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 the Eye on the Cure Podcast where we cover a variety of topics, personalities, and information related to the retina, the eye, and vision. I am Ben Shaberman, Senior Director of Scientific Outreach at the Foundation and your Eye on the Cure Podcast host.

I'm really delighted today to have with us Dr. Sheila Nirenberg. She's a PhD and the Nanette Laitman Professor of Neuroscience and Neurology at Weill Cornell Medicine. She is founder of Bionic Sight, which recently launched a clinical trial for an optogenetic therapy that's designed to restore vision for people who have lost all their vision or just about all their vision to retinal diseases like RP and potentially some other conditions. So welcome, Sheila, it's really great to have you with us.

Dr. Sheila Nirenberg:

Well, thank you for having me.

Ben Shaberman:

I just wanted to recall how I met you. It was a while ago. It was, I want to say somewhere in the neighborhood of 10 years ago. I was at the big annual conference for eye research, the Association for Research and Vision in Ophthalmology. It's this conference with like 12,000 people. I'm walking down a row of posters of different research advances. Bill Houseworth, who is a researcher at University of Florida and really one of the forefathers of gene therapy development, a really distinguished gene therapy researcher, kind of waved me over and said, "Ben, you got to look at this poster. You got to keep your eye on this." It was Sheila's poster, and Sheila was there. That's when I first met Sheila.

You never know what's going to move forward or what's not. It's really a pleasure today to see that your work is really turning into something with potential. So we want to talk about Bionic Sight and your clinical trial of your treatment. But before we do, please tell us about your path to becoming a scientist. When did you know you wanted to make a career in this field?

Dr. Sheila Nirenberg:

Well, I mean, I don't know exactly. It's always been in my personality to be a scientist, I think. I just really like to understand things, to get to the bottom of how things work. In many ways, it's just kind of like being a detective. Who doesn't want to be a detective? A detective will pull together lots of facts, but there's always one thing that doesn't fit. You ponder it and you ponder it, and you follow a lead. Suddenly, you figure it out. That's sort what being a scientist is like. Well, not as glamorous, but it's still like that.

When I worked out the neural code, when you saw that poster a long time ago, that was me as pure scientist. Then the realization that if I had that code, it opens the door to being able to make a treatment for blind people. Then I became like another person and started to work out how do I actually translate this to humans? So there's been a lot of evolution in this process.

Ben Shaberman:

That's great. It really takes a lot of patience to be a scientist because things don't happen quickly. I appreciate people like you in the science "industry" who can spend so much time on a project to see it to hopefully fruition. So you mentioned neural code, can you explain what that is? You say that you've cracked the neural code or at least in the retina. So tell us about that and how it can be applied to help people with retinal diseases.

Dr. Sheila Nirenberg:

Okay. So when we think about the code, what you're really thinking about is how the brain represents information. So everybody probably knows that it's represented in patterns of electrical pulses. So that's the language of the brain, patterns of electrical pulses. They sort of look like Morse code but more complicated. So if you want to communicate with the brain, you have to be able to speak that same language, that same code. So that's what I meant really is it's figuring out how the retina takes information in, what it does with that information, and then how it converts it in into a code.

So that's exactly what it does. It takes images in. It processes them. It converts them into a code. Then it sends the code up through the optic nerve to the brain. So if you want to make a degenerated retina be able to work again, you have to know what that code is. You have to be able to do all those same things, mimic the actions of the retina, and then convert it in into a code. So this is what our device does.

Ben Shaberman:

That's really cool. So I'm curious how you determined what that code is. What kind of studies do you do to "crack that code?"

Dr. Sheila Nirenberg:

So we started in mice, and what we did was we presented... So one thing that's convenient about the retina is that you can take it out of an animal and put it in dish and keep it alive with saline and glucose and all the nutrients, just like if you were in a hospital and you get an IV bag. So you can put it on a bed of electrodes. Then you can present movies to it and record the responses. So you can watch the retina watch the movie. You can see all the mad electrical pulses coming out of it.

So what we did was we presented many different movies of a certain kind. It's too boring to explain how they were chosen. We mapped the input-output relationship using what's called a Bayesian method. That mapping of the input and output is what cracking the code means. So that way I can test it over and over with many different images to see did I get it right every time?

Ben Shaberman:

That's pretty cool. So the bottom line is you watched rodents watch movies to crack the neural code.

Dr. Sheila Nirenberg:

Exactly.

Ben Shaberman:

That sounds like a lot of fun there. So you developed this device that creates the neural code similar to what the retina creates. So how are you using this in your therapeutic approach to restore vision?

Dr. Sheila Nirenberg:

So it's a device that has... We make a pair of goggles essentially. It has a camera on it, so it'll take images in. Then it goes through this encoder device, turns it into a code. Then its output is light pulses to activate an optogenetic gene that we've put in your eye just before. I mean, not just before, a few months before.

