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. I'm your host, Ben Shaberman, with the Foundation Fighting Blindness, and I am excited to have Michael Voevodsky as my guest for this episode. And Mike is president and CEO of MitoChem Therapeutics. And MitoChem is developing a compound that's designed or selected to boost mitochondrial function for slowing or halting retinal degenerations and vision loss in people with retinal diseases such as retinitis pigmentosa, and age-related macular degeneration. So Mike, welcome to the podcast. It's great to have you tell us about MitoChem's promising approach to preserving vision.

Mike Voevodsky:

Well Ben, it's great to be here. Thank you for the invitation to come on and speak to your audience. We're very excited about what we're doing and delighted to have a relationship with FFB.

Ben Shaberman:

And we're delighted to have the relationship and we're very excited about your work and the promise that it holds. So before we start talking about mitochondria and mitochondrial therapies, I wanted to give you a little background on Mike. He has an interesting background and we're going to talk more about it later in the program. But for now, I will tell you, that in addition to his current role at MitoChem, he advises for the University of Arizona's Tech Launch Arizona Initiative on promising life science and physical science technologies. He also holds more than 25 US and international patents in the field of ophthalmology. That's impressive. And Mike received a Bachelor of Science in Business Administration with distinction from the University of Arizona, and he earned an MBA from Harvard Business School. Very impressive. So Mike, let's dive into the science and tell us why mitochondria are a target for retinal disease therapies and let's learn more about what mitochondria are. Let's talk a little cell biology.

Mike Voevodsky:

Okay, great. Well, let me first start by saying that the reason why we're focused on mitochondria as a therapeutic target comes back to the origin story of MitoChem in the first place. So, one of our co-founders, Dr. Barb Rohrer, is a neuroscientist with an ophthalmology focus and expertise. And years ago, she was looking for any type of common denominator across retinal diseases. And what she discovered, was that all the retinal diseases that she was looking at all had a common factor of a metabolic crisis that would take place very, very early on in disease progression. And what would happen is, is that you had cell energy that would go from a very efficient form of energy creation to a less efficient. And once that happened, the retina essentially, was never able to recover. And so the thinking being, if we could stabilize the metabolism of the cell and the metabolism is really just the energy production of the cell, if you could stabilize that, then you might have a chance at helping the cells survive and either slow or halt progression of disease.

So why is energy important? Energy is important because you're talking about biological systems in the body that require lots of energy. And so, if we think about the eyes, the back of the eye, the retina, is actually, it's brain matter. It's gray matter from your brain in your retina. And the brain represents 2% of body weight, but over 20% of the energy consumption in the body. So the brain and the brain matter

has very high energy demands, and it turns out that the eye is the highest consuming energy system within the brain. So small changes in energy have really big impacts in the eye.

Okay. So how does the eye and how do cells in the body, how do they get energy? Well, there's an organelle called mitochondria. And if everybody thinks back to their high school biology or maybe college biology, mitochondria are considered the energy factory of the cell. But they actually do a lot more than just produce energy. So mitochondria are responsible for dealing with stress, right? So the eyes see lots of stress because they're constantly bombarded by the energy of light coming into the eye from the sun and sources, and that creates a lot of stress. So the eyes are constantly dealing, and the cells in the eye and the cells in the retina, are constantly dealing with lots of stress. So mitochondria are really important for that. They also are responsible for intercellular communication, talking about what the cell needs to do to deal with all the various functions of the eye.

So the thinking being, if we could target mitochondria and stabilize mitochondria, then we would have a chance to treat these diseases. And certainly, you have, with the genetic mutations within retinitis pigmentosa, a great deal of metabolic stress on top of the standard stress, the eye sees coming in. And we see the exact same thing in age-related macular degeneration. And so the company is focused on mitochondria for that specific reason.

Ben Shaberman:

And if we could sum up the function of mitochondria in maybe, a simple analogy, would you say that mitochondria are like the powerhouse or the fuel cell for cells?

