Speaker 1:

Welcome to the Eye On The Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome everyone, to another episode of the Eye On The Cure Podcast. I am Ben Shaberman, Senior Director of Scientific Outreach at the Foundation Fighting Blindness, and very happy you could join us, and I'm very excited to have with us today, Dr. Naveed Shams. He is the chief scientific officer at the company ProQR in The Netherlands, and ProQR has currently three clinical trials underway for emerging therapies in the retinal disease space. He'll be talking about those in a moment, but to get us started, welcome, Dr. Shams. Glad you could join us, and can you tell us a little bit about your role at ProQR?

Naveed Shams:

Oh, thank you, Ben. Appreciate the invitation, and I'm delighted to be part of this conversation today. As you mentioned, I'm the chief science officer for ProQR. I joined ProQR about a year ago, to help lead the early development of our products, and by early development, what I mean is that my group establishes the proof of concept, the proof of principle in man before we spend the big bucks and do a confirmatory study, which in our jargon means a product registration study. I also, and my group is responsible for the early nonclinical or lab-based testing of compounds, and translating it into those early studies in man. So basically, at the end of the day, I have to, and my teams have to establish the proof of concept for a disease or for a product.

Ben Shaberman:

That's great. Thanks for sharing that. That's obviously very important work. So now, ProQR is in the business of developing what we call RNA therapies, and in the cells in our bodies, we have DNA, but we also have RNA. I was wondering if you can help our listeners understand what RNA messages are, and contrast that to DNA.

Naveed Shams:

Absolutely. I think the DNA, most people are familiar with it, both in the common jargon and common lingo as we speak. "It's in your DNA," for example. Basically, what that means is that everybody, all living cells, have a code by which the cell, or the basic unit of life, is engineered. So the DNA carries a blueprint of what a cell, or the lowest common denominator, in that case, is going to turn out to be. For the DNA to actually do that, what it needs to do, what it needs to accomplish, is produce proteins. So at the end of the day, whatever codes we have is going to produce proteins. Proteins are the building blocks of life, and they are the ones that conduct the daily activities that help us survive, and fight disease, and grow, and things like that.

However, DNA cannot simply be translated into these proteins, and there is a step in-between, which is called a RNA. The DNA is translated into a message. That message is called RNA. In other words, most commonly referred to as messenger RNA. You might have heard of it these days with the vaccines that have been for COVID, that have been sort of injected into millions of people. We at ProQR, are interested in RNA, and how we can leverage RNA, or this message, to fix disease, or to address the biology of disease.

The difference between DNA is that DNA, in general, has... It's made up of a sugar, which is called deoxyribose, whereas an RNA has a similar sugar, but it's called ribose. It also has what we call bases,

that have conferred the message to it, or the code from the DNA and also the RNA. There are four bases in RNA, and they are different than... Two of them are different, actually, than DNA. DNA has four bases called thymine, adenine, cytosine, and guanine, but in the RNA, we have adenine and guanine, but instead of, sorry, thymine, we have uracil, and that's a key difference between the chemistry of RNA and the chemistry of DNA. The location is also different. DNA is in what we call, in the nucleus, and a little bit of the DNA can also be found in what we call mitochondria, but RNA is located in the cytoplasm, which is outside the nucleus.

Also, the function, as I mentioned, is a little different. RNA is used to transfer the genetic code, or translate the genetic code, to make proteins. That's the middle step, and that's how it differs from DNA. Usually, RNA is also very unstable, and a single sort of nucleotide. But those are some differences between DNA and RNA.

Ben Shaberman:

Great. That's a really great explanation, and thorough. So basically, DNA is the code, at least this is the way I explain it. DNA is the code and RNA are the messages that are derived from that code, and it's RNA that the cell reads to create the proteins that are so important for cell [inaudible 00:07:16]

Naveed Shams:

That is correct.

Ben Shaberman:

Got it. Thank you.

Naveed Shams:

Yes.

Ben Shaberman:

I think many of our listeners are going to be familiar with gene therapies, which are focused on replacing, in most cases or many cases, DNA, but with RNA therapies, the ones that ProQR is developing, the approach is a little different. Can you talk about how these RNA therapies work?

Naveed Shams:

Yes, indeed. As you can imagine now, you have a code in the DNA. If you know that there is a defect in the code, and that is generating a defective protein, then it also must generate a defective RNA for it to be translated into the defective proteins. So you have two ways of handling this situation. One is of course, as you mentioned, you can go and remove a piece of the DNA that is defective, with techniques that are growing by on a logarithmic scale it appears these days. You can do that, or you can wait for the next step, which is the message that the cell has produced, which will also be defective, and we can do the same thing. We can edit the RNA, and fix the message. Technically, there are two different sort of hurdles, and the fixing the DNA is, for lack of a better word, is more complicated, and could have long-lasting impact. If it works, great. If it doesn't work, it will not be good. Whereas the message can be manipulated easily and much more conveniently, and it doesn't touch the code that is built into everybody's DNA. So we have a little bit of more safely fixing the protein as compared to fixing the DNA. So pretty much what you can do with DNA, we can do with RNA, and the goal is the same, which is to produce a good protein at the end of the day.

