Speaker 1:

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

Speaker 2:

Welcome everyone to the Eye on the Cure Podcast. I'm your host, Ben Shaberman, senior director of Scientific Outreach with the Foundation Fighting Blindness. I am really excited today to have as my guest David Gamm. He's an MD PhD at the University of Wisconsin Madison, and we're going to cover a lot of ground on stem cell therapies for retinal diseases. The work David is doing is very cool and we're excited about its potential. David, it's great to have you on the podcast.

Speaker 3:

Thanks, Ben. I'm glad to be part of this. It's my maiden voyage on a podcast. I've heard of them before, though.

Speaker 2:

Well, I'm sure you're going to do a great job. We're looking forward to hearing all your great knowledge and information. Before we get into the conversation, I wanted to let our listeners know David is a professor of ophthalmology and visual sciences at Wisconsin Madison. He is the RRF Emmett A. Humble Distinguished Director at the McPherson I Research Institute and the Sandra Lemke Trout Chair in eye research. Lastly, he is a co-founder and chief scientific officer of Opsis, a company developing stem cell therapies.

David, it's been great to have worked with you for so many years. I've always thought of you as so strongly committed to strong science, and moving forward with your research very methodically and carefully. You're not a person to express a lot of hype. You're very careful about what you say when you are setting expectations for emerging therapies. I think that's really important. And really, over the years you've emerged as a leader and an authority in a very challenging field. You're my go-to person when I have questions or want knowledgeable perspectives. Again, thank you for being such a great and reliable resource.

Speaker 3:

Thanks, Ben. I think it comes from kind of a position where you want to under promise and over deliver, and also interacting with patients in my clinic over the two-plus decades now, when you're actually talking to the individuals who are hoping to have therapies down the line, you want to make sure that you're doing right by those folks that are going to be putting themselves potentially at risk for experimental therapies, and so make sure they have right-sized information and don't fall prey to all the other folks out there that are really just looking to make a buck. That's an important part of what we do. I appreciate that comment.

Speaker 2:

Well, thanks again. You communicate so well and so clearly and in a very well-balanced way. Your lab is focused on what we call pluripotent stem cells. These are the cells that can really become anything we need them to be and they're easily replicated. Usually these pluripotent stem cells are either the human embryonic or the induced variety. We can talk about that in a moment. But you can use these cells and do use these cells to investigate the causes and the pathways of retinal disease. You use these to create

models for testing emerging therapies. Most excitingly, I think, is you can use these cells as actual therapies, as emerging therapies. For this discussion, I really want to focus on emerging stem cell therapies, especially strategies or replacing lost retinal cells. Maybe we can start off by talking about, I've given sort of a of quick introduction to pluripotent stem cells, but perhaps you can compare and contrast the human embryonic variety and the induced variety a little bit.

Speaker 3:

Sure. I think you brought up an important point that I don't want to just immediately skip over, and that is the word stem cell is thrown around a lot, and there are a lot of different types. The classic one we think about are bone marrow stem cells that are used in transplants for individuals who have cancer or other problems. Those types of stem cells have a limited capacity for making different types of cells. In the case of bone marrow stem cells, it can make all the cells that you find in your blood, but it can't make anything else. When you're looking at sources of cells for brain or retina or tissues that cannot regenerate on their own, really, you only have pluripotent stem cells, and they have to be of human origin in order to be able to go back into a human. The two types are, as you mentioned, the embryonic stem cells, which kind of came on the scene in the late nineties with James Thomson here at UW Madison, and then the IPS cells, which came on in the mid two thousands with James Thomson and Shinya Yamanaka.

Just focusing now on those two types, embryonic stem cells are obtained from in vitro fertilization. You have an egg that's been fertilized and would otherwise be discarded in the process of IVF. What Dr. Thomson did was develop a way to culture those cells, keep them alive, and keep them in that very primitive state where they have the potential to become any cell type in the body. Which is a remarkable and very powerful capability, but also very daunting, because you have this single group of cells that could become anything and will become anything, and actually will become bone and teeth and a little bit of eyes and a little bit of liver. Being able to harness that power and to direct it towards the cell type or tissue type that you're interested in studying or ultimately treating is a very hard sequence of events to develop.