Mike Voevodsky:

That's right. That's exactly right. The mitochondria, they're known for their energy production. And sometimes to keep it simple, I like to think about mitochondria as let's say, the engine of your car and the engine of your car produces energy that you need to move along to function and drive the car. And sort of the normal life of your car, the older your car gets, the more energy and where there is on the engine and the same thing happens with mitochondria. And what most people don't realize, and what's unique about mitochondria, is they actually have an ability to repair themselves.

So as they build up damage over time, the mitochondria go through a quality control process. So they're actually able to cleave off, break off the damaged portions of mitochondria, and then that essentially gets recycled. And then the cell goes through what's called mitochondrial biogenesis, which is a fancy term for basically, the creation of new mitochondria. And then those new mitochondria get put into the mitochondrial network and they get fused back in there. And so mitochondria are, if they have enough energy and they're able to function normally, they're able to continually improve the quality of their duration and their ability to produce energy over time. And so if you don't take your car in and change the oil and put good gasoline into it, ultimately, what ends up happening is your car loses power, it actually pollutes more.

And we see the same thing in mitochondria. If mitochondria, over time, slowly lose their ability to produce energy, and if they're constantly stressed, then there's even more of attacks on their energy supply. So mitochondria, when we talk about stress, there's oxidative stress, which is essentially, the pollution that comes out of mitochondria themselves in their everyday working as well as the cells. And so mitochondria's ability to handle this oxidative stress is also a function of this quality control process.

So the goal here for us is, if we can keep the engine in its best producing and best functioning form, then when you have stress, if you need to accelerate and hit the gas within the cell to deal with a dangerous situation, then when you step on the gas, you actually do get the energy production that you're looking for. And what we find in cells that are under constant stress from drivers of disease or just aging itself, is

that they have less energy than is necessary and therefore, they pollute more and they can deal with the pollution and the oxidative stress in the cell less effectively.

And those are things that ultimately, end up driving pathology, the disease itself, and ends up in cell loss in the eye. And so when we look at the literature, the science is very clear that mitochondrial dysfunction is a driver of pathology and retinitis pigmentosa in age-related macular degeneration and a number of retinal diseases out there. So if we're able to stabilize mitochondria, they can continue the repair process, continue to function at their maximum capacity. And therefore, again, getting us back to slowing or halting disease progression.

Ben Shaberman:

That's a great description of why mitochondria are such an important target. And we at the foundation are very much in agreement that the science really points toward mitochondria as a therapeutic target. And I know one reason or another reason that we're really excited about this approach, is that it's gene agnostic. It's designed to work independent of the mutated gene causing the disease. And that can be true for people with RP, other retinal conditions, and it's an important factor in age-related macular degeneration. And those reasons are why we've invested pretty heavily in MitoChem and Barb Rohrer's work over the years, because of the great science and the fact that it has the opportunity to help so many people.

So Mike, can you talk about how Barb began the process along with the late Craig Beeson, a co-founder of MitoChem, to identify a compound or compounds that might help mitochondria health and boost function?

Mike Voevodsky:

Yes, absolutely, Ben. So great points on that. I think one of the elegant features of our approach is that it is designed to be gene mutation agnostic. And as most people in your audience know, there are hundreds of genetic mutations that sort of live under the umbrella of retinitis pigmentosa. And while there are great programs under development today in gene therapy, those gene therapies are really limited to the specific gene mutation. And so if we're capable of proving out what we're doing, we think there's a great chance to essentially treat all comers, which we would think would be a tremendous benefit for the amount of energy and time that goes into bringing a compound to market. We think that would be great. So getting back to your question about the process for identifying compounds.

So Dr. Rohrer and Dr. Beeson, just a bit on Dr. Beeson. Craig Beeson is a medicinal chemist and a mitochondrial expert. And when Barb identified this potential therapeutic target, she got together with Craig Beeson and said, "Do you think we might be able develop these compounds?" And he was excited about it and said, "Yes, I think this is a great approach." And so the two sat down and put together a plan to screen compounds in a publicly available database called the Cambridge database, I think there are 50,000 compounds in there. And they screened those compounds in tests to show which compounds could protect cells from stress, and they used stresses that you would find in the eye. And then they took the compounds that were successful at protecting cells from the stress in these tests, and then they ran them through a secondary screen to make sure that the protection was driven by a mitochondrial dependent function.

