mRNA gives hope for heart disease cure

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FULL TEXT

"It's really cool. I think we all knew when the COVID vaccine was so successful and so well tolerated in so many people ... those of us who are scientists immediately began thinking, 'Wow, what else can I do with this?'"

Dr. Crystal Mackall

Stanford University cancer researcher

Combining technologies that proved hugely successful against cancer and in COVID-19 vaccines, researchers at the University of Pennsylvania have shown they can effectively treat a leading cause of heart disease.

For now, the success has only been achieved in mice, but the milestone offers hope for millions of people whose heart muscle is damaged by scar tissue.

There is no effective treatment for this fibrosis, which leads to heart disease, the leading cause of death in the United States, said Dr. Jonathan Epstein, a Penn professor of cardiovascular research who helped lead the new work, published last month in the journal Science.

In his new research, Epstein reversed fibrosis by re-engineering cells, as has been done with a successful blood cancer treatment called CAR-T, which stands for chimeric antigen receptor T cells.

In this case, however, the treatment took place inside the body rather than in a lab dish.

The team delivered the treatment using mRNA technology, which has been proven over the last year with hundreds of millions of people receiving mRNA-based COVID vaccines.

"If it works (in people), it really could have enormous impact," Epstein said. "Almost every type of heart disease is accompanied by fibrosis."

About 50% of heart failure is directly caused by this scar tissue, which prevents the heart from relaxing and pumping effectively. Fibrosis also is involved in leading causes of lung and kidney disease.

In the decade-old CAR-T approach to fighting blood cancers, developed at Penn by study co-author Carl June, immune cells from the patient are taken out of the body and genetically altered to identify tumor cells.

Then, they're reinserted so they can destroy the cancer.

CAR-T has been hugely expensive because it's personalized for every patient. By working inside the body, the new approach would allow treatment with the same generic approach for everyone.

"It is now scalable. That makes it to me really more exciting," Epstein said.

Unlike cancer therapy, where every last cancer cell has to be killed to prevent recurrence, in fibrosis, almost any significant reduction will improve someone's quality of life, he said.

Though still a long way from helping people, the method shows the potential of mRNA technology, well beyond COVID vaccines.

"It's really cool," said Dr. Crystal Mackall a Stanford University cancer researcher who uses CAR-T to treat cancer and was not involved in this work.

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In the COVID vaccine, mRNA spurs cells to make a protein normally found on the surface of the coronavirus. That way, when the immune system sees the actual virus, it will recognize the protein and attack the virus before it can do serious damage.

In the new application, the mRNA trains the cells to produce a protein found on the surface of fibrotic cells, so immune cells will destroy them.
In previous studies, engineered T cells were delivered in a way that allowed them to persist over a long time, risking that the immune system would attack other fibrotic cells, including those involved in wound healing. By delivering the protein with mRNA, which only sticks around for a few days, the researchers think they can avoid this problem.
"The window for potential trouble is relatively small," Epstein said.
This short-term durability is a major advantage, he and others said.
"The idea that you could do this over a period of days is actually pretty exciting," said Dr. Stanley Riddell, a professor and immunology expert at the Fred Hutchinson Cancer Research Center in Seattle. "It's a very nice application of cutting-edge synthetic biology."
Still, unexpected problems could crop up, and the Penn team remains a long way from safely treating people with fibrotic heart disease, Epstein said.
Next, they plan to test their approach in larger mammals, before moving on to people, hopefully in about two years. They still have to work out the most appropriate dose and how many times the treatment might need to be delivered to be most effective, he said.
The research team has started a company to help advance the technology.
One advantage, Epstein said, is that imaging technology can now "see" fibrotic tissue, allowing doctors to evaluate a patient's disease and response to therapy.
"There are tools that already exist to bring this forward," he said.
Like many great scientific advances, the idea behind the new treatment approach started with a chance meeting in an elevator.
One of Epstein's graduate students had wondered aloud about the possibility of using CAR-Ts to treat cardiac fibrosis. A few days later, Epstein ran into Carl June in an elevator and posed the same question.
Graduate students led the effort, because "they have the energy to go back and forth between labs," Epstein said, "and they're smart enough to learn different disciplines."
The teams had been collaborating for several years when Dr. Drew Weissman, a Penn scientist whose research underlies mRNA vaccines, approached them to suggest delivering the treatment via mRNA.
"I just walked into Jon's office and said, 'We can do this,'" Weissman said.
Weissman, not surprisingly, is a big believer in mRNA technology, which is already being tried in other vaccines –to prevent the flu, shingles and respiratory syncytial virus, as well as cancer. The new study shows it has much broader potential, he said.
Fibrosis is a part of many diseases, not just heart disease. Duchenne Muscular Dystrophy, pulmonary fibrosis, scleroderma and COVID lung are all caused by a hardening of vital tissues, noted Weissman, who is now using mRNA as the basis for an experimental HIV vaccine. People are also experimenting with using mRNA to treat autoimmune disease and to deliver gene therapies.
"The potential for it really is enormous," Weissman said. "It's the beginning of the RNA world."
Contact Karen Weintraub at kweintraub@usatoday.com.
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