That's what we embarked on with the retina. Along came the induced pluripotent stem cell technology in the mid 2000s, and what that did was it took cells that we all have walking around either skin or later on, white blood cells that we can obtain from a simple blood draw like you might submit for a cholesterol check, that technology was able to take those cell types and then reprogram them or basically turn back the hands of time so that they essentially were at the same level of development as embryonic stem cells. That's an additional step though, and that's important when we talk later about manufacturing. With embryonic stem cells, you start with the raw material that you're going to develop your cell or tissue from. With induced pluripotent stem cells, you start with a pre material, that being either skin cells or blood cells, and there are other types of cells, too.

The benefit is you can take that from any individual walking the face of the earth. It doesn't have the same ethical underpinnings that embryonic stem cells do. But it does add that additional step where you're taking those cells, and then through a series of fairly complex steps, introducing genes, and there's roughly about four of them, that convert them back to this more primitive state. From a manufacturing standpoint, that adds additional complexity time onto the process. But ultimately, you can get to essentially the same spot. You just need that extra step when you're talking about IPS cells.

Speaker 2:

Right. I'll add that while we've used the embryonic variety in the clinic for a longer time, one of your collaborators, Kapil Barty at the National Eye Institute, not so long ago, launched a trial for AMD using induced pluripotent stem cells, so they are finally in clinical trials for retina, which is pretty exciting.

Speaker 3:

Yes. Yeah. ES cells or embryonic stem cell having been around longer, there is a longer track record in clinical trial, but IPS cells are now firmly in clinical trial, in [inaudible 00:08:41] work and others as well [inaudible 00:08:43]. So, yes, both of them have been shown and to be viable in terms of making it to clinical trial, which means it has to pass all the regulatory hurdles and all of the safety checklists that are really important and necessary to start seeing what they can do in a human patient. Yes, we're out of the gate. This isn't just something that we're pie in the sky hoping to do sometime in the near future. It's being done for some cell types.

Speaker 2:

Right. Speaking of cell types, that's a good segue to my next question. In people with retinal diseases, we know they lose rods and cones, the photoreceptors, but they also lose in some cases what are known as RPE cells or retinal pigment epithelial cells. Can you talk about why some patients more advanced disease states may need photoreceptors and/or RPE cells?

Speaker 3:

Yeah, so the photoreceptors and the retinal pigment epithelial cells are kind of like the Batman and Robin of vision. photoreceptors, the rods and the cones, they're at the apex of your visual system. They're the cells that detect light and initiate the whole process. But they're arguably the most complex and metabolically active cell in the entire body, meaning that they need a lot of help to do that job. They're kind of divas, they're high maintenance. The cell type that is predominantly responsible for maintaining their happiness is the retinal pigment epithelium, which is snuggled up right next to them. As you might imagine, diseases might either primarily affect those photoreceptors, which would eliminate the switch, the initial switch in the system and affect your vision, or they could primarily affect those maintenance cells, those helper cells, which as they perish or become dysfunctional, you wouldn't necessarily immediately lose vision because the photoreceptors are still hanging around wondering where their servants are. But eventually, in the absence of those helper cells, the photoreceptors die as well.

You have either primary photoreceptor death, and your typical ones there would be retinitis pigmentosa, or you have secondary photoreceptor death due to defects in the retinal pigment epithelium, and that would be macular degeneration and other types of inherited disorders, like Best Disease would be another one as well. Then the RP65E-LCA gene therapy trials would be in that category of primary RPE defects, too. The interesting thing to also consider is that you have to be cognizant of the course of the disease, because if you're early on in any degenerative disease, your best bet is to try and save the cells that you already have, and that could be through gene therapy, genome therapy, maybe pharmacologic interventions. But then as the disease progresses and the cells die, you then have to look for alternative approaches of which cell replacement is one

I'm mentioning this because with retinal pigment epithelial degeneration, if you get to it super early before you've lost a lot of vision, maybe you only need to replace the retinal pig epithelium, and because there's enough photoreceptors still around, they're not happy, but they haven't died yet. Whereas if you're later on in the disease where you've had substantial vision loss and photoreceptor death, you'll need to replace both. There are considerations where in terms of different diseases or

different stages of disease where you may need only photoreceptors, you may need only RPE, or you may need both.

