Announcer: Welcome to Medical Breakthroughs from Penn Medicine, advancing medicine through precision diagnostics and novel therapies. Here's your host, Dr. Charles Turck.

Dr. Turck: While messenger RNA or mRNA is nothing new, using it to provoke an immune response in order to combat COVID-19 is a novel strategy. So, today, we'll be exploring the nuances, benefits and safety of mRNA vaccine technology and tackling the coronavirus.

Welcome to Medical Breakthroughs from Penn Medicine on ReachMD. I'm Dr. Charles Turck and joining me to discuss COVID-19 vaccine technology is Dr. Drew Weissman, Professor of Medicine at Penn Medicine. Dr. Weissman, welcome to the program.

Dr. Weissman: Thank you, very much.

Dr. Turck: Now, Dr. Weissman, let's dive right in. Would you explain mRNA technology for us? Did you ever think that your research in that area would be leading the charge against a global pandemic?

Dr. Weissman: So, let me start with what RNA is: our genome, our DNA contains all of the proteins and all of the instructions that makes our cells grow and makes us live. In order to get those instructions into a protein production, they cell uses an RNA. And what the RNA does is it makes a copy of the sequence of the protein in the DNA. That's then read by a machine that produces the protein. So, the mRNA technology is kind of the middleman. When you deliver it to a cell, it immediately is read by those machines and produces protein. In the case of COVID, that protein is put on the surface of a cell and the immune system recognizes it as foreign and makes a response against it. Katie Kariko and I started studying mRNA over 20 years ago. We had discovered nucleoside-modified mRNA, that's the form of RNA that's used in both the Moderna and Pfizer vaccines. And what's different about it is that RNA therapeutics didn't go anywhere because the RNA was so inflammatory, it made animals sick when you injected it. Katie and I developed modified RNA that doesn't induce an inflammatory response and that made it much safer and much better for a vaccine.

Dr. Turck: And digging a bit deeper here, Dr. Weissman, what is the relationship between mRNA and the immune system?

Dr. Weissman: There's quite a few. RNA has been studied as a vaccine for almost 30 years and in many different formats. The one that we're using and along with Moderna and Pfizer was developed about 7 years ago, we started to investigate RNA vaccines and there's a lot of important characteristics. So, the first is that the RNA is modified to get rid of the inflammation. It's also highly purified to get rid of contaminants that could interfere. It's then put into what's called a lipid nanoparticle; it's essentially a fat droplet that both protects the RNA, but most importantly, gives an adjuvant activity, so an adjuvant helps stimulate an immune response in a vaccine. But it's a highly specialized adjuvant. It specifically drives antibody production and that's why we see such high levels of antibody produced by this vaccine.

Dr. Turck: I'd like to talk about another facet of vaccine technology how is an RNA-based vaccine different than, let's say, the flu vaccine?

Dr. Weissman: Most flu vaccines are inactivated viruses. So, what that means is that they take the flu virus, they grow it up in eggs and then inactivate it with a chemical. What that does is it presents the body the virus, so the entire virus, but the virus is not infectious. The immune system responds to all of the proteins in that virus. With RNA, we're only giving a single protein, the spike protein from COVID, so there's no chance of getting an infection from the RNA vaccine because it's one out of

hundreds of proteins that could be present in the virus. The RNA also has better adjuvant activity and for the most part, is superior to most inactivated vaccines.

Dr. Turck: For those just tuning in, you're listening to Medical Breakthroughs from Penn Medicine on ReachMD. I'm Dr. Charles Turck and I'm speaking with Dr. Drew Weissman about using mRNA vaccine technology to combat COVID-19. Dr. Weissman, what would you say to those who may question the safety and efficacy of this vaccine technology?

Dr. Weissman: I understand why they're nervous. They've never heard of this vaccine platform before and 11 months ago, it was first being developed for COVID-19. The reason why people haven't heard about it is because it's been in research hands up until then. But it's been studied for over 8 years, clinical trials, so actually giving similar vaccines to people have been going on for over 5 years, so this isn't brand new technology. It's well-established, well-understood technology. The big difference is, we had a pandemic emergency, and this platform allows for rapid development and that's what happened.

Dr. Turck: And as we now know, there are new variants of the SARS-CoV-2 virus spreading rapidly how will that impact both the vaccines that have already been rolled out worldwide and vaccines currently in development?

Dr. Weissman: So the new variants are an enormous concern to everybody. And what you hear about all of these variants are that they spread better. That means the virus is learning how to infect people better. The concern is that any changes that occur might make vaccines not work as well. That's only really been a concern with the South African strain that has shown a reduction in neutralizing, so ability to protect against that virus with current vaccines. With the RNA vaccine, it's easy to fix, and both Moderna and Pfizer are currently working on this. You simply have to put the new variants into the RNA vaccine and you'll likely, or very likely, get coverage of the new variants. In the long term it's really, as long as we haven't vaccinated the world, new variants are going to keep appearing and we're always going to have to worry, ‘Are one of these new variants not sensitive to a vaccine?'. So, the faster we can vaccinate the world, the sooner we get rid of these variants popping up.

Dr. Turck: Finally, Dr. Weissman, looking ahead to the next 15 years, what other therapeutic avenues do you foresee for mRNA technology?

Dr. Weissman: So, my lab has been working on modified RNA for 15 years. We have many new therapeutics that we're developing. We have over 30 different vaccines in animal studies; 5 of them are going into human clinical trials, soon. We also have other therapies. We're delivering monoclonal antibodies with mRNA. We're also modifying and editing the genome with RNA, and we're doing that by encoding enzymes that allow gene editing; mRNA itself in the vaccine does not change DNA, doesn't alter DNA. But by using tricks to encode proteins that edit DNA, we're hoping to be able to cure diseases like sickle-cell anemia, immune deficiencies, and others with a single injection of RNA LNPs.

Dr. Turck: Thank you, so much for providing some great perspective on the future of mRNA technology. And with that in mind I want to thank my guest, Dr. Weissman for joining me to discuss mRNA vaccine technology and fighting COVID-19. Dr. Weissman, it was great having you on the program.

Dr. Weissman: Thank you, very much.

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