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. Glad you could join us for this episode. And my guest for this episode is Dr. David Birch from the Retina Foundation of the Southwest in Dallas. And in case you weren't familiar with David, he has been a key figure and thought leader in the inherited retinal disease research field for more than four decades. And I'm guessing that he has been an investigator on more IRD clinical trials than just about any other clinician or scientist in this space. And David has also been an active member of the Foundation's Scientific Advisory Board for several decades, and he's provided important insights into the state of IRD research and where the best opportunities have been for developing treatments and cures. So David, it's a real pleasure and privilege to have you on Eye on the Cure. Welcome to the podcast.

Dr. David Birch:

Thank you, Ben. It's a real pleasure to be here. Look forward to this.

Ben Shaberman:

Me too. I'm looking forward as well. But before we get started in our conversation, I wanted people to get a little more background on you. You have a Bachelor of Arts from the University of California, Riverside. A PhD from the University of California, Santa Barbara, a strong California connection there. Fellowships from University of Florida Medical School and Mass Eye and Ear. David has been an author on more than 350 peer-reviewed publications. You've been at the foundation, the Retina Foundation for more than 40 years. And your titles, if I have this correct, are Director of the Rose-Silverthorne Laboratory for Retinal Degenerations and Scientific Director, again at the Retina Foundation. So David, my first question is you obviously went into inherited retinal disease research early on in your career, really right out of college. What inspired you to get into the inherited retinal disease space?

Dr. David Birch:

So I was a basic scientist for my PhD. I got my degree with Dr. Jerry Jacobs in Santa Barbara, and it was all monkey experiments, non-human primates. We were doing a lot of recording from the visual system trying to understand how color vision works. And then my actual degree was based on kind of a split-off from that, looking at how light damage occurred in different animal species. And ensuing my studies and the research I did on light damage, it sort of occurred to me that what I'm doing here, this is a model for a human disease and you can learn all you want about how light affects the photoreceptors and stuff and damages them, but unless you relate it to something human, it really doesn't have that much importance. So it early on got me thinking about the application of basic research to human conditions, clinical conditions.

And at about the time I was finishing my PhD, I was kind of looking for postdoctoral opportunities. The National Eye Institute had a sort of a unique program at the time where it took basic scientists, PhDs and put them into clinical programs. And there was this big gap between science and practice and application, and the idea was to put the basic scientists into the clinical environment to see what would happen. And so I began with Jay Enoch, and then I spent three years, really formative years with Eliot Berson at Mass Eye and Ear. And as your listeners will probably realize, Eliot's sort of the grandfather of

retinal degeneration. He had the initial lab devoted to the study of retinitis pigmentosa and allied conditions at Berman-Gund in Boston.

He was right there at the beginning of the Foundation Fighting Blindness, one of the initial organizers and with Ben Berman and Gordon Gund. And so I was sort there at that time, a little bit afterwards, but at the time, Eliot Berson was doing most of the work in retinitis pigmentosa and he was a very strong person and influenced me heavily on the importance of electroretinograms, vitamin A, and variety of other topics. But that sort of all led to a clinical interest. But I've always tried to approach it with basic science and doing basic science experiments.

Ben Shaberman:

That's great. Yeah. Eliot was the man back in the early '70s and definitely vitamin A and ERGs were his wheelhouse.

Dr. David Birch:

Right.

Ben Shaberman:

And what's interesting for me is that when I started with the foundation almost 20 years ago now, I mean I got to know you early on because you were at that point really embedded in our work. And over the years I've watched you be involved with so many different clinical trials. I remember the Neurotech device, you did a trial for DHA for people with X-linked RP. There was the valproic acid for RP trial. I remember doing an article on the stem cell Inc. AMD trial for RPE. You've been involved in X-linked RP gene therapy, and the list goes on. We've, I think made it abundantly clear, you've done an incredible amount of clinical research. What do you think your core strengths are when it comes to research and being involved in these clinical trials?

