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Current & Future Directions of mRNA Medicine

Announcer:
You're listening to *Innovations in Medicine* on ReachMD, sponsored by Moderna. Here's your host, Dr. John Russell.

Dr. Russell:
I'm Dr. John Russell, and joining me today to discuss the current and future directions of mRNA medicine is Dr. John Cooke. He's the chair of the Department of Cardiovascular Sciences at the Houston Methodist Research Institute. He's also the Director of the Center for Cardiovascular Regeneration, and Medical Director of the RNA Therapeutics Program in the Houston Methodist DeBakey Heart and Vascular Center.

Dr. Russell:
Dr. Cooke, thanks for being here today.

Dr. Cooke:
My pleasure, Dr. Russell. Thanks for having me on the program.

Dr. Russell:
So certainly over the last two and a half years, we've probably discussed mRNA more than we have, kind of in the history of the planet. So, it's been a very exciting time for mRNA technology. Dr. Cooke, how did we get here?

Dr. Cooke:
You know, there is the idea that this is something that's happened just recently, but message RNA was discovered in the 1960s, and since then, over the ensuing years, RNA was shown to be transcribed in the nucleus. It was transported into the cytoplasm, translated into protein by ribosomes. And then in the 90s it was recognized that one could transfect RNA into cells and the cells would make the protein encoded by that message RNA. So, the idea became current that maybe we could make therapeutic proteins by transfecting cells with message RNA. So, the early attempts at that came across two major hurdles. One is that message RNA is very fragile, and it's susceptible to cleavage in water. It's rapidly broken down by enzymes called nucleases, and those enzymes are everywhere in the environment and in the body.

In fact, when we're working with RNA, we have to be very careful. Our nucleases are on our fingertips, they're in the environment, and the RNA can be broken down very rapidly. The other problem is that it was noticed that the RNA had some toxicity, and cells recognized that foreign RNA that scientists were using to try to express a certain protein, and the cells would react against that. So, those hurdles, those problems, those challenges had to be overcome, for RNA therapeutics to get to the point we're at right now.

Dr. Russell:
So fast forwarding to today, and certainly we know about it in the vaccine space, but where are we now in the vaccine space and beyond?

Dr. Cooke:
So those problems had to be solved first John, and one of the solutions to RNA being fragile was the lipid nanoparticles. The lipid nanoparticles are like little bubbles of oil that can contain the RNA and protect it from water, where it gets cleaved, can protect it from the nucleases, where it gets destroyed, and the lipid nanoparticles also are useful for getting the RNA into the cell. So those little bubbles of oil they'll be absorbed by the cell, the cytoplasmic membrane, get absorbed into the cell and deliver the RNA into the cytoplasm, where it can get translated into protein. So that solved one of the big problems, actually two of the problems was delivery and the fragility of the RNA was solved by lipid nanoparticles. The other problem was solved, was the toxicity, because our cells recognize

foreign RNA, and that's a defense against viral RNA. It was recognized by Katalin Karikó and Drew Weissman and they published their work in the early 2000s, that mammalian RNA actually has some differences from viral RNA, and contains these modified nucleosides, John, that mark that RNA as self. So what Katalin Karikó noted was that if she used pseudouridine, which is a modified base and 5-Methylcytosine and other modifications could make the RNA better tolerated by cells. Cells now recognized that RNA as being self. It didn't stimulate excessive inflammatory signaling. So that made those two developments really made RNA therapeutics possible.

Dr. Russell:
So we had Dr. Karikó and Dr. Weissman on an earlier version of this show, so it's great to give them their props. We're picking up with them, where did it go from there?

Dr. Cooke:
Okay, so now it was shown that we could deliver RNA and it could have a therapeutic effect, so, the that led to firstly, the development of vaccine strategies. A number of vaccine approaches started to be utilized for various pathogens and for infectious diseases, and that kind of prepared the way. Those early trials prepared the way for the SARS-CoV-2 vaccine. The mRNA vaccines were, as everyone knows, were very effective in treating that virus. So, there's some new developments coming down the pike that are going to make RNA vaccines, and RNA therapeutics, even more effective. I'm very excited about the developments to make RNA more stable. RNA right now, the message RNA, only lasts for minutes to hours within a cell, then the protein that's made can, of course, last for longer periods of time, but RNA is not that stable. So there are some new developments around circular RNA, John, these circular RNAs are less susceptible to getting broken down by exonucleases, which kind of attack the RNA from both ends, like Pac-Man. Circular RNA doesn't have those ends, so it's more stable. Another one that is exciting is the self-amplifying RNA. So these are RNA molecules that can reproduce themselves, to a certain extent, and therefore you can give less of the RNA. It doesn't take as much RNA to get the desired effect.

