A bright spot during this COVID-19 pandemic has been the rapid development of effective vaccines that work by harnessing the power of messenger RNA, or mRNA. mRNA vaccines might seem like a relatively new idea, but researchers have been working on the technology behind them for decades. Now, the success of Moderna and Pfizer’s coronavirus vaccines are highlighting the immense potential for mRNA therapies—not just for infectious diseases, but also to treat cancer and genetic disorders.

“Vaccines are just the tip of the iceberg when it comes to the capabilities of mRNA,” says Lior Zangi from the Icahn School of Medicine at Mount Sinai, New York City, NY, USA. “We are just at the beginning, but I think this will be a disturbing technology in the fields of gene therapy and drug development.”

The first mRNA vaccines

We rely on proteins to carry out nearly every bodily function. While DNA contains all the information cells need to make proteins, mRNA actually does the work of creating those proteins. In the case of COVID-19, mRNA vaccines instruct cells to create the virus’ distinctive spike protein. That induces the immune system to create antibodies that recognize the spike protein. If the vaccinated individual is later exposed to the virus, these antibodies will attack it [1].

The first COVID-19 vaccine to receive emergency use authorization by the U.S. Food and Drug Administration (FDA) was developed by BioNTech in collaboration with Pfizer; a second vaccine, developed by Moderna, soon followed. The development timeline of both vaccines was unprecedented, according to John Cooke, director of the Center for Cardiovascular Regeneration and the medical director of the RNA Therapeutics Program at the Houston Methodist DeBakey Heart and Vascular Center (Figure 1).

Cooke says the situation was urgent, but also that mRNA vaccines are easier to develop and manufacture than conventional vaccines. “The first mRNA vaccine was made within 42 days of knowing the genetic sequence of SARS-CoV-2,” he says. “Within four months, that vaccine was tested in humans. That is light speed for pharmaceutical development. Prior to mRNA vaccines, it took on average about seven years to develop a vaccine and get it to clinical trial.”

Figure 1. John Cooke, director of the Center for Cardiovascular Regeneration and the medical director of the RNA Therapeutics Program at the Houston Methodist DeBakey Heart and Vascular Center. (Photo courtesy of Scott Jones.)
Making mRNA that works

Up until the early 2000s, scientists had been trying to figure out how to design mRNA strands for medical applications without activating the body's protective immune response, with no success. The breakthrough came from two scientists at the University of Pennsylvania, Katalin Karikó (now a senior vice president at BioNTech) and Drew Weissman. To create mRNA that the body would not immediately reject, they tweaked its molecular building blocks, the nucleosides that make up a strand of mRNA. This modified mRNA, in which a nucleoside called uridine is replaced with one called pseudo-uridine, is not recognized by immune cells [2].

This discovery inspired a group of researchers and venture capitalists in the USA to start a company based on the use of modified mRNA. They named it Moderna—short for modified mRNA. One of Moderna’s first projects involved treating heart disease with modified mRNA, an area in which Zangi is still doing research. Zangi says that this was supposed to be the first therapy using modified mRNA to reach the clinic, but then COVID-19 came along and priorities shifted.

Around the same time that Moderna was created, researchers in Germany founded BioNTech to research modified mRNA treatments for cancer. By the time COVID-19 had gone global, Moderna and BioNTech had been studying modified mRNA for more than a decade [3]. They were prepared to tackle this new challenge with the platforms they had been building. “There is not a single vaccine that works with mRNA, only modified mRNA,” emphasizes Zangi (Figure 2). “At the beginning, the common criticism of using modified mRNA was that it is more expensive but not necessarily better than regular mRNA. But now, we have compelling evidence that modified mRNA was the right way to go forth.”

Beyond the COVID-19 vaccine

Although Moderna and BioNTech were pioneers in commercialization of modified mRNA therapeutics, other research groups and biotech start-ups around the world are now entering the field. There are currently more than 500 ongoing clinical trials testing mRNA therapies across more than 20 disease categories [4]. “The first opportunities are going to be vaccines,” says Cooke. “They are the low-hanging fruit for mRNA therapeutics.”

