Scientists Are Working on mRNA Vaccines for HIV, Flu, Cancer and More

The technology used in COVID-19 vaccines may also be used to prevent other viral infections and to treat cancer and multiple sclerosis.

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The same messenger RNA (mRNA) technology used in the Moderna and Pfizer/BioNTech coronavirus vaccines, which are around 95% effective at preventing symptomatic COVID-19, could potentially be used to prevent or treat a wide variety of other diseases.

Moderna recently announced that it has started new programs to design mRNA vaccines for HIV, seasonal influenza and Nipah virus, adding to the company's development portfolio for several other viral diseases and cancer.

"The uniquely challenging year of 2020 for all of society proved to be an extraordinary proof-of-concept period for Moderna," CEO Stéphane Bancel said in a press release. "Even as we have shown that our mRNA-based vaccine can prevent COVID-19, this has encouraged us to pursue more-ambitious development programs within our prophylactic vaccines modality."

The mRNA vaccine approach uses lipid nanoparticles, or fat bubbles, to deliver bits of genetic material that encode instructions for making proteins. The COVID-19 vaccine, for example, delivers blueprints for making SARS-CoV-2 spike proteins, which the coronavirus uses to enter human cells. When the vaccine is injected into a muscle, the cells act as factories to produce the proteins, which trigger an immune response.

The mRNA degrades quickly in the body and does not alter human genes. But the drawback of this approach is that mRNA is fragile and unstable, making it hard to work with, store and transport—as seen with the Pfizer/BioNTech vaccine that must be kept at an ultracold temperature of minus 94° Fahrenheit.

Experimental HIV Vaccines

Researchers have spent more than three decades and billions of dollars studying vaccines to prevent HIV but with only modest success. The virus mutates rapidly, and there are many strains of HIV around the world, making it difficult to develop broadly effective vaccines.

To date, only one vaccine regimen—a canarypox vector primer followed by a gp120 booster—has

demonstrated partial protection in human studies, but it was not effective in a recent large trial. Two other large trials, dubbed Mosaico and Imbokodo, are currently testing an approach that uses an adenovirus primer followed by a booster that contains a "mosaic" of proteins from multiple HIV strains.

Taking a completely different approach, Moderna is working on two mRNA HIV vaccine candidates. The first, known as mRNA-1644, is being developed in collaboration with the International AIDS Vaccine Initiative and the Bill and Melinda Gates Foundation. A Phase I trial is expected to start this year. The second, called mRNA-1574, is being evaluated in collaboration with the National Institutes of Health (NIH), which also collaborated on Moderna's COVID-19 vaccine (mRNA-1273).

At last summer's virtual International AIDS Conference, NIH and Moderna researchers reported promising results from a study of an experimental mRNA HIV vaccine approach in monkeys.

Over the course of a year, 16 macaques received vaccines that contained mRNA encoding envelope proteins from three types of HIV found in different regions of the world along with Gag proteins from SIV, a related simian virus. These blueprints induced the monkeys' cells to produce virus-like particles that stimulate an immune response. Some animals also received booster shots containing stabilized envelope proteins.

The vaccines triggered production of neutralizing antibodies that bind to envelope proteins, which HIV uses to enter cells. The monkeys then received repeated rectal administrations of SHIV, a human-simian hybrid virus, in an effort to mimic sexual exposure. The vaccine offered "significant protection," according to the researchers. Of the seven monkeys that received the most effective vaccine combination, three did not become infected, and infection was delayed in the other four.

Employing another strategy, Drew Weissman, MD, PhD, and colleagues at the University of Pennsylvania designed an mRNA that encodes a neutralizing antibody that targets HIV, known as VRC01. In an early study, a single injection of the mRNA protected humanized mice against HIV infection.

Gene-based strategies for HIV prevention, including mRNA approaches, will be the topic of a session at the upcoming HIV Research for Prevention (HIVR4P) Conference.

Vaccines for Other Viral Diseases

In its press release announcing its new HIV vaccine effort, Moderna also outlined its development programs for a wide range of other diseases.

Current flu vaccines are only modestly effective, in part because influenza viruses mutate so rapidly and scientists essentially make an educated guess several months in advance about what strains will be circulating during the forthcoming flu season. The mRNA platform could make the process faster and more accurate, allowing scientists to substitute in genetic sequences from the predominant circulating flu strains. Moderna's flu vaccines candidates (mRNA-1010, mRNA-1020 and mRNA-1030) will cover four seasonal flu viruses recommended by the World Health

Organization. Phase I clinical trials are expected to start in 2021.