Dr. Russell:
For those just tuning in, you're listening to ReachMD. I'm Dr. John Russell, and today I have the pleasure of speaking with Dr. John Cooke about mRNA technology.

So, you really set the stage for a lot of exciting things, John. So, with this understanding, and you work at the Cardiac Regeneration Center, where is this going in therapeutics beyond vaccines?

Dr. Cooke:
That's a great question. I think John, that the opportunities for RNA therapeutics are almost limitless, and I think that they can have applications for every specialty, for applications for every disease indication potentially. We're here in the Texas Medical Center, and our center for RNA therapeutics is kind of at the bottom of a funnel in a good way, because we, are helping academic groups and we're helping small companies to design and synthesize, encapsulate their RNA therapies to test them. We have RNA biologists here. We have RNA innovators. We have clean rooms. We can make clinical-grade RNA. We're really unique in that we are an academic group driven with corporate discipline to help people with great ideas translate those ideas into RNA therapeutics. So we're seeing a lot of interesting things come through our door, and I could tell you John, applications for almost every indication you can imagine. But, you know, you mentioned vaccines, and of course vaccines are still the major target, and, we have vaccines for multiple pathogens that we're seeing. TB, Chagas disease major cause of heart failure in South America. Bad news, it's moving north into Texas and southern states, because of global warming, and, so we need to have a defense for that.

Dr. Russell:
What are some of these other diseases, where this technology beyond the cardiac space, so, maybe it can kind of help with your folks, but how about broadening it to the whole palette of Texas or Pennsylvania, or the whole U.S.?

Dr. Cooke:
With respect to that, John, so there are deficiencies, there are pediatric illnesses that are due to enzymatic deficiencies, and there's a number of RNA therapeutics that are being developed for children with those deficiencies of metabolism, and, we're actually working on one interesting project for a pediatric illness, progeria. So progeria, of course you know, is that disease of accelerated aging, and, one of the things that we've done is to show that the cells from these children can be rejuvenated with message RNA encoding telomerase. So we can actually express the telomerase protein in the cells from these children, and we've shown basically we can almost normalize their proliferative capacity and their function with RNA telomerase. So, that therapeutic could also be used to improve cell therapies. And that's another indication for RNA: improving cell therapies. I mentioned earlier, the chimeric antigen receptor T-cell therapies could potentially be improved with RNA approaches.

Dr. Russell:
So Dr. Cooke, really all this stuff we talked about, it really feels like the medical equivalent of the moon landing. How do you think we're

going to look back on this, ten years? What do you think's going to happen in the use of this technology over the next ten years?

Dr. Cooke:
You know, John, I think that the future, the promise of RNA therapeutics is almost limitless, and we've been focusing on message RNA, and of course, I just should mention interference RNA at methods to reduce message RNA expression is another therapeutic arena. We've been focused on message RNA today, but its future is almost limitless, I believe, because if we can deliver it to where it is needed, if we can make the message RNA last as long as we need it then I think there are almost no indications that message RNA won't be useful for. Those hurdles are being overcome. There's RNA methodology to make RNA last longer. There's RNA methodologies to get RNA to where it is needed, and that's going to make the technology much more applicable to other indications. I think RNA is also going to be personalized. Message RNA therapeutics can be personalized much easier than small molecules or recombinant proteins, because it's essentially biological software, and we can change the code as needed. I'll give you an example. Patient comes into the hospital with a tumor. The tumor's removed. Tumor can be sequenced. You can look for proteins that are specific to that tumor that are expressed on the surface of that tumor that you can design a vaccine against. Now you've got a personalized vaccine for that patient. I think hospital-based therapeutics are going to be possible because it doesn't take a lot of manpower or room to generate therapeutic RNA. You need GMP space, you need clean rooms you need the processes, the equipment and with a small amount of space, you can actually generate those personalized therapeutics for your hospital patients. So, I think the future's almost limitless. I think it's going to really change the way we practice medicine.

Dr. Russell:
Well, with those forward-looking thoughts in mind, I'd like to thank Dr. John Cooke for joining me today to share his insights on mRNA technology. Dr. Cooke, it was great speaking with you today.

Dr. Cooke:
Thanks, Dr. Russell. Pleasure to be on your show.

Announcer:
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