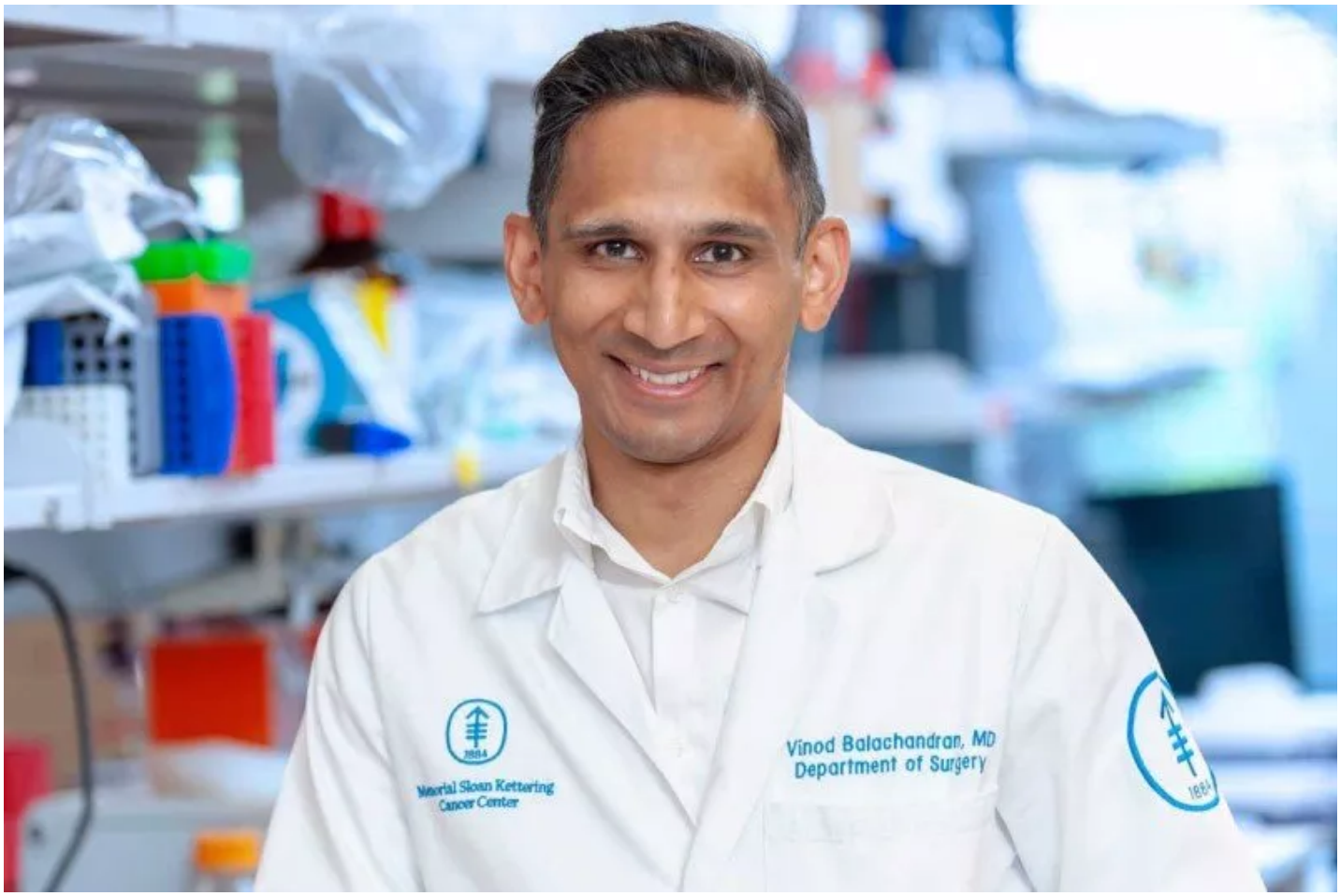
MSK mRNA Pancreatic Cancer Vaccine Trial Shows Promising Results

By Jim StallardWednesday, May 10, 2023



Vinod Balachandran says mRNA vaccines could stimulate the immune system to recognize and attack pancreatic cancer cells.

Messenger RNA (mRNA) vaccines may be the hottest thing in science now, as they helped turn the tide against COVID-19 by preventing infection. But even before the pandemic began, Memorial Sloan Kettering Cancer Center (MSK) researchers had already been testing mRNA vaccine technology with a different purpose — as a treatment for cancer.

Pancreatic cancer surgeon Vinod Balachandran, MD, has been leading the first clinical trial (research study) to test mRNA vaccines as a potential therapy for pancreatic cancer. Dr. Balachandran is a physician-scientist in the Human Oncology and Pathogenesis Program and is affiliated with the David M. Rubenstein Center for Pancreatic Cancer Research.