Ben Shaberman:

Right, right. Thanks for that explanation. And just to clarify our understanding, with gene therapies or DNA therapies, those are usually one-time treatments, and if they work, great. If they don't, then that could be not such a great thing. But with RNA [inaudible 00:09:45] those are applied... I think in your clinical trials, they're applied about every six months or so, if I recall.

Naveed Shams:

Yes.

Ben Shaberman:

And if it's not working or it's causing problems, then you just don't retreat the patient. So that, I-

Naveed Shams:

That is correct, yes.

Ben Shaberman:

That [inaudible 00:10:06]

Naveed Shams:

That is a distinct advantage.

Ben Shaberman:

Right, right.

Naveed Shams:

That is a distinct advantage of the RNA-based therapies, yes.

Ben Shaberman:

Right.

Naveed Shams:

At least the way we are deploying them at ProQR.

Ben Shaberman:

Right. So, you have, as I said at the beginning of our podcast, you have three trials underway, which is very impressive, one for a pretty common mutation in the gene CEP290, which that mutation causes LCA, mutations in the exon 13 region of the USH2A gene, and that can cause either Usher syndrome type 2A or nonsyndromic RP, and then you're addressing a pretty common mutation called P23H in the rhodopsin gene, that leads to retinitis pigmentosa.

Naveed Shams:

Correct.

Ben Shaberman:

So again, it's wonderful that there are three trials underway. Can you just give us a quick review of the progress in those three trials?

Naveed Shams:
Yes. Indeed, yes. Our most advanced program is in the condition called Leber's congenital amaurosis, or LCA, as you said. That program has several studies currently underway. The main study, which will become the basis for approval of the product, is running very well. It is fully enrolled, and we are expecting data, this is public information, sometime early next year. And that would then, based on that data, we would make an application for approval of the drug in the US, and Europe, and elsewhere. So that program is on track, and we are very, very excited about it. It will be our first product, and based on phase two data that we have, we saw a year, or maybe a little bit earlier than a year ago, gives us confidence that we will see efficacy with this product.

Ben Shaberman:

Right. In the-

Naveed Shams:

The second-

Ben Shaberman:

In the phase two, you had some pretty significant vision improvements for the recipients, if I recall.

Naveed Shams:

Yes.

Ben Shaberman:

Right.

Naveed Shams:

Yes, and that's why we feel that there's a good chance that this pivotal study is going to show good outcomes.

Ben Shaberman:

Right.

Naveed Shams:

The second trial you mentioned is in the Usher's disease, or Usher syndrome, specifically what's called type 2 Usher's syndrome. In these patients, you can have hearing defect as well as a vision problem, and we are trying to deal with the vision problem. That program, we released quite a bit of information just a few months ago, and again saw some very good signals that encouraged us to plan for two phase three trials. We are committed to actually launching these two studies, one focusing on vision or what we call corrected vision as an endpoint, and the other one focusing on visual field, which is such an important part of the disease in Usher's, which is the visual field. So we are planning, we are committed

to starting those trials by the end of this year, December of 2021, and they are going to last a couple of years, because of the nature of the diseases, that it moves a lot slowly than the LCA10 disease.

We are also excited about starting these two new programs. [inaudible 00:14:04] for quite a while, and we hope that we will have another messenger RNA-based oligonucleotide-based therapy for a very, very important disease where the need is huge, as with all the other rare diseases. So that's the status of Usher syndrome for ProQR.

The third one, as you mentioned, is autosomal-dominant retinitis pigmentosa, and just a minor sort of correction. This disease is mainly sort of expressed or present in the US. It's not as common as Usher's, or Usher syndrome, and therefore, there are challenges of its own in this population. It is also, you're looking for a very unique mutation called P23H. There are other mutations, as you know, that may exist outside the US, but this mutation is prevalent in the US.

We have a phase one study that is currently running, with about 11 patients in the study, and we are testing different doses, starting with 75 micrograms, or going all the way to 600 micrograms. It is an intraocular injection like the rest of it, putting the drug where the disease is, and based on the outcome of this trial, we really want to make sure it is safe, because it is the first time we are putting this sequence of oligonucleotides in the eye, that it is safe. Then, we will look at the data, and then decide what next study would look like. It's going well. It's fully recruited. It's a 12-month study, so not all patients have completed the trial. Some have, and some haven't, so we are waiting for that, and hopefully, we'll be able to make some decisions. Hopefully, it will be as good or going in the same direction as the other two programs.

I will also mention that there's one more program that we have initiated. It's in the front of the eye, actually, which is different than everything else, but this is a disclosed program, using the same approach. It is oligonucleotides and RNA. This is a disease called Fuchs' corneal dystrophy. We have just started the study, the first study in man, trying to confirm what we call the molecular mechanism of the disease, trying to make sure that our drug is going to be engaging the right receptor. So that's a little bitty different, I must say, but it's also a very exciting program for us. It sort of diversifies the use of our product and our platform. So we'll see how that plays out, but it's too early to say anything about it. But these three other programs are running quite well.