Speaker 2:

Right. I love your analogy of RPE being like the Robin and Batman being the photoreceptors. I think that's where you were going.

Speaker 3:

That's probably the way the analogy works. Yeah, I hadn't thought it through that deeply, but yes, that would be.

Speaker 2:

And Robin shouting out, "Holy retinal degeneration, Batman."

Speaker 3:

And not getting any of the credit.

Speaker 2:

Right, right, exactly. He's pretty important to the equation as well.

One of the things that I've been excited about that you've been working on is the combination therapy of RPE cells and photoreceptors for people who have lost both to, as you mentioned, some type of macular degeneration, maybe AMD maybe Stargardt disease, or even certain forms of RPE. One of the things you've been working really diligently on for many years is scaffolding, and that is part of this two-cell type solution. Can you talk about why this scaffolding is so important and what the scaffolding really is?

Speaker 3:

Yeah. It comes down to the architecture of the retina. We've talked about photoreceptors and retinal pigment epithelium. They're not like two ingredients mixed together in a bowl, they actually have very specific layers and orientations to one another. These aren't randomly-placed cells within kind of an amorphous tissue. And there's other layers that we haven't even talked about that the preceptors connect to and then those downstream cells connect to prior to sending the signal back to the brain. It's like a complex layer cake, and it's really just a beautiful structure altogether. But because it's so beautiful, you have to start thinking about how do we not just replace those cells, but how do we start to, even in a crude way, recapitulate that beauty, that orientation, and that structure. Usually keep it simple to start with, and so the initial approaches are simply to try and place the cells in the appropriate space underneath the retina and hope that some of them do orient and make the appropriate connections.

But as kind of next-generation approaches, one can envision making that a much more efficient process by reorienting those cells. That can be even just a single cell type, because photoreceptors have an up and a down, and RPE have an up and a down, and so if you get that mixed up, then you're trying to put the Legos together, you're only going to have a certain number of those Legos that are going to randomly line up appropriately. Being able to reorient them on a scaffold or some other device that has to be able to be placed surgically into a very delicate area, and itself not have any deleterious effects in that very delicate tissue is a tall order, but one that's definitely worth investigating. We've done that

now for many, many years. That's even more important when you're dealing with trying to replace multiple layers in that cake, in this case RPE and photoreceptors.

The reason for that is that those two cell types actually in your eye are not firmly connected to one another. They're loosely connected to one another via various processes like fluid flux, and fluid flow across the two cell types, and forces within the eyeball that holds them together. That's why if you have a detachment, that's where you always split. The split is always between the RPE and the photoreceptors. Being able to surgically manipulate two layers like that, that don't actually want to be stuck together permanently, and maintain that orientation through the process of insertion into the subretinal space, and then following that, be able to have them stay together in the proper orientation, that's tough. Having a scaffold that is ultimately biodegradable, because you're not supposed to have these artificial materials in the subretinal space, is really important. We've worked with some wonderful engineers, Sarah Gong and Jack Ma here at the UW Madison, and they will work with various biomaterials.

Actually Jack Ma, his expertise is making very, very, very tiny chips for computers. I mean, cutting edge stuff so they can jam more and more things into smaller and smaller devices on your wrist, and even smaller than that. And so, when I approached him and I said, "I kind of need that, but instead of your electrical circuits, I'm going to give you cells." He thought that was the greatest challenge in the world. He and Sarah started to work on this a number of years ago, and we've had multiple iterations now, different shapes and styles that allow us to see the RPE cells on them first and now be able to take the photoreceptors and implant those on top of them, and they're able to maintain their orientation, and also be strong enough to withstand all the surgical manipulation necessary in the manufacturing that's required to produce these things, while still being, from all testing thus far, safe and biodegradable in the back of the eye.

