mRNA: from instability to a world-changing vaccine

When our cells are ready to make a protein, parts of our DNA are copied into a messenger RNA (mRNA) molecule. The mRNA will carry this recipe to a ribosome (a chef), which will then build the specific protein.

But it isn’t easy to work with mRNA, as it is unstable and breaks down quickly. These are some of the challenges that Dr. Katalin Karikó and Dr. Drew Weissman have been working tirelessly to address for the past few decades.

Karikó and Weissman engineered mRNA to protect it from being broken down quickly. This meant that mRNA could be successfully delivered into human cells, to produce specific proteins. This was ground-breaking!

During the COVID-19 pandemic, researchers at companies like Pârzer/BioNTech and Moderna, used this work to quickly develop safe and effective COVID-19 mRNA vaccines, and protect us all from becoming seriously ill. Now, scientists are beginning to build and test mRNA vaccines against other threats, like influenza and HIV.

In our cells, proteins are the molecules that actually build things: like keratin in our fingernails, or antibodies to fight viruses. Similar to how you would use a recipe to bake a cake, our cells rely on the instructions found in DNA to build these proteins.

Just imagine: we could use messenger molecules to build vaccines! By designing specific mRNA, we can give our cells pre-packaged instructions on how to build proteins that can help us fight different viruses.

Art by Armin Mortazavi and text by Farah Qaiser. October 2022
mRNA molecules are special because they are mobile and can carry the instructions to a ribosome (a protein chef), which will then build the specific protein, in a process called translation.

Just imagine: by designing specific mRNA, we can give our cells pre-packaged instructions on how to build any protein. This opens up a world of endless possibilities!

Sadly, it isn’t easy to work with mRNA, as it is unstable and breaks down quickly. These are some of the challenges that countless scientists, including Dr. Katalin Karikó and Dr. Drew Weissman, have been working tirelessly to address for the past few decades.

In 1985, Karikó, a Hungarian biochemist with a doctorate in biochemistry, emigrated with her family to the United States, and later started working at the University of Pennsylvania. She was single-mindedly researching mRNA, for its potential applications in heart disease and stroke, convinced that it could be used to develop therapies and treatments.

Like many scientists, Karikó wrote several proposals to granting agencies, requesting funding to support her mRNA research. But Karikó’s research proposals were rejected, again and again. She was...
that injecting synthetic mRNA into immune cells triggered widespread inflammation.

Why was this happening? What Karikó and Weissman needed was a way to stop the immune system from identifying the synthetic mRNA as a foreign pathogen, and instead, convince the cells that this was an mRNA molecule to transcribe and translate into a protein.

It took many years, but in 2005, Karikó and Weissman were finally successful. The two scientists were able to chemically modify mRNA – specifically, by making a simple chemical tweak to the building blocks of mRNA, where they replaced the nucleic acid uridine with pseudouridine.

This protected the synthetic mRNA from being broken down quickly, and allowed it to slip past the body’s immune defenses. Now, the synthetic mRNA could be used by cells to produce specific proteins, without triggering inflammation. This was a game-changer.

Thanks to Karikó and Weissman, it was now possible to design mRNA to produce proteins to fight different viruses, such as HIV and the flu. It was revolutionary, because traditional vaccines will deliver a dead or weakened virus to stimulate the immune system and teach the body how to fight an infection. But with mRNA, the body’s own cells could produce a carefully chosen viral protein and simulate an immune response, without posing any risk of infection.

Karikó and Weissman were excited and braced for interest from the scientific community.

“In our minds, we had solved the problem of RNA therapy,” says Weissman. “It had been in clinical trials and failed. Everyone had given up on it. We thought we figured out how to overcome that. I told [Katalin Karikó] that the next morning, our phone would be ringing off the hook with people wanting to use our method to deliver mRNA.”

But at the time, few scientists recognized the importance of this discovery, let alone the broader public.
“Of course, nobody called us,” says Karikó. “So, we focused on things which we could still see needed to be solved.”