Dr. David Birch:

Right now I'd have to say I'm not going to stop until we get some really positive results. I mean, one of the frustrations obviously over the years has been that we haven't found anything that's been really impactful. I mean, there've been sort of hints at efficacy with DHA and a couple of other things, but nothing really dramatic to change the progression of the disease. And so my goal is to stay with this if I can, until we really have some positive outcomes. And if I'm involved in it, then people are going to believe it because I've never made up anything in the past. I've got a great history of clinical trials that did not reach their endpoints. But I think one of the things I like to think about myself, is that I'm collaborative. And I think one of the things I realized coming out of Berman-Gund and the environment at the time, there were maybe after in the '80s and '90s, there were sort of individual labs pursuing their thing.

They were all sort of isolated kingdoms and there wasn't a lot of collaboration. In fact, you get to ARVO meetings and meetings of scientists or clinicians, and they would always be attacking each other. There'd be big attacks on Eliot for the vitamin A, and there'd be big attacks on Fishman for something, either CME or whatever. And it just wasn't very collaborative and I was really determined to get away from that. So I really made a lot of connections in the early days with people at Hopkins and people at San Francisco and Oregon. And I like to think that I'm part of the generation that developed the collaborations that we have now within the Foundation of Fighting Blindness and within the IRD community where we can all work together and do these multi-center clinical trials. Because I think that's the real strength. If you can get different groups together and work on the same thing and

develop a trial and get the same kind of result at every center, then that's much more convincing than a single investigator type trial.

Ben Shaberman:

Right. I would so agree. I've watched you in these collaborative projects and moments for so many years, so I would definitely agree with that. One other thing that I think is really important, a skill set that you bring to these research efforts and it's becoming even more and more important, is your expertise with outcome measures and endpoints. Because as of late, while we have had some misses in the clinic, in clinical trials, we have seen signs of efficacy. We have seen some vision improvement. It's coming up with the right endpoints so that we can get FDA approval, that is perhaps the biggest hurdle that we have at this moment. Would you agree that your knowledge of whether it's microperimetry or ERGs, OCT, whatever, all those different ways of measuring retinal structure and function, would you agree that that's kind of your wheelhouse?

Dr. David Birch:

Absolutely. And it's evolved over the years. I mean, it was primarily electroretinograms and that's fine for early disease, for younger patients. Unfortunately, the electroretinogram is really sensitive, but it's also very susceptible to the degeneration. So once a person reaches sort of an intermediate stage of RP, the ERG is almost non-detectable. So as an outcome measure in the trials that we're doing now, where it tends to be later stage disease, the ERG has not been particularly helpful. So we've moved to other things. And one of the outcome measures that I'm particularly involved in is with optical imaging and the OCT. And I have my colleague Donald Hood to thank for a lot of the work we did together. I remember distinctly looking at OCTs over several years in a few patients and just realizing, well, you can see this change, this line of photoreceptors that you see in the OCT, it's shrinking and it's visibly shrinking over a couple of years.

And that to me, and the fact that you can measure that very precisely, gave me the idea that that could be a really good outcome measure for clinical trials. And at the time, the FDA was not particularly interested in structural outcomes. They were much more focused on how the patients felt and whether the patients' performance and behavior was affected by the disease, the progression. So it took some time to sort of convince the FDA that this was really a surrogate or a measurement that would be effective, would be influential in the patients' future. So it's evolved, as we moved into gene therapy, we had very different types of outcome measures that we had to consider. We're now treating just a small portion of the retina. So an ERG that measures the whole retina is not really going to respond much to a small change in the local region.

So we had to go to local measures. And things like microperimetry, like you mentioned, turned out to be really sensitive to these changes. And I think it was naive to think that we were going to put a gene in and suddenly get normal vision. It's going to take stages, it's going to be a graded kind of improvement as we get better at this. But I think we are, like you said, seeing some evidence of success. And as we build on that, I think we'll get increases in these outcome measures, increases in vision that will reach the FDA standard. And understandably, the FDA doesn't want just a very tiny change. If you're going to do this radical intervention in the human eye, it has to make a big difference. And we are still not seeing those big differences in most of these trials, although LUXTURNA was the big exception.