Speaker 2:

Everything you've just talked about really underscores the challenge of getting these cell-based therapies to work properly, to orient properly, to integrate properly, and of course, we want the cells to survive. One question I have is when you're putting together a treatment, an emerging therapy that includes RPE cells and the photoreceptors, is the scaffolding going in between those two layers of cells?

Speaker 3:

There's different ways you can do it, but the answer to that is no. We've worked very hard to minimize the amount of synthetic biomaterial that's required. Our initial designs had kind of a one-to-one ratio of synthetic material. It's biodegradable and theoretically safe in the eye, but it's still a burden. It's something that's not supposed to be there that has to degrade and the eye has to take away between, so one to one between that and the cells. Additional iterations of that technology has allowed us to make that one to four, so we have about four times as many cells as we have the biomaterial.

The rate limiter there is if you get too skimpy on the scaffold, it becomes too flimsy and sticky to be able to handle. It looks great in a picture or in the bottom of a dish, but if you want a surgeon to bring that up into a device, manipulate it, put it through somebody, an incision in somebody's eye and place it in the subretinal space, it's going to just fold up and disintegrate. You have to have that balance between the handle ability of the final product and then what it's potential for both good and evil in the body.

That's another part of it too, is that all of these things, and we take very the safety portion very seriously, because until you start putting it into patients you really don't know, and so you try to stack the deck in favor of an inert outcome at the worst and a good outcome at the best. But there's always

that specter of you could have something come out where a patient is harmed. That's why all of this work ahead of time is important and not something we can or want to rush.

Speaker 2:

Exactly. I think that's such an important point is this is one reason science doesn't move maybe as quickly as we'd like, because we're trying to ensure safety and of course the chances for success and efficacy. Early on in our conversation, I mentioned that you are a co-founder and chief scientific officer at a company called Opsis. I know there's still more work that needs to be done for you to move something into a trial through an Opsis therapy, but can you tell us what you're working on there?

Speaker 3:

Yeah. The opportunity to start Opsis Therapeutics in 2016 really was in partnership with Fuji Film Cellular Dynamics International, which was Cellular CDI or Cellular Dynamics International was founded by James Thomson, so you can see all of the nepotism that's involved here in Madison when it comes to stem cells. But then Fuji Film bought CDI and started a cell therapeutics arm and then approached me about a subsidiary that would be focused on ocular cell therapies. That interests me, and so we developed Opsis Therapeutics there and kind of built out a really amazing team here in Madison in partnership with the UW Madison itself. Then more recently, we've entered into a strategic partnership with Blue Rock Therapeutics in Boston and Bayer Ag in Germany, so it's really a transcontinental effort at this point. We have some amazing expertise and resources at our disposal.

What we started with though was this big question about and this challenge, how do we take what we do, what I was able to do in the lab on a very small scale kind of inefficient level, that was using techniques and reagents and steps that really were not conducive to going into a patient. I mean, I get that all the time. People say, "Hey, what are you doing in the lab? Can you stick it in my eye?" No, it would not be a good idea. We'd give you infections. There's all sorts of things that have to go on, use of clean rooms. Every single step that goes into the manufacturing of any drug or therapeutic that goes into a patient has all of these quality-control measures that need to be passed so that we don't do harm. That can cost millions and millions of dollars and take decades.

We have the good fortune of being a mile away from a company that for the prior 10, 15 years had worked out a lot of that manufacturing process that can go into eventually human patients already. I myself in my lab would never have been able to get the funding or have the number of people and assemble the expertise necessary to do that in 20 years, much less in two. We were able to combine the patents and technology we had developed here and superimpose that on the existing expertise of how to take whatever cell type you want to make from IPS cells and make that suitable for human use. That means cryo preservation, that means formulation, that means vialing, that means converting what we did in a dish to something that was in tandem three liter bile reactors, where we could, instead of making a million cells and it took us 200 days, we could make a hundred billion cells in 70 days. That sort of scale up in manufacturing we were able to accomplish in a handful of years.

