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'm very pleased for this episode to have as my guest, Dr. Henry Klassen. He's an Associate Professor at UC Irvine, and Co-Founder of jCyte, which is a biotech developing a cell-based therapy for retinal diseases such as retinitis pigmentosa, and we'll be talking more about that in a moment. This emerging therapy has moved through a phase 2B trial that enrolled 85 people, and Henry will tell us more about the results from that trial.

Henry received his MD and PhD degrees from the University of Pittsburgh, followed by an internship at the Cambridge Hospital at Harvard Medical School, and a residency in ophthalmology at Yale Eye Center. Before we get going in the conversation or the Q&A, welcome to the podcast, Henry. It's great to have you.

Henry Klassen:

Well, thank you, Ben. It's great to be here.

Ben Shaberman:

And Henry, you and I have known each other for a number of years, and I remember talking to you and doing some articles back when J site was first formed, even before J site was formed and before the clinical trial started. And I just have to say, it's exciting to have watched the treatment move forward through a couple of clinical stages. And before we talk about the trial, tell us what got you interested in cell-based therapies for IRDs, for inherited retinal diseases?

Henry Klassen:

Well, that could be a long story if I make it that way, but I'll try to give you a more simplified version. But as an undergraduate, I was very much intrigued by the central nervous system, the brain in particular, and I quickly became enamored with the idea of trying to get some kind of repair, because one of the first things you learn about the human brain is this limited ability to repair itself. And that extends throughout the central nervous system, which includes the brain, the spinal cord, and the retina. And so this interest was driving my career interests as well.

And so during medical school at Pittsburgh I started working on a PhD in parallel, and I was doing retinal transplantation. So this was transplanting embryonic tissue between rodents, and we'd transplant the embryonic retina into the brain. And if you just transplanted a mature retina, it wouldn't do much. But what was fascinating was that these embryonic retinas were able to extend projections into the host brain, and I was able to show that those connections were actually functional by driving a pupillary light reflex in the host eye that was mediated through the retinal transplant. In other words, you shine a light on the transplant and the host eyes constrict down. So that was a kind of nifty way of showing that there was a functional connection between the graft and the host.

So in a nutshell, I had this thrilling feeling like, "Oh boy, we're rewiring the brain here." When the adrenaline wore off, I realized, "Wait a minute, I have to pick a medical specialty." And so I thought about what kind of neural degenerations might we be able to treat? Now, we're not going to be able to use the type of technology of retinal tissue transplantation for a number of reasons, but I was confident

that that type of technology would evolve with time. And so what happened is I picked out RP before I knew how I was going to treat it, because I thought RP is at the same time both severe condition and very disabling, but at the other extreme in terms of how much damage is done to the nervous system, it's remarkably circumscribed lesion in the retina, the results in this incredible devastating handicap to the patient. So from a medical intervention standpoint, RP looked very attractive, where hopefully we could make a few changes and get some really impressive results.

Now that said, rps been extremely resistant to therapeutics. Many people have tried. It's a difficult proposition. But in my mind it was the gateway to the central nervous system. If we think we can do regenerative medicine as we now know it in the CNS, we should be able to at least treat RP as a starting point.

Ben Shaberman:

And this early work where you were transplanting these retinal cells into the brains of mice, when was this taking place? It's quite a while ago, huh?

Henry Klassen:

Right. So that was in the 1980s in Pittsburgh. I finished up my PhD and then I went into ophthalmology. So I did the work on the PhD, which informed which disease I wanted to treat. I went into ophthalmology because I had already fallen in love with the idea of treating RP, and then I went into ophthalmology, but I didn't know what technology I was going to be able to use to treat RP.

I got all the way to Morefield's Eye Hospital in London where I was seeing RP patients finally. I saw a few during residency, but I went to a specialty clinic where we saw inherited retinal diseases and other medical conditions of the retina, and that was a thrilling experience. But one of the first things I realized is when you meet the patients one after the other, you realize you can make these very precise diagnoses of what exactly is going on, but you just don't have a lot to offer them except the idea that, "Well, we're working on it."

Ben Shaberman:

Right, right.