Ben Shaberman:

Right. And just so our listeners know, we've been talking about OCT quite a bit, optical coherence tomography, just about anybody who goes to a retinal specialist gets an OCT scan that looks at the

different layers of the retina. So you can see how many photoreceptors are left and where there might be some untoward things going on in the retina. And you didn't mention this, I appreciate your humility, but you came up with an endpoint called EZ width or the ellipsoid zone, which actually measures ultimately how many photoreceptors or what the population of photoreceptors is left. And that's a valid endpoint, isn't it?

Dr. David Birch:

Yeah, it is. And it has been accepted as that. Yeah, it was really a small jump, but we basically went from using the OCT to sort of confirm that the receptors were missing and that it was consistent with RP, to actually measuring that and actually having an objective outcome measurement. And you take this really complicated optical coherence tomography image. It was kind of, maybe my simple-mindedness, but you say, "Let's just measure it." And it worked and it's been very successful.

Ben Shaberman:

And what's cool about that, so our listeners know, is that if I remember correctly, came out of a trial for valproic acid, for retinitis pigmentosa. Unfortunately, the results for that trial weren't very encouraging. But that's where you came up with the EZ width endpoint ...

Dr. David Birch:

A little bit before that. Actually, it's a little bit before that with X-linked RP, the DHA trial, but the valproic acid trial, that was making the transition from a linear measurement, the width to the area-

Ben Shaberman:

Ahh.

Dr. David Birch:

Which is the whole area. And the first time we used the area was in the valproic acid study.

Ben Shaberman:

Got it.

Dr. David Birch:

So that was sort of a requirement of the FDA. They wanted the area to ... in the same way they want the visual field, not just a linear extent of vision.

Ben Shaberman:

Got it. So you've, as we've talked about, have been in the field for quite some time, and I'm sure there've been some really important memorable moments, surprises throughout your career. Are there any that come to mind that you can share with us?

Dr. David Birch:

I remember distinctly having a conversation with Steve Daiger, who was sort of a long time collaborator. He's another stalwart of the Foundation Fighting Blindness from Houston. And we began collaborating very early on and having sent so many samples to him, he started identifying new mutations. And I remember just talking with him and hearing him describe four new dominant mutations. We had

rhodopsin and we had RPE RDS, the peripheral mutation, and we thought that was going to account for most of the dominant. Turns out that were many, many, many more. And just the impact that had on our thinking that we had multiple genes, that this was not just one disease, and now we knew why patients didn't all behave the same. And we began to look at differences in the behavior, in the vision of patients with different mutations, but going from a point where we did trials without even awareness or even knowledge of the mutation because nobody could identify it, to trials where they were entirely dependent on the mutation. Now it's really a change in strategy and a change in the way the field has been structured.

Ben Shaberman:

Right. And excitingly now we can genetically test people. We have a no-cost program that really any doctor in the country can order a genetic test for their IRD patients, but we can get a result and a conclusive result in about 60 to 70% of cases, and to the time that you just talked about, we didn't even know-

Dr. David Birch:

Yeah.

Ben Shaberman:

... Have a sense of how vast and diverse the genetic field would be.

Dr. David Birch:

Before that program began, we were really dependent on the goodwill of our colleagues. I would send samples to different labs, and so they sort of had to come up with their own funding to do the analyses. And we were just very fortunate to have a lot of collaborators that helped us with the mutation testing, but we couldn't do everybody, and it was very selective patients. But the FFB program really changed everything. And we began genotyping every new patient, putting them into my retina tracker, genotyping them. And that has led to these large populations now that several sites have where we can do these studies. We couldn't have done any of these gene therapy studies without the help of My Retina Tracker.

