

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:

Hello everyone and welcome to the Eye on the Cure Podcast. I'm your host, Ben Shaberman, with the Foundation Fighting Blindness. And with me for this episode are Nicole Wagner and Jordan Greco from LambdaVision, a company developing a rather unique artificial retina. And it's unique because it incorporates a light sensitive protein, so there's a biological aspect to it. And of course we're going to talk a lot more about that. But excitingly, this artificial retina holds promise for restoring vision for people with advanced RP, Retinitis Pigmentosa, age related macular degeneration, and potentially some other retinal conditions. So Nicole and Jordan, welcome to the podcast.

Nicole Wagner:

Thanks, Ben. Thank you very much. It's a pleasure being here.

Ben Shaberman:

Before we get started, I want to give you a little background on Nicole and Jordan. So Nicole is LambdaVision's President and CEO, and she earned her PhD in Molecular and Cell Biology from the University of Connecticut under the advising of Dr. Robert Burge, a pioneer in the field of light sensitive proteins. And Nicole spent the majority of her graduate career working on optimizing retinal proteins for application in devices. And during the course of her PhD research, she played a critical role in the proof of concept experiments, which helped to found LambdaVision.

And then Jordan is LambdaVision's Chief Scientific Officer. He obtained his PhD in Physical Chemistry from the University of Connecticut. And also under the direction of Dr. Burge, he focused his graduate thesis work primarily on the investigation of the structure and function of photoactive proteins using both spectroscopic and quantum mechanical approaches. And much of his work has contributed toward the application of the light activated protein, Bacteriorhodopsin, that's being used in the artificial retina under development by LambdaVision.

So to start off, Nicole, you and Jordan have been working together on this project for quite a number of years, along with, at least earlier, Dr. Burge. Can you talk about who came up with this idea and how it moved forward?

Nicole Wagner:

Absolutely. So the technology itself, as I mentioned, both Jordan and I were graduate students in Bob Burge's lab. And so my background was looking at optimizing light activated proteins for device architectures. So I worked on things like holography, photovoltaics, chemical sensors, and then it was really with the emergence of optogenetics, which I kind of think of as a fancy buzzword for using light activated proteins to restore neuro function in the early 2000s, that we started to think about ways that we could apply this protein to restore vision. So this was during our graduate thesis work, and we were looking at some of these other different proteins. I think the audience may be familiar with some of these, but there's a channelrhodopsin, which is a potassium ion pump, halorhodopsin, which is a chloride ion pump, and then bacteriorhodopsin, which is what we use, which is a proton pump. And so we have tested this now a number of different times. We've done a number of early studies, and that is what is shown promise in restoring visual function, at least in animal models for the artificial retina.

Ben Shaberman:

Right. And I like that you mentioned optogenetics because really your approach is a combination of optogenetics, the biologic side of it, the light activated protein along with the hardware, if you will, that is used in most artificial retinas. So it's kind of a marriage between the two.

Nicole Wagner:

Right. I often say it's an elegant solution between the hardware based approaches, so the hardware driven retinal prosthetics, and then the more gene therapy therapeutic based approaches. So when you're thinking about just sort of where we sit, so in the hardware driven technology, I kind of think of these as really engineering marvels. You have battery packs, wires, goggles, but there is in many cases a much more complex surgery for these patients. When you look at things like optogenetics, some of the challenges that optogenetics technologies face is that they're require a higher light sensitivity. You may require some optimization or you may need some almost goggles or something like that in order to streamline the light, because bacteriorhodopsin sits in the middle of the visible spectrum. So we're at 560 nanometers, which is where it absorbs. We won't need battery packs or wires or goggles. We can rely on ambient light intensity in order to do this.

Ben Shaberman:

That's really cool. And so Jordan, can you tell us more about this device and how it incorporates the protein, and how you get it into the retina and where in the retina it goes?

Jordan Greco:

The artificial retina itself is created through a layer by layer electrostatic deposition process where we deposit alternating layers of the protein bacteriorhodopsin and a polycation binder and alternate between those two materials 100's of times to create a multilayer thin film. This process is done on earth, and maybe that's a funny way of putting it. But in our labs, right, you'll see why we're going to talk about some of our microgravity work in a few minutes, but in our labs in Farmington, Connecticut, we use an automated dipping machine to facilitate this layer by layer manufacturing approach to create the artificial retina thin films. The idea behind the mechanism of this film is that bacteriorhodopsin is a proton pump. So in its native organism, the protein as a transmembrane protein, it absorbs light and pumps a proton from inside of the cell to the outside of the cell.