Then once you're able to make that raw material, then you can start thinking about how do we fashion a clinical trial to test to see what they're going to be doing, and that's where we're at right now with the clinical strategic partnership with BlueRock and Bayer Ag. We're in the middle of developing those protocols and we hope to initiate clinical trials in the coming few years, hopefully sooner, but one never knows. We've already had multiple conversations with regulatory agencies, and so we're pleased with where we are right now. Still a ways to go, but we have the team and the ability to get there, and so it's exciting.

Speaker 2:

It is exciting. I'm glad you touched upon manufacturing. That's a topic that can be a whole podcast unto itself. It's not trivial to make on a large scale cell-based therapies for really any condition, including the retina, so again, thanks for mentioning that. I want to say that at least generally speaking, the work that you do can apply to a lot of different diseases, RP, Stargardt disease, AMD, again, depending on what cell type you're using. But you happen to be focusing on a particular form of macular degeneration, this is in your own lab, and that condition is called Best Disease. And can you just before we close out, tell us what you're doing in Best Disease?

Speaker 3:

Sure. Best Disease is a bit different. I mean, at least the work that we're doing on it. It certainly does fit in its end stages as a condition that could be treated with cell therapies, so cell replacement. Because in folks who have had that disease for a very long time, like in macular degeneration, they're missing functional RPE cells and photoreceptors. It's also important to say that stem cells, like every other therapy, are not a magic bullet for whatever ails you. There is a window in which replacement of single cells or even two cells might be appropriate, but past a certain point, you may need replacement of the whole retina. And so, you have to right size the treatment for the disease and the stage of disease that you're at, like I mentioned earlier.

Best Disease, the work we're doing there, one of the reasons we focused on that is because it's a nice platform for looking at the full spectrum of disease and how stem cells might be able to play a role in the development of therapies. Best Disease is a relatively slow moving disease. It affects the macula, which is a small but critically important part of our retina. It's about five millimeters in diameter. It's a very imminently approachable and treatable portion of our retina. It can take decades for people to lose substantial vision, which means that we can intervene on patients as adults and still be able to preserve or potentially turn back the hands of time on patients who have yet to lose significant vision. Then ultimately, at the far end of the scale, perhaps do cell replacement.

I've already talked about the cell replacement portion of it, but one thing that hasn't been the focus is how we use our model systems to in partnership with, say, gene therapy to advance those types of treatments for patients at earlier stages of disease. What we've done is create multiple different culture systems from different patients with distinct mutations that cause Best Disease. Then we've used that platform to screen different types of gene therapy, and gene editing, based editing, all sorts of read through, all sorts of different technologies. Because we have an excellent readout system for that, we can tell if a therapy gets into the appropriate cell, in this case a retinal pig epithelial cell, we can tell how efficient it is at getting into that cell, and then we can tell whether or not it does its job by correcting the defect.

We could do that both directly by examining the direct function of the protein that's dysregulated in that disease, as well as looking downstream at the various processes that gene is ultimately important for in the function of that cell. Because we have this suite of testing material and the ability to get really rigorous information, it's become a real goldmine for us to work with companies and to develop therapies ourselves that can hopefully mitigate that disease at earlier and mid stages. Then if folks are beyond those stages, of course we have the cell therapies that we talked about earlier in the podcast.

Speaker 2:

In summary, through your cell-based modeling systems, you're really able to test a variety of gene and genetic therapies for Best Disease. That's what you're doing.

Speaker 3:

Yeah. In the case of testing, we're using diseased cells, so cells that you wouldn't want to put back into a patient because they have the defects still in them. But in this case, we're trying to correct that in the laboratory. That's how we advance gene therapies and other types of non-cell replacement therapies. In the case of cell replacement, we want a perfect cell. We want a cell that doesn't have any deleterious mutations or problems with it, either by correcting it or using kind of a universal cell that is normal to begin with.

Speaker 2:

Right. David, thank you for all this great information. I guess one thing I want to say before we close is you've covered what's been really decades of research to get to this promising point where you're preparing for human research and some other investigators have moved into human studies. It's a lot of painstaking challenging work that the foundation and other groups have funded, again, for so many years, so thanks for your commitment. This is not an easy business to be in, because you really have to work for many years until you start really seeing the potential fruits of your labor. Thanks for your commitment.