Ben Shaberman:

That's such a key point. You have to genetically screen and identify patients if you're going to put them in a gene therapy trial.

Dr. David Birch:

Right.

Ben Shaberman:

It's fundamental, but very important.

Dr. David Birch:

And it's very hard to ask the patients to pay for it because we tell them that it'll be for their own good, and it's good to know what the mutation is and all that, but do they really want to spend a couple of hundred dollars or whatever? It's a tough sell sometimes.

Ben Shaberman:

I totally agree. Totally agree. So we've alluded to one success in the field, the identification of all these mutated genes and being able to catalog and capture all the patients that are affected in My Retina Tracker. What do you think some of the other key achievements and successes in the field have been in your career?

Dr. David Birch:

Certainly, I would say almost perfection of subretinal surgery now, the fact that these brave surgeons took on the task of placing these genes under the retina and creating what's essentially a retinal detachment. And there was a lot of resistance, fear about what that would lead to. But over time, it became clear that the retina is extremely resilient, that if it's only detached for an hour or so, it'll recover almost perfectly or perfectly. And it's very different from a detachment that you might have from trauma or from breaking the retina. So I think the perfection of the delivery tools for getting these genes into the retina has been a huge, huge step.

Ben Shaberman:

Right. And can you explain exactly what a subretinal injection is? You've mentioned it sort of by talking about the detachment, but where's the needle actually going that injects the therapy?

Dr. David Birch:

So it has to go into the retina and it has to go beyond the photoreceptors, but not go through the pigment epithelium. So you actually lifting up the retina from the back of the eye and creating a space there to put the gene.

Ben Shaberman:

And the needle is actually going through the retina.

Dr. David Birch:

Yeah.

Ben Shaberman:

I think that's the part that kind of freaks me. You don't think about, it's not just underneath the retina, it's kind of through the retina as you're alluding to, this is a commonplace surgery now, I mean, being done.

Dr. David Birch:

Now we're doing it with OCT again, with optical coherence tomography. So we actually see the needle advancing in the retina. We can go exactly the depth we need to go without the risk of going too far, which is the worst possible outcome. So it's really, it's done to visual control. It's much more controlled than it was in the first days.

Ben Shaberman:

Exactly. So we've talked about some of the successes. What do you think are the big challenges moving forward? We've gotten so many clinical trials off the ground, we've seen some signs of success in some of those trials. What do you think needs to happen if we're going to cross the finish line more?

Dr. David Birch:

I think there has to be sort of a recalibration of how we do trials in a sense. Because what we're doing now, as we're getting some investment money together, some support for the trial, we're doing the trial and it's either make or break. You either reach your endpoint and get FDA approval or you don't. And if you don't, the whole thing just ends, falls apart. And what we need, are follow-ups on these unsuccessful ones, the Nightstar trials in choroideremia are a great example where we had a lot of patients who benefited from the treatment, but just not enough. And so the follow-up is to find out which patients benefited, which didn't, what variables are involved in the success. But it wasn't just something to be abandoned.

And fortunately, there are some pioneers who are staying with it and following these patients over a long period of time. And hopefully there'll be some more work in choroideremia with a similar or modified approach. But I think that we have to get to the idea that we have to evolve these treatments. They're not just going to happen all or nothing. It's going to be step after step after step, and we have to be willing to stay the course.

Ben Shaberman:

Yeah, I think those are great points. And we have to realize, and you take the Nightstar choroideremia trial as an example, even though it didn't ultimately lead to a successful FDA approval, there were things that were learned. There were some vision improvements-

Dr. David Birch:

Absolutely.

Ben Shaberman:

... And to take that information and apply it to the next trial is really important.

Dr. David Birch:

Absolutely.

Ben Shaberman:

So you do a lot of different things with patients and research. What gives you the most satisfaction on a day-to-day basis in your clinic for what you do with patients and the research?