Ben Shaberman:

That's great. A lot of promising activity at ProQR. And just to summarize, both the LCA, the CEP290, and the USH2A therapies are in... Or well, the USH2A therapy is moving toward phase two/three. The LCA trial is in phase two/three. And those would be hopefully the last phases, and if they're successful, you would hopefully be able to seek regulatory approval. I wanted to note that-

Naveed Shams:

[inaudible 00:17:44]

Ben Shaberman:

... the Foundation Fighting Blindness is investing seven million euros in the USH2A product, through our defund, our venture philanthropy fund, so we're very excited about the promising early results from there. And if people want to learn more about these therapies, if you visit fightingblindness.org, there are articles on all three therapies, and if you're interested in the trials, you can also go to clinicaltrials.gov, and learn more about these trials, the inclusion and exclusion criteria, the sites,

because they're ongoing in the US, and potentially in Europe. So, check out clinicaltrials.gov if you're interested. I just had one last-

Naveed Shams:

Ben?

Ben Shaberman:

... question, to help our listeners understand a little more about RNA therapies. My understanding is that in RNA therapy, what you're injecting into the eye are these tiny pieces of genetic material. Can you tell us how that genetic material works to address the mutation in the RNA?

Naveed Shams:

Definitely. Before I answer that, can I-

Ben Shaberman:

Sure.

Naveed Shams:

... take just a second to actually thank Foundation Fighting Blindness for their very generous support of the USH2 program. We could not have been at this point without your support, guaranteed. So we've had a very good relationship and partnership, and we hope we are going to be successful. So thanks to all the patrons of Foundation Fighting Blindness and the team at Foundation Fighting Blindness. It's been a tremendous impact on our program, so yep, if it works, it'll be because you guys helped us out.

Ben Shaberman:

Well, thank you.

Naveed Shams:

So many, many thanks for that. Yes, so there are... I think there is one maybe clarification required. There are many kinds of RNA. There are many structural differences between these RNAs, which means the way these RNAs are made is very different. What you can actually have, what's called a messenger RNA, which is a synthetic piece of RNA, that carries a message, that can then be translated. That's what people use to treat COVID, or that's the vaccination for COVID.

In our case, we are trying to fix a problem in the RNA itself. That's how different these two things are. So therefore, we sequence the RNA, or we find out where the problem is, and then we design an approach to fix that piece of the RNA. There are several things that we can do. For example, we can stitch over the pieces of RNA, like these nucleotides. We could call that splicing, you know? So if you find two ends of a bad zone, you can skip the bad zone and splice the good area, so that now you can produce a god protein, albeit it may be a slightly shorter protein, but it'll be functional. So that's one way we do things. That's the approach we are taking with one of our products, in this case, let's say the USH2 program, the USH gene on chromosome 13. So that's one approach.

The other approach is you can simply synthesize a complementary piece, which then binds to the bad portion of the RNA, that may not be functioning, and just inactivate it, so that you don't have to make a bad protein, which may be causing problems, especially in what's called a recessive disease, where you

can remove part of it, and then the other good protein that is being made by the other gene... As you know, we all have two copies, and so we can change the balance between the good and the bad. So that's another way of handling it.

So I just described to you three different ways of how RNA can be used, or synthetic RNA can be used. And you're absolutely right. These are small pieces of these nucleotides, go on the inside of, say, your cell. We are focused on fixing the problem rather than using a normal RNA to generate a protein, like people interested in vaccinations do.

Ben Shaberman:

Got it. Thank you for that very thorough, in-depth explanation. We appreciate that. So, Dr. Shams, thanks for all the time you've given us today to talk about RNA, RNA therapies, and the great work of ProQR, your three clinical trials in the retinal disease space. We greatly appreciate your time and the work you're driving for our patients. And I want to remind our listeners, if you have questions, you can send an email to podcast@fightingblindness.org. Any last comments or observations, Dr. Shams?

Naveed Shams:

I would just say the famous quote from somebody, that, "Keep hope alive." We are working very, very hard in partnership with people just like at Foundation Fighting Blindness, to find treatments and cures for these devastating diseases. We are committed to doing something about it. Unfortunately, biology is tough, and it takes a little bit of time to get from here to there. But I am very confident, with all of the progress we have made in the gene therapy space, and the cell therapy space, and the RNA/DNA space, technologies are getting there. We are going to get there sooner rather than later. So your help, everybody's help, is much appreciated, and your patience is also much appreciated. I wish we could do this faster, but it takes time, so I would say keep hope alive. We'll get there.

Ben Shaberman:

Well, thank you, Dr. Shams. Yeah, science, good science, takes a while. It's not a quick and easy thing. But thanks to your trials and these early encouraging results, you are definitely keeping hope alive. So thanks, listeners, for joining us for this episode, and please tune in again for our next episode. And have a great couple of weeks until we join together again. Thanks again, Dr. Shams.

Naveed Shams:

Thank you. Thank you, Ben, and thank you to everybody.

Speaker 1:

This has been Eye On The Cure. To help us win the fight, please donate at foundationfightingblindness.org.