Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/innovations-in-medicine/a-review-of-regenerative-medicine-future-mrna-applications/14008/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Review of Regenerative Medicine & Future mRNA Applications

Announcer:
Welcome to *Innovations in Medicine,* sponsored by Moderna. This is a non-certified educational series produced and controlled by ReachMD and is intended for healthcare professionals only. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to Innovations in Medicine on ReachMD. I'm Dr. Charles Turck, and joining me today to explore the potential of mRNA therapeutics in regenerative medicine is Dr. John Cooke, who's 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. Cooke, welcome to the program.

Dr. Cooke:
Thank you, Dr. Turck. Thanks for having me on the show.

Dr. Turck:
Well, to start us off, Dr. Cooke, what can you tell us about the potential utility of mRNA therapeutics and regenerative medicine?

Dr. Cooke:
Well, it's very exciting, Dr. Turck. And I believe that the potential for RNA therapeutics is almost limitless. Because RNA is essentially biological software. If you're developing a therapeutic, you can simply write the code for that. RNA is a code that encodes proteins, one can encode a therapeutic protein rather quickly. And that flexibility, that speed was shown to us very starkly in the pandemic when, in January of 2020, the sequence of the SARS-CoV-2 was first published by Chinese scientists, within just a few days Moderna and Pfizer-BioNTech had developed a vaccine in principle, and written the code for a vaccine. And that led quickly to clinical trials within a few months of developing that RNA construct. So the lightning speed of RNA therapeutics is something new to medicine. And I believe it's going to cause a therapeutic revolution in many areas, including regenerative medicine.

Dr. Turck:
So with that in mind, let's dive into some of the specifics. Given what we know about mRNA therapeutics, how do you think they'll impact tissue engineering and targeted tissue restoration?

Dr. Cooke:
That's a great question. I do think mRNA therapeutics can solve some significant problems that we have in tissue engineering and in targeted tissue restoration. And for example, one of the problems with targeted tissue restoration is restoring the vasculature that supplies the organ. If you don't have a vasculature, if you don't have the conduit vessels, if you don't have the microvasculature, the tissue won't survive. So that has been a problem that's plagued tissue engineering and tissue restoration.

And one of the approaches to that is to encourage vascular growth in the tissue that you're trying to regenerate. And a good example of that is a trial of vascular endothelial growth factor mRNA currently underway, and this is a Moderna and AstraZeneca trial. EPICURE results were presented about nine months ago. The EPICURE trial is a trial of VEGF mRNA in patients undergoing coronary artery bypass grafting. Now, when we do a coronary artery bypass graft, we try to fully revascularize the heart, but often that just can't be done and there are some areas of the heart that are still not getting sufficient blood supply. So in this trial, at the time of coronary artery bypass grafting the surgeons injected areas of the heart directly, the myocardium directly with VEGF mRNA. mRNA encoding vascular endothelial growth factor 30 injections directly into the heart. Now, vascular endothelial growth factor is the most potent angiogenic factor we know, meaning it stimulates the microvasculature to grow. And so, the idea was revascularize the heart as much as one can

do, bypassing the narrowings in the coronary blood vessels, and then enhance the growth of the micro vasculature. So the results of the phase 2A trial were reported out recently. And in that trial, there was an improvement in the left ventricular ejection fraction and other indicators of benefits, walking distance on a treadmill, for example, and BNP levels, which are markers of heart failure those went down. So, it looks promising. And that is potentially an example of how we might improve tissue restoration with targeted delivery of message RNA.

Dr. Turck:
Now, how about in the area of cellular reprogramming, what kind of a role might mRNA therapeutics have there?

Dr. Cooke:
I think that's also a great question, because I think RNA therapeutics may have a particularly useful role in reprogramming. First of all, what is cellular reprogramming? It's basically inducing a cell-fate transition. So the Nobel Prize was awarded in 2012 to Shinya Yamanaka and John Gurdon for their work in this area. Shinya Yamanaka, in particular, had shown us that you can reprogram a fibroblast, basically a scar cell, a fibroblast, it can be reprogrammed to an induced pluripotent stem cell, an IPSC, by overexpressing four transcriptional factors. So these transcriptional factors are proteins that activate the transcriptional proteins that activate genes that are required in this case for pluripotency. So the four factors he found that were sufficient to induce pluripotency were Oct4, Sox2, Klf4, and c-Myc. These are transcriptional proteins that turn on a cascade of genes that are required for pluripotency. So overexpressing those genes in a fibroblast would, over a period of time, few weeks, turn that fibroblast into an induced pluripotent stem cell. And what that is a cell that is like an embryonic stem cell, it can become any other cell type given the right direction.