Dr. David Birch:

I think explaining the research to patients. I really enjoy telling patients about what's going on and what's happening. And I try to do it in a sort of truthful and reasonable way. I don't try to present them with false hope. I just try to make it clear that there's a lot of effort. They're not alone. There's work being done, and it's just a question of time. And especially with younger patients, I think that's really an important message for them to have because on the one hand, they just see a continual decline, especially if they have family members who've lost their vision. They see sort of a bleak future. But I think letting them know that there are some really strong possibilities for intervention in the upcoming years. It's important. And I enjoy seeing their attitudes change, and I don't want them to leave with false hope, but I do want them to leave with hope.

Ben Shaberman:

Well, one thing I love to do is to refer patients to you because I know they're going to get great care. You're going to conduct all the necessary tests that need to be done, but that you're going to spend time with them, help them understand their condition and the research that's underway, and ultimately communicate hope, which is very real at this juncture. So we've talked about some of your collaborators over the years and excitingly you're going to have a new collaborator very soon. Can you tell us about that new collaborator?

Dr. David Birch:

Yeah, absolutely. We're delighted. It's part of a transition process for me. I mean, I'm not going to be able to do what I'm doing forever, but I intend to stick around for a while. But as part of our transitional planning, our transitional process, we began recruiting, trying to recruit somebody to come to the foundation. And we were successful in recruiting Mark Pennesi. And as you know, Mark Pennesi is one of the leaders of the field. He is head of the genetics program at Oregon Health Science Center. He's an unbelievable guy. And we actually worked together. He grew up in Dallas, which I think is part of the appeal of the foundation. He's a Dallas kid, Texan. And I think the growth of the Retina Foundation, the fact that we can become almost an international destination for patients, I think that sort of appealed to him, and I expect him to grow the foundation to the next level.

I think I'm proud of what I've done, taking it from nothing to where it is now, but he's going to take it and take it another huge leap. So tremendously excited. We'll overlap for a few years. When he gets sick of me, he can throw me out. Or when I decide to go fishing, I can do that. But there'll be a transitional period. The patients will be in fantastic hands. We'll collaborate with OHSU too. He's going to go back and forth, and we're going to have some collaborative projects. We already have a new imaging system that we're having somebody at OHSU build for us. So it's an exciting time.

Ben Shaberman:

That's such a cool partnership that you're going to have, really a dynamic duo if you will. We're excited to see Mark going to the Retina Foundation of the Southwest.

Dr. David Birch:

Or squabbling siblings, one of the two models.

Ben Shaberman:

Well, both you and Mark are very affable collaborative people, so I'm sure it'll be just fine. The sum of the parts will be greater than the whole-

Dr. David Birch:

Amen.

Ben Shaberman:

... So I hope you stick around for a while to work with him-

Dr. David Birch:

Yeah. I'll do that.

Ben Shaberman:

... Because I think together you're going to do a lot of great things. But speaking of collaborators, I know your wife is at the Retina Foundation of the Southwest.

Dr. David Birch:

Absolutely, absolutely.

Ben Shaberman:

And she's in ophthalmology. Tell us a little bit about Eileen Birch, Dr. Eileen Birch.

Dr. David Birch:

So yeah, we actually met in graduate school and coordinated our careers throughout our post-docs. We managed to get two post-docs in the Boston area. She went to MIT, worked with Dick Held, and she's an infant development person. She spends all her time with kids that are at risk for amblyopia, and other congenital kinds of issues. And so she's been a tremendous help. We worked together on some testing of infants at risk for RP and stuff. And one of our big collaborations 15, 20 years ago was on infant formula. We worked with a guy at the med school, Medical School UT Southwestern, and looked at the importance of adding DHA, nutritional supplement to pre-term and full-term infant formula. And it's the only clinical trial I've ever been involved in where it was stopped before the end because the improvement was so obvious, they no longer allowed us to randomize the kids to standard formula.