And so there is a fancy instrument called the seahorse instrument. The seahorse instrument is like a treadmill, and you can put cells into this instrument and test what their capability is... What their ability to walk, jog, and then run. And what they wanted to do is, they wanted to make sure that the compounds that they were looking at were protecting, based on their ability to protect metabolism or restore metabolism. So those items were screened as a secondary step to identify the ones that were

impacting mitochondria in a positive manner. And then ultimately, what ended up happening, was that as they were looking at these compounds, they found that a couple of them overlapped in three-dimensional space, and Craig recognized that there would be a unique, what's called, pharmacophore structure, that the company ultimately then used to start synthesizing very specific compounds that were protective for cells in a mitochondrial dependent manner.

And so over a thousand compounds were produced that met these criteria. And ultimately, what we did is we ran them through a number of tests to find out which ones had the highest level of protection, and then, specifically for the therapeutics that we're interested in, those being able to be delivered to the eye, looking at ones that could be delivered in an eye drop. And as we think about retinitis pigmentosa, oftentimes, we know that because it's an inherited retinal disease, you can identify children who are most likely susceptible to this. And so you'd begin, ideally, treatment as early as possible. So the idea of an eye drop as a consumer patient friendly form of therapeutic delivery was a goal. And so we looked for compounds and we screened and optimized for compounds that were able to be delivered topically to the eye so that the compound could reach the retina.

Ben Shaberman:

That's great. I think finding local delivery like that, an eyedrop approach would be awesome. And I know that's challenging to get drug from the front of the eye to the back of the eye, but it's great that Barb and Craig were considering compounds that might be amenable to that from the get go. So you touched on something that I think is interesting about when to treat. Who will benefit most. And obviously, if you can boost mitochondrial function early on in disease, you may have the best opportunity to preserve vision. But do you think this approach could also benefit people with maybe mid-stage or later stage disease as well?

Mike Voevodsky:

I think the simple answer is yes. Obviously, the sooner, the better because what you want to do is you want to protect the cells from reaching a point of cell death. But these diseases are slow progressing and so even if you are mid-stage or late stage, preserving photoreceptors in vision is still very much a possibility. One of the interesting things we found with the compound in some of the animal models that we've run is that not only is the compound able to preserve the structure, the specific photoreceptors themselves, from cell death, but they're able to actually improve the function. So when we think about the eye, we think about rods and cones, rods seeing light, cones seeing color. And as human beings, we really rely on the cones, really for a fine visual acuity. So when we think about looking at something in the distance or reading a book or driving, we're really using the cones in an area of the eye called the macula, which is really cone dense.

And then around the macula are the other photoreceptors, the rods, that see light. So what is known about the biology within the eye is that there's a symbiotic relationship between rods and cones. And that while, let's say, diseases like retinitis pigmentosa affect the rod receptors, we end up losing cone receptors because cones rely on rods to survive. There's structural reasons and there's actually chemical reasons. So the rods give off an important chemical, a neurotropic factor that cones need to survive and function. And what was interesting is, one of the studies we've done had shown that not only can we preserve rods and cones, but we actually get cone function to improve between 30 and 50%.

So when we think about the stage of progression of disease, there is the potential that these therapeutics could actually restore or improve vision to some degree, based on the fact that cone function improved. So we're excited about that, and I think that those at FFB on the science advisory

Board are excited about that as well. And so we think that these compounds can work for every stage. Ideally, the sooner, the better.

Ben Shaberman:

Exactly. And I would agree that many of our scientific advisors are excited about this approach. So the compound selection and compound refinement have been underway for a number of years, and if I'm correct, you do have a lead compound now?

Mike Voevodsky:

Yes.

Ben Shaberman:

And so what needs to happen from here on out to get to a clinical trial? What are your next steps?

