Speaker 3:

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 the Eye on the Cure podcast. I am Ben Shaberman, the host of your podcast and senior director of scientific outreach at the Foundation Fighting Blindness. And today I'm really pleased to have with me Daniel Chung. Daniel is chief medical officer at SparingVision, and his role will be to lead the clinical development and research around an emerging therapy called SPVN06. It's a gene agnostic gene therapy for RP, Usher syndrome, and potentially some other conditions. And Dan will also lead the education of medical and patient communities. And I know, Dan, that's a role you did quite a bit at Spark, the educational side. But just a little background on Dr. Chung. He received his medical degree from the New York College of Osteopathic Medicine in 1994 and undertook extensive postgraduate training at the National Eye Institute, Summa Health Systems and Cole Eye Institute at the Cleveland Clinic Foundation in Cleveland. And I have to ask, I grew up in Cleveland, when were you in Cleveland?

Dr. Daniel Chung:

So that was I believe 2000 to 2000 and... No, let's back up here. I'm getting my dates mixed up. I think that was 2001 to 2003. I did a fellowship at the Cleveland Clinic in pediatric ophthalmology and ocular genetics research. So I was there two years, and it was just really a time where my mentor, Elias Traboulsi, really introduced me to the whole world of inherited retinal diseases. And it was just fascinating. And the need for therapeutics was extremely high, and it was just something that really intrigued me. I had done a retinal gene fellowship at the National Eye Institute prior to my residency and fellowship training, and I think that was just very complimentary of that. And from there on I had the opportunity really to do more work in retinal gene therapy with Jean Bennett and that group at the University of Pennsylvania, and that's really how all this really got started.

Ben Shaberman:

Sure. And we'll talk a little more about Spark in a minute or so. But I'm curious, when you were a kid growing up or maybe a little older in high school or college, did you know you wanted to be in medicine? Did you have an interest in ophthalmology or vision?

Dr. Daniel Chung:

I really liked the idea of ophthalmology because it gave you an opportunity to do fine microsurgery using the microscope and things of that nature. It also gave you an opportunity to develop patient relationships in the clinic, so it's the best of both worlds. And because I had an interest in research, it was just a great springboard into the world of research as well and doing a lot of basic science, translational work, and things of that nature. So the whole package is quite interesting. Now, obviously I didn't know that at the very get go, but as I got more into ophthalmology, that was becoming more and more apparent that this is definitely a role and a field that I wanted to be a part of.

Ben Shaberman:

That's great. And so let's go back to Spark, and just to let our listeners know, in case they don't know, is that Spark was a spinoff of Children's Hospital of Philadelphia to help get the gene therapy, which eventually became Luxturna across the finish line. And if I'm correct, Spark was founded in 2013.

Dr. Daniel Chung:

Correct.

Ben Shaberman:

And so you came out of the University of Pennsylvania to join Spark, is that correct?

Dr. Daniel Chung:

That's correct. So while I was at University of Pennsylvania, I was also working some at Children's Hospital of Philadelphia. That's where the clinical trial really started, both phase one and phase three, prior to the formation of Spark. And so I was involved in those clinical development stages at CHOP, and so that's what really introduced me to the whole thing. And obviously working with Dr. Bennett, Jean Bennett, who really was one of the key drivers of the whole RPE65 story. It was a natural progression to get into the clinical trials and be a part of that.

Ben Shaberman:

Right. Yeah, that must have been quite an experience to watch that RPE65 gene therapy move through the clinic and get such traumatic results. Do you remember what it was like when in December of 2017 the gene therapy, which, again, became Luxturna, got FDA approval? This is a gene therapy that had restored vision in kids and young adults, and what was that like for you and Spark when you crossed the finish line?