Henry Klassen:

So I was sharing their frustration because I wanted to be able to deliver some kind of good news, and I really wanted to work on that kind of thing. That's why I was an MD/PhD, was my real interest was in innovating to come up with something that would treat people. But at that point I was quite frustrated because there I was seeing RP and how devastating it is, and at the same time, the work in the lab was not going in the direction I had hoped. We try various things and we get various results, but I really wanted something that looked like it had a pathway to the clinic, not just a gee whizz paper, but something that had legs that could get all the way from bench to bedside.

And it was right about that time that I countered the neural progenitor cell story. So it was my buddy Mike Young who was working at Scapens called me in the middle of the night to tell me he had integration in the retina working with cells that he had gotten from Rusty Gage at the Sulk Institute. Long story short, I think if you bang your head on the wall hard enough and long enough, you appreciate a good thing when you see it.

So I wasn't the first one to jump on the cell wagon by any stretch. I had been doing all my clinical work, but what was remarkable was this amazing cell technology had been developed in the meantime. So the

timing, although it was a close call, it was actually good timing because just as I was struggling to think, how am I going to come up with something good for these patients, something very promising showed up. And we saw that these brain progenitors could integrate into a rat's retina, and not only in a retina, but it was proportional to the amount of disease in the retina.

So if you had a normal retina the cells wouldn't integrate at all, but if the retina was degenerating these progenitors cells would move right in. So there was something about the disease process that was alerting these progenitors to do something. And what they did was really quite spectacular. They could move into this mature retina, and start lining up and taking on morphologies that mimicked the morphologies of normal retinal neurons. And I just can't tell you how impressive that was to me. And basically at that point, having waited long and hard for something that looked promising, I jumped all in on this. But that's just the beginning of this story.

So that's how I became interested in cells and committed to the cell story, but there were many twists and turns to this. So first off, we were trying to get new rod photo receptors out of these progenitor cells, and they were making all these retinal neuronal types, but they just weren't making rod photoreceptors. They seemed to have an allergy against making the most common cell in the retina. So that was kind of a head scratcher. What's the hangup here? And I thought about it, I go, "Well, wait a second. These cells are very plastic and flexible, shape-shifting, they can do all these amazing things." But think about it, they came from the brain and now you're putting them in a retina. Well, maybe they've been specified to a point where they can't make photoreceptors anymore. Maybe that's something more intrinsic to a retinal progenitor cell.

Now, that seemed like a promising idea, but you couldn't just go out and order retinal progenitor cells in those days. Now, people knew there was such a thing. There were lots of studies by people like Connie Cepco, showing the role of retinal progenitors during development in the intact embryo of rodents. But that's different than saying, oh, we're going to grow a human retinal progenitor cell product. So there was this pivot to retinal progenitors, but then we had to figure out how to grow them. First thing I did was try to grow human retinal progenitors cells, and that's something that Tom Ray's lab had showed was feasible to some extent. But the question was, can we turn this into a viable product?

Ben Shaberman:

So ultimately you wanted to use retinal progenitors in the clinic, and can you talk about exactly what retinal progenitors are?

Henry Klassen:

So one way to look at a retinal progenitor is like it's a stem cell for the retina. So a true stem cell can make any cell type in the body, or at least it is renewing itself for the life of the individual, depending on your definition. But a progenitor is much more limited and circumscribed in its function. So the cells that a progenitor makes are restricted to the cell types present in the mature tissue. So the progenitor cell is literally the mother cell for all the mature cells in that tissue. In the case of the neural retina, so this is what people think of when they think of the retina. All the neurons in that retina are derived from retinal progenitor cells, and even the Mueller glial cells, if you know what those are, those are cells that help support the retinal structure and function. Those cells are also derived from retinal progenitor cells.

So these retinal progenitors, they're very flexible in what they can do. They divide, they make daughter cells, and those daughter cells can become all these different cell types. But by the same token, the retinal progenitor cell cannot make pancreas or liver or bone. But that's all fine for us from a clinical

standpoint, because we don't want any of those tissue types present in the eye after we transplant the cells.