Mike Voevodsky:

So our next steps are sort of twofold. Technically, where we are now is, we need to run this compound. The compound is called MC 16, and it's been formulated into an eye drop that we have studies that demonstrate efficacy, both preservation of structure and function in animal models. And now this compound needs to go through the safety and toxicology studies required before the FDA will allow you to treat human beings. So there are about two to $3 million worth of toxicology studies necessary to conduct so that we can file a document called an investigational new drug, an IND, to the FDA, which upon their allowance, will allow us to move forward and start treating human beings in a first in man clinical trial.

Ben Shaberman:

That's great. We obviously wish you expedience in moving the compound forward through those studies to get it into the clinic. So Mike, thanks for reviewing mitochondria as a therapeutic target and giving us a great overview of the therapeutic approach that MitoChem is taking. When we were preparing for this podcast, you sent over a bio and I want to switch gears a little bit and talk more about you because I think it's interesting how you made it into this space. You didn't just come through the traditional eye research path, and in your bio, it says that you have extensive experience with disruptive technology companies. That sounds both intriguing and a little ominous. So can you tell us more about what you mean by disruptive technologies, and then tell us how you ended up at MitoChem after a pretty interesting and varied career.

Mike Voevodsky:

All right. Well, what I mean by disruptive, is a technology that actually makes significant change. That's truly innovation. So there's a full range of new products and innovation. Some of them are evolutionary and some can be described as revolutionary. And so I've always been intrigued and fascinated, and frankly, I've been driven my entire life by innovation or what would, in my later years, I'd understand to be innovation. So the idea of creation and bringing something new to market would be great. And the ones that are, I think, most thrilling for me to be involved with, are the ones that actually make a real change and make a real impact. So disruptive technologies come in, so you think about, let's say, the Pony Express being disrupted by electronic communication. So the ability to really transfer the horse to the car as opposed to more horses possibly making it faster, just really thinking about a new approach.

And so I've been driven to seek out, working with really bright people, working on great innovation. And so I've been fortunate to have had a career that has allowed me to do that. And when you said, "How did I get into this?" So I've had inventors and creators in my family for generations. Probably most notable was an uncle who was a PhD in cybernetics out of Stanford and had made a number of key inventions. And so as a young boy, I was always fascinated about what he was doing because my father, on the other hand, was a lawyer, and that was about as dry of a subject as you could have as a child.

Ben Shaberman:

An important role, but not usually all that innovative.

Mike Voevodsky:

Right, right. Yeah. And some people would actually say the legal counsel, your lawyers try to stifle innovation, try to minimize risk, as opposed to driving towards risk. So when I got to college, I was trying to think of what do you study to get into invention? And I started my career as an engineer and it quickly became apparent that there didn't seem to be a lot of creativity in engineering. And luckily, there was an entrepreneurship program that was started at the University of Arizona my junior year. It was an honors program. I applied and I got into it my senior year and ended up doing a technology transfer in high-tech optics. So I co-wrote the marketing and business plan for the company, we got a contract with Los Alamos National Labs for a large laser fusion project, and ultimately, that company was making large, lightweight mirrors, ended up producing the optical test bed for the James Webb Space Telescope.

So as people think about these amazing images that are coming back from the James Webb Space Telescope, I'm just excited it's a low profile place to be, but it's just wonderful to know that our company was involved in making that technology a reality. So fast-forward, I've looked for opportunities to work, places that were doing high innovation and disruptive activities, overturning leaders, bringing new products to market. And just prior to joining MitoChem, I was involved in a startup where we were looking at using therapeutic radiation to treat wet macular degeneration. And so it was identified by a very smart doctor, also a physicist, that radiation has long been used to treat abnormal blood vessel growth for well over a hundred years. And the current standard of care for wet macular degeneration is an injection into your eyeball every four to six weeks. And if you're one of the lucky people that it works for, you're on this therapy for life.

