Can mRNA Vaccines Help Treat Cancer?

The success of the mRNA COVID-19 vaccines could help accelerate clinical research on vaccines to treat cancer.

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The coronavirus pandemic has thrown a spotlight on messenger RNA (mRNA)—the molecule that carries a cell's instructions for making proteins. Hundreds of millions of people worldwide have received mRNA vaccines that provide powerful protection against severe COVID-19 caused by infection with SARS-CoV-2.

As stunningly successful as the mRNA COVID-19 vaccines have been, researchers have long hoped to use mRNA vaccines for a very different purpose—to treat cancer. mRNA-based cancer treatment vaccines have been tested in small trials for nearly a decade, with some promising early results.

In fact, scientists at both Pfizer-BioNTech and Moderna drew on their experience developing mRNA cancer vaccines to create their coronavirus vaccines. Now, some investigators believe the success of the mRNA COVID-19 vaccines could help accelerate clinical research on mRNA vaccines to treat cancer.

"There's a lot of enthusiasm around mRNA right now," said Patrick Ott, M.D., Ph.D., who directs the Center for Personal Cancer Vaccines at the Dana-Farber Cancer Institute. "The funding and resources that are flowing into mRNA vaccine research will help the cancer vaccine field."

Dozens of clinical trials are testing mRNA treatment vaccines in people with various types of cancer, including pancreatic cancer, colorectal cancer, and melanoma. Some vaccines are being evaluated in combination with drugs that enhance the body's immune response to tumors.

But no mRNA cancer vaccine has been approved by the US Food and Drug Administration for use either alone or with other cancer treatments. "mRNA vaccine technology is extremely promising for infectious diseases and may lead to new kinds of vaccines," said Elad Sharon, M.D., M.P.H., of NCI's Division of Cancer Treatment and Diagnosis. "For other applications, such as the treatment of cancer, research on mRNA vaccines also appears promising, but these approaches have not yet proven themselves."

With findings starting to emerge from ongoing clinical trials of mRNA cancer vaccines, researchers

could soon learn more about the safety and effectiveness of these treatments, Dr. Sharon added.

How do mRNA vaccines work?

Over the past 30 years, researchers have learned how to engineer stable forms of mRNA and deliver these molecules to the body through vaccines. Once in the body, the mRNA instructs cells that take up the vaccine to produce proteins that may stimulate an immune response against these same proteins when they are present in intact viruses or tumor cells.

Among the cells likely to take up mRNA from a vaccine are dendritic cells, which are the sentinels of the immune system. After taking up and translating the mRNA, dendritic cells present the resulting proteins, or antigens, to immune cells such as T cells, starting the immune response.

"Dendritic cells act as teachers, educating T cells so that they can search for and kill cancer cells or virus-infected cells," depending on the antigen, said Karine Breckpot, Ph.D., of the Vrije Universiteit Brussel in Belgium, who studies mRNA vaccines.

The mRNA included in the Pfizer-BioNTech and the Moderna coronavirus vaccines instructs cells to produce a version of the "spike" protein that studs the surface of SARS-CoV-2.

The immune system sees the spike protein presented by the dendritic cells as foreign and mobilizes some immune cells to produce antibodies and other immune cells to fight off the apparent infection. Having been exposed to the spike protein free of the virus, the immune system is now prepared, or primed, to react strongly to a subsequent infection with the actual SARS-CoV-2 virus.

Cancer research led to speedy development of mRNA vaccines

When the pandemic struck, mRNA vaccine technology had an unexpected opportunity to demonstrate its promise, said Norbert Pardi, Ph.D., of the University of Pennsylvania Perelman School of Medicine, whose research focuses on mRNA-based vaccines.

"The production of mRNA vaccines today is easy, fast, and can be scaled up as needed," Dr. Pardi continued. The same manufacturing procedure can be applied to any mRNA sequence, he added.

Historically, the process of developing vaccines has taken 10 to 15 years. But both the Pfizer-BioNTech and the Moderna COVID-19 vaccines—the latter of which was developed in collaboration with NIH—were designed, manufactured, and shown to be safe and effective in people in less than a year.

"To develop an infectious disease vaccine during a pandemic, you need to be fast," said Lena Kranz, Ph.D., co-director of Cancer Vaccines at BioNTech. "The current pandemic has confirmed our hypothesis that mRNA technology is well suited for fast vaccine development and rapid manufacturing on a global scale."

The groundwork for the speedy design, manufacturing, and testing of the mRNA COVID-19

vaccines was established through decades of work on cancer vaccines. During this period, immunotherapy, including drugs such as immune checkpoint inhibitors, emerged as a new approach to treating cancer, leading, in some people, to dramatic and long-lasting responses.

“There’s a lot of synergy between research on immunotherapy and mRNA cancer vaccines,” said Robert Meehan, M.D., senior director of clinical development at Moderna. “Vaccines are building on the success of immune checkpoint inhibitors and expanding our knowledge of the underlying biology.”

Modifying and protecting the cargo of mRNA vaccines

Technologies that can deliver mRNA to the body are essential for the success of these vaccines. If an mRNA sequence were injected into the body without some form of protection, the sequence would be recognized by the immune system as a foreign substance and destroyed.