So IPSC has galvanized the field of regenerative medicine, because now we could generate these IPSCs and differentiate them into any other cell type for regenerative medicine, or for other purposes. And what they're actually being used for most is to understand pathophysiology. So you can take a fibroblast from a person that has a particular disease. We're doing this with progeria children, and, we can generate an IPSC from their skin fibroblasts. And now we have that IPSC, we can differentiate that into any other cell to understand the pathophysiology of the disease. So that's been very useful and mRNA can be used for this purpose. We've successfully made IPSCs using mRNA encoding those four factors I just mentioned. So that's a way in which RNA therapeutics can help this field of regenerative medicine.

Dr. Turck:
For those just tuning in, you're listening to *Innovations in Medicine* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. John Cooke about mRNA therapeutics and regenerative medicine.

What are some of the clinical hurdles we need to overcome to make mRNA-based regenerative therapy a reality?

Dr. Cooke:
Well, Dr. Turck, there are still some things that must be done to make messenger RNA therapeutics widely applicable. There is still a stability issue. RNA, I mean, it’s a blessing and a curse. Because RNA only lasts minutes to hours, it is designed to fall apart. And that is because cells make these messages. They're just transient copies of the DNA. They're like pages out of the recipe book. And when you have a recipe to make you need that page that RNA is transcribed into protein. But once you've transcribed the RNA into protein, you don't really need the RNA to stick around very much longer, you can use those nucleotides for something else. And so the RNA is degraded fairly rapidly after the protein is made. So on the other hand, if you're trying to make a therapeutic RNA, you would like it to stick around, perhaps, if for some indications, you'd like it to stick around a little bit longer.

So, that issue is being addressed. We and others have developed methods to enhance the stability of the RNA. There’s something called circular RNA. It doesn't have an end. So linear messenger RNA, standard messenger RNA that were used in the vaccines, they get broken down from either end by these exonucleases, three prime and five prime exonucleases that eat up the RNA like Pac-Man from the ends, just gobble it up. Well, the circular RNA doesn't have an end, so those exonucleases don't have a way to purchase. You get gain purchase on the RNA, they don’t have a way to break it down. So the circular RNA lasts longer. So that's one potential solution.

Another problem with RNA is our cells are designed to keep foreign RNA out. So therapeutic RNA is essentially foreign RNA. We're trying to get that foreign RNA into a cell to change the cell in some way to provide this therapeutic protein. And the cells will resist exogenous RNA. Some things have been learned. So we’ve learned that viral RNA is very different from mammalian RNA. Drew Weissman and Katalin Karikó found that modification of the nucleosides are important for the RNA to be recognized as self, and that made therapeutic RNA possible. So they are potential candidates for the Nobel Prize for that discovery.

Another problem is delivery, because currently the vaccines are delivered in lipid nanoparticles. And that works fine for a vaccine, but if you're trying to deliver those lipid nanoparticles systemically, they end up mainly in the liver. The liver is very good at gobbling up lipid nanoparticles. So, we need better methods for delivery so that we can deliver to organs other than the liver. And preferential tissue

delivery is going to be something very important for the field to develop. And I think that we'll beat that problem at some point.

Dr. Turck:
Before we close, Dr. Cooke, do you have any final thoughts or takeaways you'd like to share with our audience?

Dr. Cooke:
Well, this is an exciting field. And if you're a physician, or a pharmacologist, or a nurse, if you're in an allied health field, you want to keep an eye on this field because it is going to change the way we practice medicine. If you're a young physician, just starting out, young scientist, young allied health professional, you might want to get into this area. There's going to be a lot of opportunities for people to get into RNA therapeutics either at the scientific level or the clinical level. And I just think it's going to be a lot of fun to see this field grow and see new therapies for our patients and see how this field revolutionizes the way we take care of patients.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank Dr. John Cooke for joining us to share his perspective on the potential of mRNA therapeutics in regenerative medicine. Dr. Cooke, it was great speaking with you today.

Dr. Cooke:
Likewise, thank you Dr. Turck.

Announcer:
This episode of *Innovations in Medicine* was sponsored by Moderna. This is a non-certified educational series produced and controlled by ReachMD and is intended for healthcare professionals only. To access this and other episodes inthis series, visit ReachMD.com/Innovations in Medicine, where you can Be Part of the Knowledge. Thanks for listening!