We harness that proton pumping mechanism and orient all the proteins on artificial retina in the same direction to create an ion cloud or an ion gradient. And that ion gradient is then utilized to stimulate the neural circuitry of the retina that's degenerated. So for individuals with healthy retinas, just to take a step back, the retina is the light sensitive tissue that absorbs light and transmits a signal to the brain to generate visual perception. For patients with retinal degenerative diseases like age related macular degeneration and retinitis pigmentosa, the light sensitive cells of the retina, the photo receptor cells or the rods and the cones are lost and our artificial retina is put in place of those cells. It's essentially an artificial photo receptor cell layer. So when that implant is placed into the subretinal space in place of those cells, the implant absorbs light, generates that ion cloud or that ion gradient that I mentioned from the proton pumping of the protein, and then is capable of stimulating the remaining cells in the retina to generate visual perception.

Ben Shaberman:

So this is a thin piece of film, and it goes really where somebody had photo receptors subretinally. And I take it it's only appropriate for somebody who's really lost all or most of their photo receptors? So this is really for advanced vision loss, is that correct?

Jordan Greco:

Yes, that's correct. For where we are now with the development of our technology and how we envision treating patients, it would be for advanced stages of retinal degeneration and specifically advanced retinitis pigmentosa to begin with in our preclinical path.

Ben Shaberman:

Right. And how thin is this film?

Jordan Greco:

The film itself, so I don't think I mentioned before, but we use an ion permeable scaffold as a platform for these alternating layers of protein and polymer. The combination of that scaffold and the layers of protein and polymer, it's about 80 micrometers thick.

Ben Shaberman:

So is that like a sheet of paper or maybe a little wider?

Jordan Greco:

Yeah, roughly that thickness, I would say on that.

Ben Shaberman:

It's super thin, obviously.

Jordan Greco:

Right.

Ben Shaberman:

Obviously a protein is a biologic. And because it's a biologic, I think of it as not being a permanent thing. But the way you've put it in the layers of this device, if you will, is the protein always there or does it degrade? Will you need to replace the device at some point?

Jordan Greco:

Yeah, this is meant to be a long term implant, and bacteriorhodopsin is very unique in a number of ways. One of which is that it's incredibly stable. It's found in this extremophile, this halobacterium salinarum organism that I mentioned before. It's produced in salt marshes and the protein, I keep referring to it as a protein. It's actually what we isolate as a lattice of proteins within the cell membrane, and we incorporate that lattice into artificial retina architecture. That lattice structure really makes this biomaterial very, very stable. It has a melting temperature over 80 degrees Celsius, which is much higher than the temperature of the human body.

And the protein also has a very high cyclicity, meaning that it could absorb light millions and millions of times before degrading. So this protein has been studied since the '70's and has been incorporated into

a number of non-native device architectures outside of the artificial retina as well. The founder of LambdaVision, Dr. Robert Burge, made his career on incorporating bacteriorhodopsin into optical computing technologies, biosensors, many non-native environments. And besides the unique photochemistry of the protein, the fact that the protein is so stable allows us to incorporate it into these devices and expect a long term lifetime for its function.

Ben Shaberman:

That's great. Thanks, Jordan. So Nicole, what stage of development is this device? You've tested it in some preclinical models, and hopefully at some point you'll get it into a human study.

Nicole Wagner:

Right. I mean, to date, we have done a number of in vivo and ex vivo preclinical studies. We've done some work that was recently published in the Journal of Neuroengineering last year at the end of 2021, which was really our critical proof of concept studies, which looked at an ex vivo study on a rat model of retinitis pigmentosa. So we did this work in collaboration with Dr. Ralph Jensen at the Boston VA Hospital. And the main goal here was to show that in the presence of our implant, the cells, we could get signals from the bipolar and ganglion cells by monitoring through extracellular recording. So think of a really tiny, tiny little pin that is touching a cell and we can monitor whether or not that cell is getting a response or firing. So we did quite a rigorous study there with Dr. Jensen. That was the proof of concept study, like I said.

And that was recently published. We have also done some in vivo studies in larger models, animal models in this case, mostly in a [inaudible 00:11:54] pig model to look at how do we get this in the back of the eye? What does that surgical procedure look like? How big of an implant is this going to be? So these are mostly feasibility studies. And so that work was done in collaboration with a group at Wake Forest Baptist Health and a group called Preclinical Translational Services to support that. But all of that has gotten us to a point where we have a good fundamental understanding of how the protein works and how the implant works. But of course, I think the next step here is supporting more rigorous IND-enabling studies. So studies that'll support us in getting into clinical trials. And so that's where we are today is starting to focus on those types of studies.