Nipah virus causes a range of illnesses, including fatal encephalitis. Severe respiratory and neurologic complications currently have no treatment beyond supportive care, and the case fatality rate may be as high as 75%. Moderna's Nipah virus vaccine candidate, mRNA-1215, was codeveloped with the NIH Vaccine Research Center.

The company is also working on preventive vaccines for several other viruses, including cytomegalovirus (mRNA-1647, now in Phase II); Epstein-Barr virus, which causes mononucleosis, certain types of lymphoma and nasal cancer (mRNA-1189); human metapneumovirus and parainfluenza type 3 (mRNA-1653); respiratory syncytial virus, or RSV, which cause respiratory illnesses, especially in children, seniors and people with weakened immune systems (mRNA-1345); chikungunya virus (mRNA-1944); and Zika virus (mRNA-1893).

Cancer Vaccines

Moderna and BioNTech are among the companies exploring vaccines that stimulate the immune system to fight cancer. In fact, the mRNA technology was first developed for use in cancer vaccines.

Experimental cancer vaccines contain blueprints for tumor-associated antigens that trigger an immune response. To create personalized vaccines, a patient's tumor is sequenced, and an algorithm is used to predict which neoantigens—proteins expressed by mutated cancer genes—are most likely to trigger a tumor-specific immune response.

Moderna's customized cancer vaccine, known as mRNA-4157, can contain up to 34 different neoantigens. When given along with Merck's checkpoint inhibitor Keytruda (pembrolizumab)—which restores T-cell activity—mRNA-4157 shrank tumors in people with head and neck cancer not caused by the human papillomavirus (HPV) in a small Phase I trial presented at the 2020 Society for Immunotherapy of Cancer annual meeting.

Five of the 10 patients in this group responded, for an overall response rate of 50%, including two complete responses. Four others had stable disease with no further progression. The median progression-free survival time was 9.8 months. Both measures compare favorably with previously published results for people treated with Keytruda alone. However, no responses were seen in a group of 17 patients with colorectal cancer. A Phase II study of the same combination for melanoma is underway.

Another Moderna cancer vaccine candidate (mRNA-5671) targets cancers with KRAS mutations. Other experimental vaccines aim to drive T-cell responses against cancer by injecting mRNA encoding immune-modulating cytokines directly into tumors. Phase I trials are now underway for lymphoma, ovarian cancer and other solid tumors.

In a Phase I study, BioNTech's BNT111 vaccine showed promise in people with advanced melanoma. In an interim analysis of 25 people treated with BNT111 alone, one had complete

remission, three had partial responses and seven had stable disease. Of the 17 people treated with BNT111 plus a checkpoint inhibitor, six had partial responses. What's more, in people who received the vaccine once monthly, memory T cells that recognize the antigens in the vaccine persisted for more than a year.

Multiple Sclerosis and Heart Disease

Researchers recently reported that an mRNA vaccine showed promise in treating autoimmune conditions such as multiple sclerosis.

Ugur Sahin, MD, PhD, of BioNTech and Johannes Gutenberg University in Mainz, Germany—who, with his wife, Ozlem Tureci, MD, pioneered mRNA technology—designed an mRNA that encodes normal bodily proteins, known as autoantigens, that are mistakenly attacked by immune cells in people with autoimmune diseases. The idea is that the injected mRNA would be expressed by dendritic immune cells in a way that teaches T-cells to tolerate the normal proteins.

In mice bred to have experimental autoimmune encephalomyelitis, a condition in which the immune system attacks neurons (akin to what happens in people with multiple sclerosis), the mRNA therapy reduced symptoms and prevented disease progression. And, unlike existing treatments for multiple sclerosis and other autoimmune conditions, it worked without broadly dampening immune function, which can increase susceptibility to infections.

Finally, AstraZeneca is testing an mRNA therapy (AZD8601), originally developed by Moderna, that encodes vascular endothelial growth factor A, which promotes the development of blood vessels. Injections of the mRNA may improve outcomes in people undergoing coronary artery bypass surgery for heart disease.

Although this research is not yet ready for human testing, it demonstrates the far-reaching potential of the mRNA technology that is helping turn the tide against COVID-19.

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