Traditionally, vaccines use recombinant proteins to train the immune system to attack viruses exhibiting similar proteins. However, manufacturing these proteins is complicated and time intensive. In contrast, mRNA vaccines encode protein fragments into a single strand of mRNA and then rely on cellular machinery to make the proteins. “Cells are much better at making proteins than we are,” says Cooke. “In an mRNA vaccine, you just have to get the mRNA into the cytoplasm of the cell and its instructions will be read to create the desired protein.” Buoyed by the success of the COVID-19 vaccines, there are now mRNA vaccines against rabies, Zika, influenza, HIV, Nipah, and other viruses advancing through clinical trials [1].
Another potential application of mRNA technology is in cancer treatment, where researchers are studying how to use mRNA to encode cancer-specific proteins that teach the immune system to recognize and target a tumor. For instance, BioNTech has 19 drug candidates in its pipeline for pancreatic cancer, breast cancer, prostate cancer, melanoma, ovarian cancer, head and neck cancer, and other solid tumors.

Although there are dozens of trials testing the efficacy of mRNA therapies against viruses or cancers, a few companies have focused their efforts on other applications, including using mRNA to replace missing or defective proteins. In many rare genetic diseases, mutations in DNA can result in abnormal mRNA sequences, resulting in dysfunctional or deficient proteins. Researchers are exploring the ability of mRNA therapies to regulate protein expression in order to fight back against such diseases.

The mRNA therapeutics company Translate Bio is working on a treatment for cystic fibrosis, a deadly genetic illness caused by mutations to the cystic fibrosis transmembrane conductance regulator gene. They are currently conducting a clinical trial for an mRNA treatment that is delivered to the lungs via a nebulizer. And BioNTech has been working with researchers to use mRNA to treat mice genetically engineered to develop a disease similar to multiple sclerosis, an autoimmune disease in which myelin, the fatty covering of the nerve cells, is attacked by the immune system. In mice, the treatment appeared to slow and reverse the effects of the disease.

The future of mRNA therapy

However, there are challenges in bringing mRNA therapeutics to the clinic. Vaccines have been a popular first approach because they require just one or a few doses: Once the immune system is stimulated to attack the specific threat, the protein produced from the mRNA degrades. But when repeated doses of mRNA are needed to replace a protein over a lifetime—to treat chronic or genetic diseases, for instances—patients may experience more side effects.

These potential side effects could be due to the body’s inflammatory response to the mRNA itself or to the buildup of lipid nanoparticles, the protective bubbles used to surround the mRNA and carry it through the body [1]. To design safe, effective therapies for different diseases, researchers are working on ways to tweak the structure of the mRNA to make it appear more natural to the body as well as delivering it in biodegradable lipid nanoparticles [5].

In addition to mitigating side effects, these therapies face the challenge of targeting mRNA to specific tissues and producing lasting benefits. mRNA vaccines work well because they can be injected to the skin or muscle, but other methods of delivery will be necessary to distribute mRNA elsewhere in the body.

Another issue is the stability of mRNA in the body. It gets degraded rapidly within our cells.

“Ninety percent of the endogenous RNA in our cells lasts two minutes to two hours,” says Cooke. “It’s basically a blueprint or working copy to make a protein.” Cooke and other researchers are studying ways to make mRNA last longer, for instance by making the strands circular, masking it from the enzymes that would normally eat away at the ends of the strands. “These hurdles—getting the mRNA to the right spot and making it last long enough to be effective—we’re working on solving these issues and mRNA is going to be a useful therapeutic for many diseases,” says Cooke. “RNA therapy will transform the way we take care of patients.”

Zangi also sees a great deal of promise in mRNA therapeutics. He and others are figuring out the optimal ways to deliver such medicines, whether it is via intravenous injection, pills, inhalation, or intranasally—and at the same time, ensure that the mRNA is translated into protein in targeted cell types only.

ZANGI COMPARES THE goal of researchers like himself to technology from the original Star Trek series. He says that the character of Dr. McCoy had two medical tools that he used to diagnose and treat nearly everything: a scanner and an injector. “We have scanners today, such as MRI and EKG,” says Zangi. “We can identify problems. But with his
injector, he could give any patient an injection and it would treat their problem wherever it was in the body. That’s what we are working on—creating the syringe of Dr. McCoy. That’s the future of modified mRNA therapeutics.”

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