Ben Shaberman:

That's great. And I know of course a big advantage to your approach as a device, if you will, and maybe I'm not being fair calling it a device, but it is a piece of material. The advantage is there are no electronics like you would have in an artificial retina. The question I have is, do you think it can perform better [inaudible 00:13:04] than an artificial retina in terms of the vision it can restore?

Nicole Wagner:

I certainly do, right? So I know here we keep calling it a device, actually it is going to be regulated as a drug.

Ben Shaberman:

Okay.

Nicole Wagner:

So it's because the primary mode of action for the artificial retina is going to be the protein piece. So that's the active component, but it is an implantable. So it does feel very much like a device in that sense. But in terms of function, right, so you're thinking of these electrode based approaches where you have a number of little electrodes on a chip, and that electrode needs to hit a neural signal or a neuron in order to generate a signal. And so that in theory, you could put many more electrodes on there, but unless there's a neuron, right, there for it to connect to or some neural signal, you're not going to get an impulse that's sent to the brain. Our approach, again, because of the biomimetic nature of it, so by using something that sort of mimics the native signal transduction cascade, we are anticipating much higher resolution.

So think of it as almost, again, like Jordan said, an ion cloud. So we're creating a change in that ion environment around those cells, and that's what's causing it to fire. So we get a much greater reach than some of those electrode-based approaches. And so certainly surgical placement is going to be important. You're going to get certainly a better signal the closer it's placed to the fovea, where more of those cells are going to exist, proximity towards the bipolar and ganglion cells is going to impact its function as well. But those are all things that we are currently looking at now in some of the surgical preclinical studies that we're doing.

Ben Shaberman:

Right. So let's switch gears a little bit. Land division has been getting a lot of really cool press for the low gravity manufacturing experiments that have been done in space, and of course I want to talk about those. But Nicole, who came up with the idea of making this solution in low gravity, and why is that beneficial?

Nicole Wagner:

Well, let me tell you, it has been a wild ride, right? The way that we make this, as Jordan mentioned, it's through this layer by layer deposition approach, and that process is very much subject to the effects of gravity. So imagine you're sitting at home and you have six glasses of water on your table, and you are going to have something sitting on the top of that water glass, in this case it's our substrate material. Well, everything in that glass is subject to the effects of gravity. So you're going to have a gradient of solutions, so it's going to be more dense towards the bottom, less dense towards the top. You're going to have things like evaporation are going to play a role. So whatever evaporates out of those glasses and then surface tension. So how it sits on those solutions is going to play another impact or have another role on that.

As we look forward, we knew that there were some challenges in how we did this. It takes over 200 times of this dipping process or coding process to get the thin film that we would be intending to use. So you can imagine if there's any imperfections at the earlier layers that that imperfection gets compounded by the time you hit layer 200. So in a microgravity environment, you don't have that. You have molecules that are nice and evenly spread out, or you get a much more homogenous solution. And so ultimately, that leads to better more homogenous thin films. So how we got involved with that, very serendipitously, let me tell you, we were part of Mass Challenge in 2016, which was actually based in the seaport area of Boston. And I was sitting at a table one day, and literally they come around and knock on your table and say, "There's pizza down the hall, free pizza, Come check us out."

That's exactly what happened. So they knocked on the table and they said, "There's a panel down the hall CASA, which is the Center for Advancement of Science and Space in Boeing, are hosting a presentation to talk about the impact of microgravity on work that's being done on the ground." So I attended that presentation and I learned about the awesome things that are going on in low earth orbit,

so bioprinting, tissues on chips, and really this whole idea of in space production of materials. And so that's where the light kind of clicked in my brain that said, maybe we can use microgravity for the work that we're doing.

And like I say often, it's not that we never thought we could do things in microgravity, but it's how the heck do you get to microgravity, right? How do you get to the International Space Station? When I started to think about projects there, I was Googling raspberry pies and automation in space. So that's certainly not our expertise, but fortunately, we have been paired with a group called Space Tango out of Lexington, Kentucky that does all of that miniaturization for us and allows us to focus our efforts on what we're best at, which is the protein coating, the protein on the scaffold, and the idea of how do we translate this into something that can restore vision.

Ben Shaberman:

That's so cool. So Jordan, how many of these experiments have occurred? How many times has your solution gone into space, and what have you learned thus far from those experiments?