So this limited ability to make various cell types is actually fortuitous from a clinical therapeutic standpoint, because you don't run the risk of making different cell types that you don't want to be present. The downside is that these cells do not self-renew indefinitely, but the good part of that is they do self-renew for a period of time. So we're able to manufacture these cells and expand them in culture.

Ben Shaberman:

Right, right. So in the jCyte trial, you injected these retinal progenitors into the vitreous, into middle of the eye. And what's been the goal of these injections? What are you hoping the progenitors do?

Henry Klassen:

So these progenitors have a lot of different capabilities I just mentioned how they can make all the various cell types that are present in the mature retina. They can also regenerate those cell types after transplantation with certain limitations. So I don't want to get too complicated for the audience. Every time I mention something, I can think of exceptions to it. So don't take this as extreme scientific gospel, but in broad strokes, these cells can regenerate the cell types present in the retina, including photoreceptors. But they can also support the microenvironment in ways that promote wound healing. In other words, they can be beneficial in what we call a neurotrophic manner. So they can provide support to the disease retina and kind of shift the balance of the homeostasis back in the direction of a more normal state.

Ben Shaberman:

So I've heard you talk about these cells before, and you've talked about them releasing growth factors, secreting growth factors.

Henry Klassen:

Yeah. If we wanted to replace photo receptors, we would transplant these cells under the retina, as other people have done, because that positions the cells immediately adjacent to the location where you want them to form the photoreceptor. If on the other hand you want a neurotrophic effect, there are benefits to putting the cells in the vitreous. One of those benefits is that the procedure is much simpler for the patient and for the physician, and it's much less risky and it's more cost effective. Another benefit is that the cell's position in the vitreous are going to put out these factors, they're going to diffuse into the retina, so you don't have to worry too much about where you put the cells. If you were putting them under the retina, they're going to be positioned right where you put them. But if you put them in the vitreous they'll kind of float around here and there a little bit, and they can secrete from wherever and those factors will drift around and then they'll find their way to the photoreceptors and adjacent cell types. So it's a diffusible way of benefiting the host retina.

Ben Shaberman:

So talk about the first jCyte trials where you injected these, again, into the vitreous in the middle of the eye, and most of these patients were RP patients, or they had conditions like RP, if I recall. Talk about the trial and what you observed.

Henry Klassen:

So you're right, it was RP. So we were enrolling RP patients and we were not discriminating in terms of the underlying genotype. So this kind of neurotrophic effect is agnostic to genotype, which means it just doesn't matter what your mutation is. We're trying to benefit the patient later in the course of the disease. So we know you already have the problem, we're just trying to mitigate it. So in terms of trials, yeah, we can talk about phase one, phase two, and phase three.

Now these can be embellished with little slashes and A's and B's and so on, but the basic principle here is the first trial is a safety trial, and the second trial is also a safety trial, but it's focused more on efficacy. The third trial is about taking your intended commercial product, the same product you intend to treat patients with, and then testing that. So it's repeating everything you did only with a commercially manufactured product. So that's the basic layout of the clinical pipeline. And so we're basically through the first two of those, and the third is coming up.

So in the first safety trial, we enrolled people with RP, and we were not specific about what kind of RP in terms of genes, but we were also not excluding people with syndromic RP. So we had quite a few patients with ushers in both of our trials so far, and we've seen benefit in those patients. So we see no reason to be more picky about genotype or syndromes.

Ben Shaberman:

What kind of benefit were the patients experiencing, or what did you observe?

Henry Klassen:

Okay. Well in the first trial, which we called a phase 1/2A, but it was an initial safety trial, we did see good safety for putting these cells in the vitreous. That wasn't really a given. We had a lot of animal data to support that. There were plenty of skeptics out there who thought that was a really bad idea. But I think the key point is that although some cells behave very badly when they're put in the vitreous, and by that I mean fibroblast and RPE cells, our cells being retinal progenitors, they're back in their native habitat more or less. And so they've been shown to be fairly well-behaved in this vitreous. So that was nice. The cells were also tolerated. There wasn't an immune response, so that's something we predicted from the animal data, but it was really nice to see that that was also the case in humans because humans have a very sophisticated immune system, so you just never really know till you try.