Ben Shaberman:

Right. So that optogenetic therapy, if I understand correctly from reading up on this, is applied to the ganglion cells which survive after somebody's lost other photoreceptors to RP or perhaps another condition. If I understand correctly, the device sends the code to those ganglion cells. Is that correct?

Dr. Sheila Nirenberg:
Right. So it's one thing to have the code, but now you have to get the code into the body. You have to get somebody to send the code from the eye up to the brain. So that's what those ganglion cells do. So we send in an optogenetic vector. It just gets injected in a doctor's office. It's just one injection, and it takes a few seconds. Then it gets into the ganglion cells. The ganglion cells are the ones that form the optic nerve. So then we can just send light pulses into the eye, and it'll land on those ganglion cells. Then they'll send the signals up to the brain in the right code.

Ben Shaberman:

Right. Very cool, very cool. So I think what's most exciting is that you formed a company and launched a clinical trial. Just recently in that trial, you dosed, as we say in trials because it's really not a treatment until it's FDA approved.

Dr. Sheila Nirenberg:

Right.

Ben Shaberman:

So you dosed four patients with the lowest dose. Tell us about those early results.

Dr. Sheila Nirenberg:

Okay. So we've dosed five now, two with the lowest dose, and then three with the next dose up. But we've only tested four so far. The next one will get tested in two weeks. So all of these patients had total blindness or near complete blindness. So some had really essentially no light perception or very, very, very little. So what did you ask me, what happened so far? Is that what your question was?

Ben Shaberman:

Yeah. So these are RP patients basically. I think they're all RP patients?

Dr. Sheila Nirenberg:

Yes, all RP.

Ben Shaberman:

They came to the trial with virtually no vision. So what are they seeing now?

Dr. Sheila Nirenberg:

Okay. So the first thing that happens is about two or three months after they're injected, the patients, it happens with all four of them. They started texting that they're starting to see something, a little bit of light, a little bit of motion. What was amazing is like this was in the very beginning of COVID. Everybody was so miserable. Then you'd get these joyous texts of, "It was Hanukkah. My wife lit the candles, and I saw the Hanukkah candles." Then another one is, "I could see my dog running in the snow. I can't see exactly that it's a dog, but I can follow him, my black lab running in the snow because it's very high contrast." So there were lots of these.

Then we brought them into the lab safely with serious masking involved. We tested them objectively and quantitatively. The results showed that the two patients that got the lowest dose were more than 20 times more sensitive to light. The two that got the slightly higher dose, three times higher or was more than a hundred times more sensitive to light. The two higher dosed ones could also see the direction of motion. So remember they couldn't see anything before. But now they can see a bar moving to the right or to the left and be able to tell me which way. More than 80% of the time they got it right.

Ben Shaberman:

That's really, really phenomenal.

Dr. Sheila Nirenberg:

One thing I want... Can I add one more thing about it?

Ben Shaberman:

Of course.

Dr. Sheila Nirenberg:

So one thing that was... After we were testing them formally because we have to do it all properly, but then you can't help yourself. You sort of are playing with it. So I was interested to see comparing the case without the device versus with the device. So I was standing in front of a patient, so he just has the gene therapy, but he doesn't have the device also. I was asking him can he see me? He can't see what I'm doing. He can barely tell where I am. In fact, he probably can't tell where I am.

So then he looks through the device. Now, I can move my arm up and down. I can wave at him. He can tell the difference. He's like, "Arm up and down. Oh, I can see your hand. I can see the fluttering of your fingers in a way." Or if I moved my whole body, and he could see it. So it was really thrilling honestly. Yeah, I'll do it again with him and film it. We have some film of it, but it's kind of awkward. We are all wearing masks, and it looks sort of silly. But go ahead, you were going to ask something.

Ben Shaberman:

Well, I was just going to say it's thrilling to hear you tell those stories, to hear that people are getting some vision back when they were previously completely blind. How did the patients feel about the results at this early juncture?

Dr. Sheila Nirenberg:

It's a whole range. Of course, they're excited. That's why they're texting to say, "I can see this. I can see that." When that patient could see that, I hugged him. I think I might have accidentally knocked his mask slightly off. I mean, there was a lot of joy, a little bit disorganized happiness at that moment.

Ben Shaberman:
Well, that's very cool. So I guess I'll combine these next two questions. You obviously have next steps in the trial, you're going to treat more people. What do you hope people will ultimately see? How much vision do you hope you can restore?

Dr. Sheila Nirenberg:

Well, because of the device, there's the potential to go way up to a much higher quality vision. When the dose is low, there isn't that much optogenetic protein in the cells. So even if we're driving it with the device, there's not that many proteins to receive it. So as the dose goes up higher to the highest dose that we're going to try, it should be much more significant.