The vaccines are custom-made for every person. They use proteins in the pancreatic tumors, called neoantigens, to alert the immune system that cancer cells are foreign. The hope is that the vaccine will reduce the risk of the cancer returning after the main tumor is removed by surgery. The mRNA vaccines train the body to protect itself against its own abnormal cancer cells.

Phase 1 Pancreatic Vaccine Trial Results

Now results from the phase 1 trial, reported May 10 in *Nature*, suggest that the vaccines cause an effective and lasting immune response. In 8 of 16 patients studied, the vaccines activated powerful immune cells, called T cells, that can recognize the pancreatic cancer specific to a patient. These patients also showed delayed recurrence of their pancreatic cancers, suggesting that the T cells activated by the vaccines may be having the desired effect — to keep pancreatic cancers in check.

“These exciting results indicate we may someday be able to use vaccines as a therapy against pancreatic cancer,” Dr. Balachandran says. “The evidence supports our strategy to tailor each vaccine to each patient’s tumor.”

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Next Steps After Promising Results

A larger, randomized clinical trial is set to open involving patients at multiple sites in various countries. MSK expects to begin enrolling patients in the trial this summer.

Here, Dr. Balachandran discusses how the initial laboratory discovery and a collaboration with Genentech, a member of the Roche Group, and BioNTech, an immunotherapy company, led to this potential treatment for pancreatic cancer.

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What do these recent findings tell us about using mRNA vaccines to treat pancreatic cancer?

It shows that we are on the right track: An mRNA vaccine can trigger T cells to recognize their pancreatic cancers as foreign. Moreover, the vaccines stimulated many such T cells, and these T cells could last in patients up to two years later, even though patients received chemotherapy after vaccination. At a median follow-up of 18 months, in patients with such vaccine-expanded T cells, the cancers had not come back. In contrast, cancers came back approximately 13 months after surgery in patients where vaccines did not expand T cells.

One of our patients, Barbara Brigham, received the vaccine in 2021 and continues to do well.

It's exciting to see that a personalized vaccine could enlist the immune system to fight pancreatic cancer — which urgently needs better treatments. It's also motivating as we may be able to use such personalized vaccines to treat other deadly cancers.

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What are the next steps for making the cancer mRNA vaccines more effective?

We will continue to analyze data from the pancreatic cancer trial so we can better understand what factors help the vaccine work in patients. Of course, we want to find out why some pancreatic cancer patients didn't respond to the vaccine and find solutions to this problem. In this quest to make the vaccine better, we published research in May 2022 that suggested ways to choose the best neoantigens.

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What was the inspiration for using a vaccine against pancreatic cancer?

There has been great interest in using immunotherapy for pancreatic cancer because nothing else has worked very well. We thought immunotherapy held promise because of research we began about eight years ago. A small subset of patients with pancreatic cancer manage to beat the odds and survive after their tumor is removed. We looked at the tumors taken from these select patients and saw that the tumors had an especially large number of immune cells in them, especially T cells. Something in the tumor cells seemed to be sending out a signal that alerted the T cells and drew them in.

We later found that these signals were proteins called neoantigens that T cells recognize as foreign, triggering the immune system attack. When tumor cells divide, they accumulate these neoantigens, which are caused by genetic mutations. In most people with pancreatic cancer, these neoantigens are not detected by immune cells, so the immune system does not perceive the tumor cells as threats. But in our study, we saw that neoantigens in the pancreatic cancer survivors were different — they did not escape notice. They, in effect, uncloaked the tumors to T cells, causing the T cells to recognize them.

Even more striking, we found that T cells recognizing these neoantigens circulated in the blood of these rare patients for up to 12 years after the pancreatic tumors had been removed by surgery. The T cells had memory of the neoantigens as a threat. This is similar to the memory that vaccines trigger against pathogens, which can sometimes protect people for decades.

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How did the neoantigen discovery lead to a pancreatic cancer vaccine?

My colleagues and I published our findings about immune protection in long-term pancreatic cancer survivors in *Nature* in November 2017. While working on this, we were also looking for ways to deliver neoantigens to patients as vaccines. We were particularly interested in mRNA vaccines, a new technology that we thought was quite promising. The vaccines use mRNA, a piece of genetic code, to teach cells in your body to make a protein that will trigger an immune response.

Coincidentally, at this time, BioNTech co-founder and CEO Uğur Şahin emailed us that he had read our paper and was interested in our ideas. He and his team were working with Genentech on individualized neoantigen-based mRNA therapies. In late 2017, we flew to Mainz, Germany, where BioNTech is based. They were still a little-known company at that point. We had dinner with Uğur and his team in Mainz as well as with Ira Mellman from Genentech. We discussed the potential of mRNA vaccines for pancreatic cancer — as well as the possible use of the mRNA platform they have developed.

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What makes creating an individualized cancer vaccine challenging?