One interesting thing is that for a readout, we were looking at best corrected visual acuity. So that's basically looking at the eye chart, reading off the letters, and as we went up in dose, so that's the 2A part of our initial trial was dose escalation. We kept going up in dose, it was still safe. And as we went up, more reports started coming from the patients about seeing better, and we were able to document some of that in terms of letters of improvement in visual acuity. Now that's a pretty big deal, because coming into this project, we were thinking of neuroprotection as something that was going to slow the dissent from the disease. So if RPs like a downhill run, this was going to be putting a parachute on the patient's retina to try and slow down the progress so you never get to the bottom of the hill, so you always have some preserved vision. That was really our goal. But what we were seeing is was more like a paraglider that people were going up. So that was pretty amazing and that was seen best in the highest dose.

Now, this was not a randomized controlled type of trial, it was a safety trial. And so we had to go into phase 2B where we had a randomized mask trial with different dose levels, where the patients didn't know if they were getting the drug, or how much of it, or getting it at all. So some people were randomized to the control group.

In that phase 2B trial, we also saw a very similar safety record to the previous. So that carried along. And we also saw indications of a treatment effect, and we were able to show that the higher dose had a stronger effect than the lower dose. The challenge came when we looked at the control group, they also seemed to have an effect. So there was this evidence like of a sham treatment effect where people who didn't actually get the drug appeared to be performing better. Well, they did perform better, and the question was, "Why is this happening?" And that denied us the P value we needed for statistical significance, even though we were very close to getting it at both six months and 12 months out from treatment. But close isn't good enough in statistics. You have to hit your 0.05 level. Closest we got is 0.07. Well that's like 93% confidence, but they went 95%.

So we went back to our data and started looking at it much more closely to see where we might find variability in a way that we could use for future trials like the phase three type of trial. So what we did is we looked at the data and we looked at evidence from other trials as well. And it turned out that a common issue was that if the patients have a large disparity in how well they see between their two eyes that can introduce problems when you're testing the worsting eye. So let me back up a little bit. So we know that RP is a bilateral condition, and it's roughly symmetric. But when you get to the point where the macula is involved, which is fairly late in the disease, the stage where you've already lost peripheral vision, but you're starting to lose central vision. At that stage, the two maculas can lose photoreceptors at differing rates. So there can be a kind of disparity there.

And so if one of the maculas is severely impaired, the patient will preferentially use their better eye, for obvious reasons and the kind of neglect of the worsening eye carries over that when they start testing through that worsening eye, they perform rather poorly, more poorly perhaps than the anatomy would suggest. And so as they continue to be tested, there's this training effect and they get better. Remarkably better. They can get better even if they're not treated, which is good, but it's bad for our statistics. So we have to eliminate that issue.

Now, I want to let the patients know that that doesn't mean that people with the big disparity between their eyes won't benefit from this treatment. All it means is that that's not going to be helpful for our statistics because of this sham effect, but we do think it would still help those eyes just as well as any other eye.

Ben Shaberman:

So how does this inform possible phase three trial, what you've learned?

Henry Klassen:

What we did is we took our phase 2B data that looked so close but was a little bit off because of that sham effect, and we removed the people who had more than 15 letter disparity between the eyes, which is a pretty big difference. And then when we looked at that data, it looked much better. The sham effect was diminished, the treatment effect was also accentuated. And at that point, the P-values looked mighty good, both at 12 months and six months. So we felt like that alone would probably get us over the hump in terms of the follow on trial.

But then we looked at it further and we looked at other ways of how much of the photoreceptor layers still present in the macula of the patients as they go into the trial because the more the better. And in other words, if we're going to try and treat photoreceptors, there have to be photoreceptors still left to be treatable. And so you can't just count them one by one. We need some clinically reasonable ways of getting a handle on this.

