RNA worked for COVID-19 vaccines. Could it be used to treat cancer and rare childhood diseases?

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A few weeks ago, a group of Philadelphia scientists reported that they had injected mice with genetic instructions in the form of RNA, prompting the animals' cells to produce customized proteins.

If that seems like no big deal at this point, now that millions have undergone a similar process in being vaccinated against COVID-19, guess again.

These injections were not vaccines, and the mice in question were fetuses, so the RNA had to be administered with slender glass needles the width of a human hair. The experiment, conducted by researchers at Children's Hospital of Philadelphia and the University of Pennsylvania, marked a first step toward using RNA to treat rare genetic diseases before birth.

RNA—ribonucleic acid—made sense to use in a vaccine. That's because it can be encoded with the recipe for a specific protein—in this case, the protein "spikes" that protrude from each coronavirus particle. The person's immune system gets a chance to practice on a fragment of the virus without being exposed to the real thing.

But long before the coronavirus, scientists envisioned using RNA to produce other kinds of proteins, enabling them to treat a variety of human diseases. These include conditions in which the person's natural proteins are deficient in some way, such as cystic fibrosis and sickle-cell anemia. And before the pandemic, trials were underway on RNA vaccines designed to treat cancer, with promising early results.

Treating disease before birth is the next horizon, said William Peranteau, a fetal surgeon at CHOP and co-senior author of the new study in mice, published in *Science Advances*.

While he and his colleagues successfully induced the production of proteins in the fetal mice, they did not target a specific disease in this initial proof-of-concept study. Years of research are needed before the approach can be tried on human fetuses.

But the appeal is obvious, Peranteau said. Treating a disease during pregnancy would allow physicians to intervene before it is too late, potentially warding off various developmental delays and other conditions that can be fatal.

"These would be diseases that cause problems before the baby is born," he said. "Problems that are not easily reversible, and for which there isn't a great treatment after birth."

The messenger of life

Scientists began to piece together the various roles of RNA not long after they figured out the famous double-stranded helix of its chemical cousin, DNA, in 1953. They soon determined that one type of RNA seemed to act as a courier—carrying the genetic instructions in DNA to the cellular "machinery" that uses those instructions to make proteins: the building blocks of life.

As millions of high-schoolers now learn every year in biology class, that crucial "messenger RNA" is abbreviated as mRNA. Moderna Inc., the maker of one of the RNA vaccines, even uses the abbreviation for its stock ticker symbol.

The idea of using RNA to treat disease took a big leap forward in the

early 2000s, when a pair of Penn scientists, Katalin Karikó and Drew Weissman, cleared a series of technical hurdles. A key advance: They synthesized RNA so it could be safely administered to the human body without triggering inflammation. (Karikó is now a senior vice president at BioNTech SE, the German firm that joined with Pfizer Inc. to produce the other RNA vaccine for COVID-19.)

But another hurdle remained. RNA degrades quickly, so scientists needed a way to protect it for delivery inside human cells. The solution: Package the genetic instructions inside tiny spheres made from fatty substances called lipids.

That's the delivery vehicle that has worked so well with the two RNA vaccines, and it also is the approach that Peranteau and his colleagues used in the fetal mice.

Targeting organs

Penn bioengineering professor Michael J. Mitchell, the other senior author of the mouse study, tested various combinations of lipids to see which would work best.

The appeal of the fatty substances is that they are biocompatible. In the vaccines, for example, two of the four lipids used to make the delivery spheres are identical to lipids found in the membranes of human cells—including plain old cholesterol.

When injected, the spheres, called nanoparticles, are engulfed by the person's cells and then deposit their cargo, the RNA molecules, inside. The cells respond by making the proteins, just as they make proteins by following the instructions in the person's own RNA. (Important reminder: The RNA in the vaccines cannot become part of your DNA.)

Among the different lipid combinations that Mitchell and his lab members tested, some were better at delivering their cargo to specific organs, such as the liver and lungs, meaning they could be a good vehicle for treating disease in those tissues.

One candidate for prenatal RNA treatments is a family of metabolic diseases called lysosomal storage disorders, Peranteau said. They are characterized by protein deficiencies and the buildup of toxic byproducts, leading to various consequences in the developing brain, heart, and bones.

Mitchell and Peranteau oversaw the mouse research as senior authors. Three first authors were responsible for the bulk of the hands-on work: Rachel S. Riley, a former Penn engineer who is now an assistant professor at Rowan University, Penn engineering graduate student Margaret M. Billingsley, and Meghana V. Kashyap, a former CHOP research fellow who is now at University of Nebraska Medical Center. Weissman, who did the early RNA experiments at Penn, also participated.

The ability to guide the nanoparticles to specific organs would be crucial in treating fetuses, Riley said.

"We can, to a certain extent, dictate where we want them to go," she said. "Especially in a fetus, you want to minimize any off-target effects."

It took a pandemic to prove the point, but now that the lipid particles have been such a success with the vaccines, Riley said friends and family finally understand the importance of what she's been working on for years.

"Now everyone's asking me about nanoparticles," she said.

Tackling cancer

Training the immune system to fight off infectious disease is fairly straightforward. Training it to fight off cancer is far more challenging.

Yet here, too, scientists hope that RNA can help get the job done. This approach is called a therapeutic vaccine, meaning it is designed to treat someone who already has cancer, as opposed to a vaccine for preventing disease like COVID-19.

But in both cases, the goal is coaxing the recipient's cells to make custom proteins.

In an RNA cancer vaccine, the genetic molecules carry the recipe for proteins in a patient's tumor. The recipient's cells make the proteins, and ideally, the immune system learns to recognize them as foreign, and responds by destroying the tumor itself.

A key challenge in treating cancer is that tumors have evolved a variety of mechanisms for suppressing the immune system. The hope is that RNA vaccines can help to overcome this suppression, especially when administered in conjunction with other immune-boosting drugs.

If needed, the RNA can even be tailored to match cancer mutations that are unique to a particular patient. Moderna and BioNTech, the makers of the COVID-19 vaccines, both have tests of these personalized cancer vaccines underway.

And much as with the COVID-19 vaccines, an individualized cancer vaccine can be fashioned quickly. It's just a matter of assembling the correct code.

A year ago, the drug manufacturers were able to fashion coronavirus

RNA in a matter of days. Now they are doing it again, tweaking the protein recipe to match the mutations in some of the emerging virus variants.

If Peranteau and Mitchell are successful, someday rare infant diseases could be treated the same way: with the messenger of life.