is one vaccine course and you have lifelong immunity," says Jenkins. "But it's also possible that the virus can produce mutated variants, and then we're more in a situation where we're looking at seasonal vaccination, like the flu. I hope that's not true, but even if it is, it's better than nothing."

T-cell stimulation

Jenkins is working on a T-cell-based vaccine with David Masopust, PhD, professor, and Ryan Langlois, PhD, associate professor, both in the U of M Medical School's Department of Microbiology and Immunology.

"All of the other major vaccines are based on the idea that the host will make antibodies against the spike protein of the coronavirus, so-called neutralizing antibodies," he says. "The one we're working on uses a different protein, one that is inside the virus and not available for antibodies to bind to."

The COVID virus has to get inside human cells to replicate. Jenkins and collaborators are targeting a T-lymphocyte, which "scans" the cells in the body, looking for fragments of foreign protein—like a coronavirus. When the T-lymphocytes encounter bits of foreign protein, they "kill" the infected cell, Jenkins says. "That might sound like a bad idea, but because you have stem cells that can replace the lung epithelial cells, it's okay to kill it."

"Our strategy is aimed at generating a huge number of these T-lymphocytes," he says. "Any virally-infected cell would be killed and, after the vaccine is administered, we would have a thousand times more of these T-cells distributed throughout the body. Normally, they're in the lymph nodes, but after vaccination, they would be in the lungs so infection can't spread."

Jenkins' research is in the preclinical animal-testing stage, but he says an experiment with hamsters has shown that it will protect from a live COVID-19 infection. "We need to test this in many more hamsters, then demonstrate that the method of protection is in T-cells," he says. "If that is reproducible, we would then face the decision of whether we want to find a corporate partner to take the vaccine forward."

Nanoparticles to create immune response

Fang Li, PhD, professor in the U of M's College of Veterinary Medicine, University of Minnesota, was doing research on coronaviruses before the current pandemic began, Jenkins says. "A lot of people now would think that was a neglected area of research."

Li used recombinant DNA technology to create a special form of the spike protein. "He took that spike protein and created a form of it that would self-assemble into a virus-like particle," Jenkins says. "The immune system likes to see aggregated stuff; it gets activated more efficiently by aggregates."

Jenkins says Li's research is still in the animal-testing stage, and has shown effectiveness in mice. "The mechanism in that vaccine would be antibodies," he says. "You inject the host with the spike nanoparticles and hope for antibodies that can neutralize the virus."

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Professor of Microbiology and Immunology and director of the Center for Immunology, U of M Medical School

NK-cell-facilitated vaccine

Geoffrey Hart, PhD, assistant professor of medicine, and Marco Pravetoni, PhD, associate professor of pharmacology, both in the U of M Medical School, are also working on a vaccine strategy that would be based on antibodies, Jenkins says, but to produce the kind of antibodies that are recognized by a "natural killer cell" that can recognize antibody-coated cells and attack them. This research also is in preclinical animal testing. **MM**

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