Disappointed, but undeterred, Karikó and Weissman continued their work to better understand mRNA. They applied for, and received, patents, and even founded a small company. Karikó went on to work at an RNA pharmaceutical company, called BioNTech, in Germany.

All of this changed when the COVID-19 pandemic hit the globe. The first COVID-19 cases were reported in late 2019, but it wasn’t until January 2020 that the sequence for SARS-CoV-2, the virus which causes COVID-19, was uploaded online. It only took days for researchers in academic institutions and pharmaceutical companies, like Pfizer/BioNTech and Moderna, to use these viral sequences and generate potential mRNA vaccine candidates to test in both cells and animal models, and later, in human clinical trials.

Specifically, researchers used Karikó and Weissman’s discovery to synthesise COVID-19 mRNA vaccines which contained the code to the ‘spike’ protein that the virus SARS-CoV-2 uses to enter cells. By delivering these instructions via the COVID-19 mRNA vaccine, our cells could now recognize the virus and learn how to fight it off. Still, despite this approach, the vaccines also needed a transport system that could safely deliver this synthetic mRNA into human cells. Researchers decided to use lipid nanoparticles, developed in part by Dr. Pieter Cullis’ laboratory at the University of British Columbia. Essentially, these are tiny protective bubbles of fat, which protect the mRNA and deliver it into target cells. Together, Karikó and Weissman’s discovery, and Cullis’ lipid nanoparticles, meant that researchers were able to quickly develop safe and effective COVID-19 mRNA vaccines.

To say that the COVID-19 mRNA vaccines were ground-breaking is an understatement. The first COVID-19 mRNA vaccine, outside of a clinical trial, was administered in December 2020. This lightning speed was only possible thanks to the many earlier decades of research into mRNA. Almost two years later, over 700 million doses of the COVID-19 mRNA vaccines have been administered. These mRNA vaccines have changed the course of the pandemic, decreasing the likelihood of serious illness, hospitalization, and death.

“I never imagined a pandemic like this,” says Weissman. “I had thought [our research] would probably have been used in a vaccine, maybe during a pandemic, but more likely in an influenza [outbreak], like the one we had in 2009. The COVID-19 pandemic was unprecedented.”

In recognition of their extraordinary impact, Karikó and Weissman were awarded a Canada Gairdner International Award in 2022. Their pioneering work in developing modified mRNA – one of the foundational technologies necessary for developing safe and effective COVID-19 mRNA vaccines – continues to have far-reaching impacts today.

As a young child, Weissman would take everything apart, from doorknobs to toasters. “I wanted to see how things worked,” said Weissman, reflecting on his childhood. “For a youngster thinking about science, I think the important things are creativity and curiosity.”

Now, Weissman’s lab is working on over 20 other vaccines for various diseases, from malaria, tuberculosis to HIV. Several of these vaccine candidates are in human clinical trials. Weissman is also deeply focused on ensuring that everyone, not just those living in wealthier countries, have access.
to mRNA vaccines. He is working with several countries, including Thailand, Rwanda, and South Africa, to develop and test affordable COVID vaccines.

“The idea was that we wanted local production of vaccine, so you’d have local delivery,” says Weissman. “That means both making the vaccine there, but also having the scientists there who design the vaccine, and the next vaccine after COVID.”

“I’m happy back in my lab, working,” adds Weissman, noting that the attention from his research has taken some time to get used to. The attention has ranged from requests for autographs from strangers on the street, and sadly, death threats too.

Karikó is now a senior vice president at the pharmaceutical company BioNTech. She uses interviews as an opportunity to showcase scientists in the public sphere, speak about the importance of vaccines, and encourage the next generation of scientists to be confident and believe in themselves.

“You have to believe,” says Karikó, and refers to how she, as a butcher’s daughter in Hungary, ended up at an Ivy League school. “You have to believe, no matter where you come from.”

This scientific story is an excellent example of how much work and time is involved in making scientific discoveries. People tend to think the science of COVID mRNA vaccines was rushed, but in reality, several decades of research was necessary to get to the finished line!