A solution employed by some investigational cancer vaccines is to encase the mRNA in lipid nanoparticles, which are tiny spheres that protect the mRNA molecules. Other delivery vehicles include liposomes, which are also a type of vesicle, or bubble.

“The most advanced mRNA-based vaccine platform uses mRNA encapsulated in lipid nanoparticles,” said Dr. Pardi. Now that the Pfizer-BioNTech and the Moderna coronavirus vaccine trials have demonstrated the effectiveness of lipid nanoparticles, the technology could certainly be used in future cancer vaccine trials, he added.

Another key feature of the Pfizer-BioNTech and the Moderna coronavirus vaccines is the use of modified forms of mRNA, according to Jordan Meier, Ph.D., of NCI’s Center for Cancer Research, who studies mRNA modifications.

The mRNA in these vaccines incorporates pseudouridine, which is a modification of a naturally occurring nucleoside. Nucleosides are the building blocks of mRNA, and the order of specific nucleosides determines the instructions that mRNA gives to the protein-making machinery in cells.

“The [pseudouridine] modification seems to make the mRNA itself almost invisible to the immune system,” said Dr. Meier. The modification does not alter the function of the mRNA but may enhance the effectiveness of the vaccines, he added.

Cancer researchers have been testing both modified and unmodified forms of mRNA in their investigational treatment vaccines. More research is needed to better understand the relative advantages of each approach for the development of cancer vaccines, Dr. Meier said.

Developing and testing personalized mRNA cancer vaccines

For more than a decade, cancer researchers have been developing a type of treatment known as a personalized cancer vaccine using various technologies, including mRNA and protein fragments, or peptides.

The investigational mRNA vaccines are manufactured for individuals based on the specific molecular features of their tumors. It takes 1 to 2 months to produce a personalized mRNA cancer vaccine after tissue samples have been collected from a patient.

“Speed is especially important for individualized cancer vaccination,” said Mathias Vormehr, Ph.D., codirector of Cancer Vaccines at BioNTech. “A highly individualized vaccine combination must be designed and produced within weeks of taking a tumor biopsy.”

With this approach, researchers try to elicit an immune response against abnormal proteins, or neoantigens, produced by cancer cells. Because these proteins are not found on normal cells, they are promising targets for vaccine-induced immune responses.

“Personalized cancer vaccines may teach the immune system how cancer cells are different from the rest of the body,” said Julie Bauman, M.D., deputy director of the University of Arizona Cancer Center.

Dr. Bauman is co-leading a clinical trial testing a personalized mRNA vaccine in combination with an immune checkpoint inhibitor in patients with advanced head and neck cancer. The study initially included patients with colorectal cancer, but this group did not appear to benefit from the therapy.

For patients with head and neck cancer, however, the early results were positive. Among the first 10 participants, 2 patients had all signs of their tumors disappear following treatment, known as a complete response, and another 5 had their tumors shrink.

“We were surprised to see two complete and enduring responses in our first group of patients with head and neck cancers,” said Dr. Bauman, noting that the study has been expanded to include 40 patients with the disease.

“The number of patients treated is small, but we are cautiously optimistic,” she added. The study is sponsored by Moderna, which makes each personalized vaccine in about 6 weeks.

The manufacturing process starts with the identification of genetic mutations in a patient’s tumor cells that could give rise to neoantigens. Computer algorithms then predict which neoantigens are most likely to bind to receptors on T cells and stimulate an immune response. The vaccine can include genetic sequences for up to 34 different neoantigens.

The promise of personalized immunotherapy with mRNA vaccines is “being able to activate T cells that will specifically recognize individual cancer cells based on their abnormal molecular features,” said Dr. Bauman.

Advancing the science of mRNA cancer vaccines

“A lot of immunotherapies stimulate the immune response in a nonspecific way—that is, not directly against the cancer,” said Dr. Ott. “Personalized cancer vaccines can direct the immune response to exactly where it needs to be.”

Some companies are also investigating mRNA cancer vaccines that are based on collections of a few dozen neoantigens that have been linked with certain types of cancer, including prostate cancer, gastrointestinal cancers, and melanoma.

In addition to clinical trials, fundamental research on mRNA cancer vaccines continues. Some investigators are trying to enhance the responses of immune cells to neoantigens in mRNA vaccines. One study, for example, aims to improve the responses of T cells that become exhausted while attacking tumors.

A challenge for the field is learning how best to identify neoantigens for personalized mRNA cancer vaccines, several researchers said.

“There’s still a lot we need to learn and many questions to answer,” Dr. Ott said. It’s not yet clear, for example, how personalized cancer vaccines should be best combined with other treatments, such as immune checkpoint inhibitors, he added.

As cancer researchers pursue these questions, other investigators will be developing knowledge from the growing number of people around the world who are receiving mRNA coronavirus vaccines.

Insights about the composition of mRNA or the way mRNA is packaged that emerge from studies of viruses could potentially inform work on cancer vaccines, said Dr. Breckpot.

“Unfortunately, it took a pandemic for there to be broad acceptance of mRNA vaccines among the scientific community,” she added. “But the global use of COVID-19 mRNA vaccines has demonstrated the safety of this approach and will open doors for cancer vaccines.”

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