Designing a cancer vaccine tailored to an individual is complex. Because cancers arise from our own cells, it is much harder for the immune system to distinguish proteins in cancer cells as foreign compared with proteins in pathogens like viruses. But important advances in cancer biology and genomic sequencing now make it possible to design vaccines that can tell the difference.

This builds on important work done at MSK that has shown how critical tumor mutations are to triggering an immune response. In parallel to our work, major discoveries in mRNA technology over the past decades by scientists such as Dr. Sahin and BioNTech co-founder Özlem Türeci paved the way to use mRNA in medicine. We all felt optimistic about the potential and decided to move ahead.

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How does the experimental mRNA pancreatic cancer vaccine work? How is it tailored to each individual tumor?

After a patient has a pancreatic tumor surgically removed, the tumor is genetically sequenced to look for mutations that produce the best neoantigen proteins — those that look the most foreign to the immune system. The vaccine is manufactured with mRNA specific to these proteins in that individual's tumor. While the vaccine is being made, the patient gets a single dose of a checkpoint inhibitor drug. We think checkpoint inhibitors can work in conjunction with these vaccines to boost immune responses.

The mRNA vaccine is given in nine injections. When the vaccine is infused into a person's bloodstream, it causes immune cells called dendritic cells to make the neoantigen proteins. The dendritic cells also train the rest of the immune system, including T cells, to recognize

and attack tumor cells that express these same proteins. With the T cells on high alert to destroy cells bearing these proteins, the cancer may have a lower chance of returning.

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When did the phase 1 trial start? How was each person's vaccine made?

In December 2019, we enrolled the first patient in a clinical trial to test if this vaccine was safe. The process to make individualized vaccines is more complex than making a preventive vaccine for an infectious disease, where each vaccine is the same and can be manufactured in large batches. An individualized therapeutic mRNA cancer vaccine must be tailored to each patient's tumor.

To do this, we must perform a very complex cancer surgery to take out the tumor and ship the sample to BioNTech in Germany. They sequence the tumor and make the vaccine, which is then sent back to New York — all in a short time, and in the middle of a pandemic! Thanks to the diligent teams and the elegance of the mRNA technology, we at MSK were up to the task and finished enrolling our target total of 20 patients nearly a year ahead of schedule.

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How did you manage to conduct the clinical trial in the middle of a pandemic?

Our team here at MSK is fantastic, and so are the teams at BioNTech and at Genentech, which funded the study. When the pandemic began, we knew we needed to adapt quickly to make sure our patients were not affected. Thanks to our research team, led by Cristina Olcese, we coordinated very complicated logistics to make sure the trial ran smoothly. When we started, our estimated time to complete the trial was two and a half years. We finished it in 18 months.

That's due to the amazing leadership of our Acting Hospital President and Department of Surgery Chair Jeffrey Drebin, MD, and Hepatopancreatobiliary Service Chief William Jarnagin, MD. Dr. Drebin recognized the importance of this trial early on and has been the strongest proponent of the study, enrolling most of the patients himself.

Medical oncologist Eileen O'Reilly, MD; computational biologist Ben Greenbaum, PhD; physician-scientist Jedd Wolchok, MD; and biologist Taha Merghoub, PhD, were also invaluable in pushing to make this trial happen. We also received tremendous support for the study from the Stand Up To Cancer organization, the Lustgarten Foundation, the Ben and Rose Cole Charitable PRIA Foundation, and the Damon Runyon Cancer Research Foundation, without which this study would not have been possible.

This has been a great example of MSK's forward-thinking vision in cancer care — to bring the most exciting medicines to people with cancer. We were working with mRNA vaccines before they were popular to test our scientific discoveries in patients.

Key Takeaways

Some people with pancreatic cancer survive many years after diagnosis.

In these patients, the immune system keeps the cancer from returning.

A messenger RNA vaccine based on this concept is being tested in combination with another type of immunotherapy.

Early results suggest the vaccine is having the desired effect on the immune system.

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The research reported in Nature was supported by a Stand Up To Cancer Convergence Award, the Lustgarten Foundation, the NIH U01 CA224175 Pancreatic Cancer Microenvironment Network Cancer Moonshot Award, the Damon Runyon Clinical Investigator Award, the Ben and Rose Cole Charitable PRIA Foundation, the Mark Foundation ASPIRE Award, and the Pershing Square Sohn Prize-Mark Foundation Fellowship. Services of the Integrated Genomics Core were funded by the NCI Cancer Center Support Grant, Cycle for Survival, and the Marie-Josée and Henry R. Kravis Center for Molecular Oncology. The team at MSK sponsored the clinical trial. The imCORE Network, Genentech, BioNTech, Stand Up To Cancer, the Lustgarten Foundation, and the National Cancer Institute Pancreatic Cancer Microenvironment Network funded the clinical trial and the biomarker studies.