And so while it works and people are benefiting from it, there's a large group of people that aren't benefiting from it, and there's the opportunity to find a better way to deliver a therapeutic. So we ended up starting a company and building around a technology to deliver a minimally invasive approach that would be a one and done therapeutic for wet macular degeneration. And that company is currently a clinical stage company, working it's way through, with the promise that ultimately, upon commercialization, there may be the ability to actually have a single treatment, without actually ever having to put a needle into your eyeball, that will stabilize and improve vision without ever needing another injection.

So when I was introduced to MitoChem, the idea that you could actually slow or halt progression for a really important patient population, those suffering from retinitis pigmentosa, and an orphan disease, and do it in a manner that allows a single therapeutic to treat all comers, just struck me as something that was really worthwhile doing and has been driving me since I joined the company four years ago to bring this potential therapeutic to market.

Ben Shaberman:

Well, we're delighted that through your journey from the James Webb telescope to this radiation therapy, that you ended up at MitoChem and you brought your smarts and your entrepreneurship to the mission of Fighting Blindness, and we're very excited about the potential for Mitochem's compound to get into trials and hopefully, out to people. But I do have one question before we conclude here on the wet AMD therapy that you referenced. So you mentioned that that's one and done, are the investigators putting a tiny piece of radioactive material into the eye near the blood vessel growth? Tell us more about how that works.

Mike Voevodsky:

Sure. So the therapy involves delivering a therapeutic dose of radiation, and that's done with a type of radiation called beta radiation. So everybody knows about X-rays, that's gamma radiation. That's like a bullet. You shoot this bullet and it'll pass through paper and glass and walls, and it has lots of energy and goes a long distance. Beta radiation only travels a very short distance. And the brilliance of that is, is that if you can place this radiation source for a short period of time at the vascular lesion that causes wet AMD, hold it there for what essentially, amounts to about five minutes, and then remove it, then the radiation that's delivered is able to essentially, force the body's natural process to remodel the vasculature and normalize it and essentially, resolve the growth of new blood vessels that cause wet AMD.

And this is all done without actually ever going into the eye. It's a small incision, it's called conjunctiva. It's like a bed sheet that sits over the eye, and then this curved cannula that has the radiation source in it, is slipped underneath the eyelid and then gently placed to the back of the eye, and then the surgeon looks through the dilated pupil of a patient and uses a light that's on the tip of this cannula, this little probe. When that light reaches the target, they start a clock, hold the radiation source there at the target for five minutes, and then when the five minutes is up, they remove it. This is a procedure that can be done in a physician's office in a sterile field, without ever having to violate the eye itself.

And so, it's a great promising therapeutic delivery that I hope, makes it to market through its clinical trials because I think, one, it'll be able to address a lot more of the people that aren't responding to the current standard of therapy. And for those who are in the current standard of therapy, gives them an option to have a one and done treatment, as opposed to a lifetime routine of injections into the eye.

Ben Shaberman:

That's really cool. It almost sounds like science fiction. You really don't have to penetrate the eye and it's one dose. That's really elegant.

Mike Voevodsky:

Yeah.

Ben Shaberman:

Well Mike, this has been a lot of fun and very informative. I compliment you on your ability to communicate science well, which is something I try to do. So it's fun to have you as a guest and to explain again about mitochondria and MitoChem's emerging therapy. So we appreciate you taking time out of your busy schedule to educate us and update us on where MitoChem is at. And constituents out there can be assured that I will provide updates on MitoChem on our website, and potentially, through other sources as they become available.

So again, Mike, thanks for joining us and good luck in your endeavors with Barb Rohrer and MitoChem.

Mike Voevodsky:

Thank you, Ben. It was great to speak with you today. And I just want you and the audience to know how much we greatly appreciate the support that we receive from the foundation and all those who donate to the foundation, and just know that we're really driven to try to get this therapeutic to market as quickly as possible, because there are so many people who desperately need a therapy for these horrible vision loss diseases.

Ben Shaberman:

Very well said. That's exactly what our constituents want to hear. And listeners, thank you, as always, for joining Eye on the Cure. We look forward to having you back for the next episode.

Speaker 1:

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