Dr. Daniel Chung:

Well, obviously it was a huge milestone in the field of ophthalmology, and especially inherited retinal diseases that really did not have any therapeutic modality prior to that. And although it was just one of the 270 different genes, and it only represented one of them, it was really a breakthrough for those patients and really hope for the whole community. I think for the entire team, it was just a huge sense of accomplishment. And I was just very fortunate to play a small role in the whole development. And I thought of the founders really who set all this emotion, and to just see their elation and all the hard work that they had put in to see the therapeutic actually come to life and now be available for patients. So it was obviously a very jubilant day and things of that nature, but we also thought that there's a lot of hard work left to do because the drug was approved, but now we have to get it to patients and we have to educate patients and educate physicians and optometrists and the whole healthcare field about what the product can do.

So there was still quite a bit more work to do, but that day was extremely special, and I'll always remember that. I'll remember the FDA advisory board meeting down in Maryland and everything that went on with that. And like I say, I was just very humbled and privileged to be a small part of that.

Ben Shaberman:

Well, Spark was lucky to have you. And in terms of education, Dan, that's where our paths crossed very often at seminars and meetings that the foundation held. We presented together, and I can say you do a great job communicating the challenging science, and that was part of your role at Spark. What else did you do at Spark besides the education component?

Dr. Daniel Chung:

Well, thanks for the kind words there. So I was the first ophthalmologist and first person in medical affairs that Spark had hired, and, as you said, one of my main responsibilities was a educational role, not only externally, but also in training folks internally on different aspects of ophthalmology and other related topics. But it really ballooned from there where you became somewhat of a subject matter expert for the internal workings of the community and things of that nature, so I really was privileged that I could work with a lot of different groups within Spark, whether it was marketing and commercial, or even in some of the payer discussions, and obviously in clinical. And then of course there was my background that I had at Penn doing a lot of basic science research. I could definitely lend a voice into our preclinical work that was going on at the time. But obviously we had great expertise in all these fields, but I was just able to contribute a little bit of my knowledge for all of them.

Ben Shaberman:

Right. And I've heard and seen over the years people talk about the multi-luminance mobility test, and I know you and I have talked about this test, the maze that patients navigated, but you've gotten credit for helping develop that. That's a big deal, a new endpoint that the FDA has validated for these clinical trials.

Dr. Daniel Chung:

Well, that was definitely a lot of work with a lot of members of a huge team that brought that forward. And I think the whole impetus was that there really was a dearth of approved, or even I guess, relevant endpoints in ophthalmology other than visual acuity. But visual acuity was really not a great factor in the sense of inherited retinal diseases, because, as you know, inherited retinal diseases, many of them, rod cone dystrophies, you can have very small visual fields, but yet you still have great visual acuity. And so walking around with a 10 degree field is not what we would consider normal vision. And so we tried to get the idea that there's something called functional vision, which is a vision that you and I use every day to carry out activities of daily living, and how do we capture that in a quantifiable manner?

And so that was what really set us on that path to try and get a mobility test, a functional vision test that incorporated different aspects of visual function into a quantifiable measure. So there were a ton of people behind this working all different kinds of areas, and I was just, again, very fortunate to be a part of that team.

Ben Shaberman:

And I will say that years later now I see a lot of companies are using variations of that test when I see them do their presentations in their clinical trials. There's another maze, there's another obstacle course. The development of that test really is helping a lot of people advance their therapies. So let's switch to SparingVision and what drew you to SparingVision?

Dr. Daniel Chung:

Well, obviously I enjoyed being at Spark and I was there for over six years, but it came a time where there were other modalities and other therapeutic strategies that were coming apparent, and I thought that it might be interesting to go into one of those that was doing something gene agnostic, in a sense, where they weren't really talking about gene augmentation or gene replacement, replacing the gene that had the underlying mutation of variant, but something that was independent of that genetic etiology. And the reality is that there are over 270 different genes for inherited retinal diseases. There's something like 60 to 70 different retinitis pigmentosa genes.

And unfortunately, the development of each one of those genes could take decades and tons of resources. And unfortunately, some are relatively rare that may not get the attention of a lot of groups. And this might be a way of fulfilling a unmet need in a little more broad way than just single gene replacement, which is still fantastic and we always advocate that if they have good safety and good efficacy results, but this would be another way of potentially alleviating some of the deficits in vision from some of these genetic disorders. Now, obviously, gene replacement, if you look at Luxturna, it's really more about restoration of function, whereas we are thinking a little more about preserving and delaying the progression of deterioration.