Speaker 3:

Yeah, I'll be the last to complain about it. It so amazes me to get up in the morning and to think you can take a blood cell and turn it into a photoreceptor cell, something that will detect light at the same level in a dish or close to the same level as a photoreceptors in the center of your own eye or that of a non-human primate. I mean, that's pretty exciting stuff. To be able to work with that material is a big privilege.

I do want to say that the Foundation Fighting Blindness was way ahead of the curve on this back in the mid 2000s when everyone else was just kind of saying, "Hey, this is too hard. There's no way you're going to be able to take this, I mean, it's cool cells, they have a lot of potential, but to be able to really harness them and use them in a patient, I don't think so." Even I have to admit that I kind of felt the same way at that time. It just seemed like such a long way to go. But FFB had the confidence and rolled the dice on it, and they were way ahead of the curve, even on the federal government and myself and other stem cell researchers at the time. I think they had more confidence than we did. I've always appreciated that.

Speaker 2:

Well, we appreciate your great work and for taking what seemed like science fiction and making it a reality, so thank you. Before we close out, you're a busy guy. You've got a lot of projects going on, working with a company, your own lab, you're a professor, and you even see patients, if I'm correct.

Speaker 3:

Yep. [inaudible 00:31:01] all my years. Yeah.

Speaker 2:

Do you ever take a break? We're in the middle of summer. Have you been able to go on vacation, anywhere fun?

Speaker 3:

Oh, yeah. Yeah. I get to sit here and talk about it, but I'm not a one-man band work the cymbals with my knees and what have you. I work with an amazing teams. In every part of every hat that I wear, I'm fortunate to have folks that are supremely talented in what they do and also are of good nature. I think that's the main thing. I think ultimately, you're not limited in what you can do by who or what you have access to, but whether or not it's tolerable and fun.

I mean, it's amazing what you can get done if you enjoy doing it. If it's a chore, if it's a slog, if you have to work with folks that you'd rather not talk to, then that wears you down. From our sponsors, from our donors, from the people that support our lab financially, to my collaborators, to the folks that work in my lab, the company, my patients, everybody is just a delight to work with. Talk about privileges, that's a huge privilege. Not enough credit goes to the legions of folks that are so dedicated to helping people with incurable blinding disorders.

And getting the word out, Ben, like you. There you go.

Speaker 2:

Well, like you said, I have the privilege inside the foundation and outside between the constituents and great investigators like you. I agree. It's a real privilege. But you didn't answer my question. Have you been able to take a vacation?

Speaker 3:

Well, yeah. Yeah. I mean, my oldest daughter's getting married in October, and so the older my kids get, the harder it is to get everybody together. Most of the time I'm always home for dinner. That's my rule. I'm always home for dinner. I always go for a walk with my wife almost every evening, weather permitting. But mostly I'm kind of a homebody. I like hiking and going up north and relaxing, but I'm not a jet setter. My idea of a good time is reading a mystery novel or something like that, having coffee and not having to do anything. I can get that done just about anywhere. Yes, the answer is yes, I do have downtime.

Speaker 2:

Good.

Speaker 3:

Most of it involves my family. I think family's the most important thing to me. I've got some great grown kids and love spending time with them and extended family, too.

Speaker 2:

Well, that's great. I'm glad you have time to be with their family, appreciate your family. Everybody needs downtime. David, this has been a great conversation. It's great to reflect a little bit on the work that's been done over the years, and especially what you're working on now. It ultimately gives a lot of hope and encouragement to our constituents, so thank you for talking about it with me today. It's been a great conversation.

Speaker 3:

Thanks, Ben. These podcast things are kind of painless. I don't mind them. They're all right.

Speaker 2:

Well, that's my goal, to make it painless for both you and our listeners. Hopefully we're imparting some good information.

Speaker 3:

I'm not that oblivious. I kid. Yeah.

Speaker 2:

I know. I know. Thanks again, David. As always, thanks to our listeners for tuning in. Come back in a couple of weeks for our next new Eye on the Cure Podcast. Hope everybody's having a great summer.

Speaker 1:

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