So one way is to use the OCT scan to look at just how thick is the central retina. Because in the very center of the fovea, there's just photoreceptor layer present. So if you look at how thick that layer is, you get a handle on how many photoreceptors are left, at least in the very center of the vision. And so that looks like a promising way of going about this. Another thing we looked at is the central visual field. And so that's looking more to the side, but it gives you an idea of how many preceptors are spread out within the macula. So it's not just looking in one spot, but taking in a broader region, but still a very restricted one. And we found that about eight degrees is a pretty good cutoff if patients have lost so much field that they're down smaller than eight degrees, and that's going to be problematic. But the good news is if we take those patients out of our data, the results are absolutely stunning.

So these are post hoc analyses. They're not strictly predictive of what you're going to find when you start a new trial, but the magnitude of the differences we saw when we apply these criteria compared to how far we needed to get is very promising. So that's where we are right now and we're gearing up for the next phase.

Ben Shaberman:

Right. So I guess the bottom line from what you're saying is the best people for the next phase would be those with less disparity between their eyes, and in general those with better vision, more remaining retinal structure. And so what are the next steps moving forward?

Henry Klassen:

Well just to clarify that for people, we're still talking about late in the disease. So if you have been diagnosed with RP and you're still 20/20, you're too early for this. That doesn't mean that someday when the safety profile is mapped out that maybe people get treated earlier and earlier. There may be benefits there. But within the population of people who have lost central vision, we are going to enroll people who have lost central vision. I want to make that clear, but what we want to know is how many sick photoreceptors are still hanging around? So we have to make the distinction between sick photoreceptors and dead photoreceptors. Once they're gone, they can't help us anymore with this type of treatment, but if they seem to be gone, but they're still physically present, then that's the patient we're looking for. So I think we'll be enrolling people who are severely impacted, but there has to be a physical rationale for why they might respond.

Ben Shaberman:

Understood. Thanks for clarifying that. So what are your next immediate steps moving forward?

Henry Klassen:

Well, we're very busy with the manufacturing process. The whole thing falls under this category called CMC, which is all the commercial grade depths and controls and processes involved in documentation, it's very important to the FDA to document how this is being made. You want to make it replicable so it doesn't depend on any one person, or it can't be a boutique type of treatment the way it has been. It has to be something generalizable, reduced to paper as they say, so that there's instructions that can be followed by someone reasonably skilled in the art to be able to replicate what you're doing. So you have to take it away from the level of sorcery, if you will, and reduce it to a factory type process. And so that's the step of generating the cells that will be used in the next trial. So once we have those cells and once we have approval from the FDA on our trial plan, we will utilize those cells in the trial and that'll be our pivotal trial, we hope to get this into the patients.

Ben Shaberman:

That's great. And I'm sure there are a lot of people listening who look forward to that.

And Henry, thanks for going into so much detail about not only how the treatment works, but the effect it had on patients, that the sham eyes had a reaction in addition to the treated eyes. I think this discussion, what you talked about, really helps people understand that vision improvements, or even saving vision in a trial is not just a binary thing. There are nuances and complexities to it. And it sounds like you and your colleagues at jCyte have really done a great job figuring out who the best patients are for the next step, and that's so critical for success. So thanks for explaining it to our audience, and thanks for just going through those studies so you're increasing the chances for success when you do move to that next phase.

Henry Klassen:

Right. Well, thank you. It's my pleasure.

Ben Shaberman:

So Henry, thanks for taking time out of your busy day to tell us about retinal progenitors and jCyte and the trials that you've conducted and what you're working toward. It's been a pleasure and it's exciting for me. Again, I know you and I have been talking for so many years and it's nice to see the emerging therapy at this juncture. So a little congratulations. I know you'll be a lot happier when you can get into the next phase and hopefully see continued success.

Henry Klassen:

Yeah, and I know the patients are waiting too. I never forget that. There's a sense of urgency in what we do. Things like the COVID epidemic didn't help, but we're still moving forward and I want people to know that.

Ben Shaberman:

Great. Thank you for saying that. And audience, thanks again as always for joining the Eye on the Cure podcast. It's great to have you. Come back in a couple of weeks for our next episode. And Henry, thanks again for telling us about your trials and emerging therapy. We're excited about it.

Henry Klassen:

Yes. Sure, man. Thanks. My pleasure.

Speaker 1:

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