Ben Shaberman:

Right. And so the lead candidate that the the founders of SparingVision have been working on for many, many years is called rod-derived cone viability factor. Can you tell us how that works and who it might benefit?

Dr. Daniel Chung:

Yeah, so this really came from 20 years ago or so. Two individuals, José Sahel, who is a very well known inherited retinal disease ophthalmologist based back then at the Institut de la Vision in Paris, and now he's the chairman at University of Pittsburgh Medical Center, along with his colleague, Thierry Léveillard. They basically asked the question, "Why do all these rod specific genes that cause deficits in rods then lead to cone destruction?" And so after doing a lot of research, they were able to identify a factor known as rod-derived cone viability factor, and what they found was that this factor is actually produced by rods and it is there to maintain the health and the function of the cones. But, as you know, in rod cone dystrophy the rods are dying so that product is no longer being produced. And so by adding that back in, they've shown in different rodent models of retinitis pigmentosa they were able to slow the generation of cone cells.

And there are really two mechanisms that works on. One is really about facilitating glucose uptake and aerobic glycolysis is leading to an increase in protein production, and this basically protects the cone structure and function. And there's another isoform that's also there that is one of the more powerful antioxidants, because as you know, the retina is an area of high oxidative stress. So these two factors work synergistically, and they helped protect the function of the cone photo receptor. So therefore you maintain at least central vision, and daytime vision, and color vision, and things of that nature that cone photo receptors are doing.

Ben Shaberman:

Right. So it's all about saving the cones.

Dr. Daniel Chung:

It is about saving the cones, and that's why the patient population will probably slightly later in the disease progression than maybe some of the monogenic gene augmentation therapies. But there's still a lot of work to be done, and we're still obviously in the pre-clinical stages, although we hope to get our application to the regulatory agencies by the end of the year. So that's really what SPVN06 is all about.

Ben Shaberman:

Right. And if you can preserve even a small number of cones for a lot of people, that still gives them some visual acuity, the ability to see faces and navigate somewhat. I've heard Dr. Sahel talk about this a

lot, that if you can just save, again, even a small population of cones, you may not be an airline pilot, you may not be able to drive, but you can still function pretty independently. So that's very exciting. Just tell us briefly how this therapy is delivered.

Dr. Daniel Chung:

So right now we're under the idea that this would be a subretinal injection targeting different cells in the posterior retina, so basically the cone photo receptors and the RPE. So obviously subretinal injections has been widely developed, and safety profile has been relatively good, and there's a lot of data on it right now, so at this point that is the process that we plan to do.

Ben Shaberman:

That's great. So recently, I want to say it's been the past week or two, SparingVision announced the acquisition of a new technology, a new therapeutic approach that also addresses cones but a little differently. And can you tell us about that?

Dr. Daniel Chung:

Sure. I think you're referring to SPVN20, and this is a recent acquisition. Basically it's another gene agnostic approach of saving... Or in this case it's actually the idea of restoring functioning cones, and it's targeting something that the developers of this, so this is coming out of Denise DeCaro's lab and her work, and I'm sure many other people are involved in this, but they've coined the term of dormant cones. And dormant cones are simply cones that no longer have function, but physically they're still present. Their outer segments are mostly gone. And basically what they do is the idea of a channel protein known as GRC2, and this basically allows the restoration of the short photo transduction cascade, and this can prolong visual acuity and color vision. So it's basically enhancing or bringing back some of that cone photoreceptor function.

Ben Shaberman:

Right. So as I understand it, you have cones that may stopped working, but they're still alive. And this new therapy, SPVN20, can resurrect those cones to make them light sensitive again. So the first therapy we were talking about is all about preserving the cones that are still working. The second therapy, if I have this correct, is all about getting cones that have stopped working to start working again.