Jordan Greco:

I think we're on our sixth flight. Nicole, correct me if I'm wrong. So we've been very fortunate to have a number of opportunities to perform our experiments on different missions to the Bay Station over the past four or five years or so. We started, as Nicole mentioned, we received that case as Boeing Prize in 2016, and it took about two years to get up and running with Space Tango. We had our first experiment on SpaceX, CRS 16 in late 2018. And at that point, we were sort of I would refer to as a pilot or a pathfinder mission, trying to miniaturize the layering device that Nicole was describing. And again, it's very different than the dipping approach that we perform in our labs in Farmington. We transferred this to more of a fluidic chamber device where fluids are flowing over the film. So it was developing the hardware needed for these experiments. It took a lot of prototyping and we're still prototyping to this day. But that first flight was, I would say, pretty successful in demonstrating the capabilities.

Ben Shaberman:

Right. So my question is, when you feel you've perfected this manufacturing process, will you need to do it in space or can you get a microgravity environment here on earth to do the actual manufacturing?

Jordan Greco:

Yeah, unfortunately there's no way for us to replicate a microgravity environment on Earth. Certainly there are means to do that more in an instantaneous fashion. We need approximately a week to manufacture a 200 layer film, so that duration of time can't be simulated.

Ben Shaberman:

So you will make these in space, but obviously you're getting a lot of opportunities to take it into space, so you just need to come up with a long term solution to do that?

Nicole Wagner:

Yeah, certainly, I mean, think there's a lot of opportunity here. I mean, right now we're doing a lot of proof of concept studies where evaluating the impact of microgravity on the overall integrity and deposition and quality of those thin films. But beyond just the actual science, I mean, I think a lot of the work that NASA has supported and ISS National Labs to support has been foundational and really

helping us understand the function and the quality of these thin films. A lot of the discussions that we've been having now, certainly this is new. There isn't anybody, at least to my knowledge, that is manufacturing something for human benefit that could be used in clinical trials right now on the International Space Station. So we're having those very, very broad discussions. What would that look like? How would you scale a system for microgravity? There's certainly some unique advantages for technology like ours, which makes this feasible.

Unlike manufacturing a whole warehouse full of stuff, is that, first of all, the artificial retina itself is very small, so it has a small footprint, which makes it feasible to do on the International Space Station. The whole process that we're doing is autonomous, which means that we don't need a lot of astronauts or people to physically carry out the experiment. So we can encapsulate it into this. It's about the size of a shoebox, send that shoebox to the ISX, it gets hooked up to power, and then that shoebox comes back and then we disassemble it. And we can make quite a few thin films and that shoebox size. So from a feasibility standpoint, I think this is a really good application for use on the International Space Station should we need to continue to manufacture it there. And I think the other thing I like to point out about why artificial retinas in space too, the other thing is that that protein is very, very stable.

So some of the cases that make things difficult or not necessarily difficult, but a little bit more challenging to do in space, are things that are cold experiments or they need heat, they're temperature sensitive, right? Our technology, like Jordan mentioned very early on, bacteriorhodopsin is incredibly stable. And it's that inherent stability that allows us to do these things on the International Space Station and not need constant power or constant cooling. If we were together right now, I carry a vial of the protein with me in my wallet and an implant in my wallet as well, right, just because it is so stable. And so a lot of people who work with proteins, even many of the optogenetic proteins that I described earlier, they don't have that luxury because they're not as stable as the protein that we're using. And again, a lot of that stability comes from the fact that this is an [inaudible 00:22:53] protein, a halophile, something that grows and is expressed in very, very extreme conditions.

So I think there is a lot of opportunity there. I think there's a lot of work still to be done. But those are the kind of discussions that we're having now and sort of thinking towards the future of if it is better in microgravity or it's the quality of the thin films is better, the impact to patients potentially certainly makes it worth it. And so that's our goal, I think, at the end of the day, is how can we get this into patients faster? How can we change? We want to be able to help people restore functional vision, improve the quality of people's lives. And that's really what keeps Jordan and I going. There's not a shortage of challenges day to day that we face, but it's the emails that we get from potential patients or somebody who says their mother has macular degeneration, or they've watched their child navigate difficult challenges because they've lost their sight. These are diseases that really affect the quality of life of patients. And so our goal is to try to as much as we can help those patients and offer some hope.

Ben Shaberman:

Right. Well, we appreciate the really creative, innovative work you're doing and the promise it holds for restoring vision for people with advanced retinal diseases. And thank you, Nicole and Jordan for taking a chunk of time out of your day to tell us about your artificial retinas. And please keep us posted on your progress when you're able to get started on those IND-enabling studies and get it into the clinic. We're very excited about the potential for your solution to restore vision. So thank you again.

Nicole Wagner:

Thank you, Ben. Thank you very much.

Jordan Greco:

Yes, thank you.

Ben Shaberman:

Thank you again to all our Eye On the Cure listeners. It's always great to have you, and we look forward to having you back for our next episode. Take care everyone.

Speaker 1:

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