So when we test this in mice at the highest dose that we tried, it seemed to... The protein responds every time. So that's the next really big step is how much can a patient see when we're at the highest dose? So we start the next cohort. We've got permission to start the next cohort to the next dose a couple weeks ago. So I just did the baseline testing on... Well, I didn't, but our team did the baseline testing on the first patient for the high dose.

Ben Shaberman:

Well, very cool. I'm glad you're moving forward. I will add, this is a phase one/two trial, correct?

Dr. Sheila Nirenberg:

Yes.

Ben Shaberman:
Really the goal of these early clinical trial phases is safety. So the fact that you're getting some early results is really, really heartening. The trial is underway on Long Island at... It's OCLI, correct?

Dr. Sheila Nirenberg:

Mm-hmm.

Ben Shaberman:

I forget what OCLI stands for.

Dr. Sheila Nirenberg:

Ophthalmic, I forgot too.

Ben Shaberman:
They're on Long Island, OCLI. If people want to learn more about this approach, they can go to the website, bionicsightllc.com. Again, that's bionicsightllc.com. They can also inquire about being a part of the trial. I'm sure you're getting a lot of inquiries. How many people will you ultimately enroll in this phase one/two?

Dr. Sheila Nirenberg:

Well, the protocol allows 20, but I think we'll try to expand it. We'll try to double that or at least go to 30. But I have to write to the FDA to get permission to expand. But we have lots of vector, so we had good manufacturing. So we should be able to accommodate that many people.

Ben Shaberman:

That's great. I think often when we talk about therapies like gene therapies and trials, we don't appreciate the need for quality manufacturing of the gene therapy. It's not a simple process. So that's good news that you're doing well on the manufacturing side.

So I want to switch gears a little bit. Thanks for telling us about those really great early results. But you've been at this a long time, and it's a long path to starting a company and to launching a clinical trial. I'm just curious if there are certain challenges or milestones that stick out for you during this journey to getting this treatment off the ground?

Dr. Sheila Nirenberg:

Well, clearing the FDA is of course a massive milestone because the document is like 700 pages, and all of the safety data and all of the efficacy data that you have so far. It's a huge job. I learned a tremendous amount doing that because I was going from being a basic science to being able to set this up, and then putting together a team to do it. I want to put a plug in for OCLI, even if I couldn't remember what the initials stand for. They're a wonderful team, and I want to thank them. Dr. Glenn Stoller is the one who does the injections.

Ben Shaberman:

I'm just curious, were there moments where you thought, wow, you've hit a roadblock, or you might not be able to move forward? Or were there certain people or milestones where things really kicked into gear for you?

Dr. Sheila Nirenberg:

Well, meeting Bill Houseworth was a wonderful part in the beginning. I was wanting to make this virus. I had the neural code, and I needed a way to get it in. I talked to him. I just cold called him, and he listened to me. He's like, "I love this." He said, "I'll help you." So we just became bonded and lifelong friends over it. Then he later on introduced me to AGTC. They helped fund the company and fund the project. It's a gene therapy company.

It's always like this. Everything is two steps forward, one step backwards. You have to raise money. You have to convince people. You have to tell your story 500 times, although telling it to you is just fine, but you know what I mean. Then people aren't easy in many ways. Somebody told me that when I first started that the science is easier than managing all the people that you have to manage to get yourself through. Because there's pride and ego and all sorts of things that you have to make sure everyone's happy. My personality is to try to make everything win-win, so it's good for everybody. Anyway, I try.

Ben Shaberman:

Well, thanks for being honest and congratulations on... Obviously, you've made everybody happy at least to this point, to get to this point, so congratulations. So I don't have any further questions. I don't know if there's anything more you wanted to say, Sheila. But thanks so much for joining us on the Eye on the Cure Podcast and talking about this approach, which holds such promise for people who have

lost really all of their vision. It is gene agnostic. I want to add that. It's designed to work regardless of the mutation causing somebody's retinal disease.

Dr. Sheila Nirenberg:

I'd also like to add that right now our focus is on the very blind, but I think it will ultimately work on people that are less blind. So it could come in at an earlier stage. Then even if it comes in and we can help people see for a while, over time they'll still lose their photoreceptors. But we'll be there for that too because we can help them all the way through from boosting their vision to replacing their vision. I think that's helpful and comforting to know that as it's deteriorating, this method is still there.

Ben Shaberman:

Right. Well, I'm sure people out there are really rooting for your continued success. So again, thanks again for what you're doing. So that basically concludes our podcast today. Listeners, if you have questions, comments, and any good cheer to pass along, you can send an email to podcast@fightingblindness.org. Thanks again, Sheila, for taking time to tell us about this great emerging therapy and thanks everyone again for joining us. Stay tuned for our next installment of the Eye on the Cure Podcast.

Speaker 1:

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