Dr. Daniel Chung:

Correct. And they're both gene agnostic in that sense, because they're not working on the underlying genetic mechanism.

Ben Shaberman:

Right. And is there potential for these two to work together, do you think?

Dr. Daniel Chung:

Obviously that's definitely a possibility. I think right now we're trying to get the preclinical packages together on both of these separately. And obviously later down the road there are other considerations of potentially maybe they have a synergistic effect.

Ben Shaberman:

Right. How do you know when somebody has cones that are dormant, that they've stopped working but they may be resurrectable, if that's a word?

Dr. Daniel Chung:

Yeah, a lot of that is they're obviously functional tests that will show deficits in your phototopic response and things that you look for when central vision goes, things like color vision, visual acuity, things of that nature. But then there's also the structural evaluations that you can do, OCT and other forms of visualizing the retina and possibly the cells still being there. So you put those two together and you can get an idea of where you are when it comes to the functionality of these cone cells.

Ben Shaberman:

Interesting. So good imaging studies will help identify the patients that are most amenable [inaudible 00:18:59] approach.

Dr. Daniel Chung:

Yeah, absolutely. Functional and structural studies together will [inaudible 00:19:04] good in determining that.

Ben Shaberman:

Got it. So just to reiterate, both of these approaches are gene agnostic, so shouldn't matter what mutated gene somebody has. And I know we're talking about, at least at first, people with RP, and I presume Usher syndrome, since Usher syndrome is RP just with hearing loss, are there any other conditions that you think this approach may be amenable to?

Dr. Daniel Chung:

Yeah, I think when it comes to being gene agnostic, it's relatively gene agnostic in a certain class of disease. So for SPVN06, we're looking at rod cone dystrophies, and a example of that is retinitis pigmentosa, and obviously the stage of disease is when the rods are no longer functioning because they're not producing the RdCVF anymore from the rod photo receptors. And then we would intervene at that point when the cone cells are starting to lose function. So it would be probably into the more moderate or progressive nature or severe state of the disease. When it comes to the other program, SPVN20 with GRC2, that might be at a time where your cone cells are a little more advanced in their disease because we're really talking about non-functional cone cells and being able to sort function in those. And it doesn't necessarily have to be with a GRC2, it's really looking at the cone cells themselves. So I think the idea is where can we intervene where cone function is at a deficit, and maybe we can look at restoring that as well.

Ben Shaberman:

Well, I'm sure there are a lot of people out there excited about the potential for both approaches. So thanks for the great work that SparingVision is doing and that you're now helping SparingVision do. I'm guessing we'll probably hear about progress later in 2021 as you get closer to that filing to launch a clinical trial. And we at the Foundation Fighting Blindness, we actually fund SparingVision so we're very excited about the potential for those therapies. We're very excited, Dan. You're a part of the program now, and we will be sure to report on any developments there. So Dan, that concludes my questions, my interview. I don't know if you have any parting thoughts or comments. Feel free to share.

Dr. Daniel Chung:

Well, number one, Ben, I just appreciate the opportunity and thanks for inviting me on this. And as you know, in the world of gene therapy development and the retina, it can take a little bit of time, so we want to make sure we do all the right things in our preclinical package and things like that. So that's where we are today and hopefully we'll get to the regulatory submissions by the end of this year for SPVN06, and then obviously we're very early in the development of SPVN20, but obviously we'll keep the foundation definitely informed.

Ben Shaberman:

Well, thanks again, Dan. We appreciate your keeping us in the loop. And again, we're very excited about the work you and the rest of that great SparingVision team is doing. So that's it for this podcast. I want to thank all the listeners for joining us to learn about great emerging therapy coming through the pipeline. And remember, if you have any questions or comments or just good cheer to send them along, you can send those through email to podcast@fightingblindness.org. That's podcast@fightingblindness.org. Thank you again, Dr. Chung, for joining us. It's been great having you.

Dr. Daniel Chung:

My pleasure.

Ben Shaberman:

And we look forward to all our listeners out there joining for our next podcast. Thank you.

Speaker 3:

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