And so within a couple of years of doing that work, and unfortunately this was before everybody had patents and commercial interest and stuff. So we did this, our funding all came from National Institute and Mead Johnson provided the formula to us without any costs. So it was kind of a nice arrangement. But once the study was successful, Mead Johnson added DHA to its formula and upped its price. The commercial side of it took over. But it was a great set of studies to be involved in.

Ben Shaberman:

[inaudible 00:27:46]

Dr. David Birch:

Mostly hers.

Ben Shaberman:

Right. But that's such a great story, and together you made such a difference. It's kind of ironic that the one collaboration you did from a research standpoint with your wife was wildly successful.

Dr. David Birch:

That's what I know.

Ben Shaberman:

That's a real testament to marriage.

Dr. David Birch:

I should get her involved in more of the DHA trials. I mean the X-linked RP trials. Right?

Ben Shaberman:

Exactly. I think that's your lesson from that collaboration.

Dr. David Birch:

Okay.

Ben Shaberman:

So just to round things out, to help people understand a little more about David Birch, I know we've been talking a lot about research, and I presume with your wife, you talk a lot about research when you get home in the evening. But what do you like to do for fun? How do you relax and have a good time?

Dr. David Birch:

I'm a big reader. I love to read. I probably read a book every week or every other week. I'm also still trying to stay active. I play a lot of tennis. It's not the way it was when I was 30. I mean, they talk about Djokovic being ancient at 35 or 36. I mean, I'm ancient, but I'm still able to get a few of those shots back. And I still like to water ski and do things like that, get out to the lake, do a lot of hiking. So it's kind of a California sort of mentality. A lot of outdoor stuff, the ocean. And why am I in Dallas? I mean, it's interesting.

I probably get to the ocean more than some of my relatives in California. It's when you don't have it, you want it, you go there. So we do a lot of trips. And actually the south, the Gulf Coast is really, really beautiful and fun. Great, great food. So I travel and that's one of the things I do look forward to, is more time to travel and not having to worry about the talk I'm going to give when I do travel.

Ben Shaberman:

Right. I can relate to that. Yeah. When you have work, when you have a talk. Yeah, it's work.

Dr. David Birch:

It detracts from the day off. Yeah, it does.

Ben Shaberman:

Yeah, right. Exactly. So are you from Southern California originally?

Dr. David Birch:

Northern.

Ben Shaberman:

Northern.

Dr. David Birch:

Berkeley, Berkeley.

Ben Shaberman:

Berkeley?

Dr. David Birch:

You can imagine Berkeley in the '60s. That's where I'm from.

Ben Shaberman:

Well, that says a lot more about you, David.

Dr. David Birch:

It does. It does.

Ben Shaberman:

Okay. Well that's pretty cool. Are you a fan of Grateful Dead, Jefferson Airplane?

Dr. David Birch:

Absolutely. Yep.

Ben Shaberman:

David Birch-

Dr. David Birch:

And we go out, we go out to Golden Gate Field on the weekends and the Fillmore, and it was a good time.

Ben Shaberman:

That's pretty cool.

Dr. David Birch:

But unlike some of my friends, I got out, I knew when it was time to do something else. If I stayed in Santa Barbara or in Berkeley, I would've had a totally different life. No question about it.

Ben Shaberman:

Well, we're glad you moved to Dallas and thank you for just all the great work you've done for research for patients. And yeah, there've been a lot of challenges in the field, but you, along with many of the people you mentioned, Steve Daiger, Eliot Berson, and now Mark Pennesi, you've done and are going to continue to do great things to move more treatments across the finish line. So David, I greatly appreciate you taking time out of your busy day to talk with me. And honestly, for all the time that I've been with the foundation, which again is approaching 20 years for myself, it's been an honor and a privilege to know you, and you're always a great resource for information when I have questions about, "What's going on with this trial, what do you know about this endpoint." So thank you for all you've done.

Dr. David Birch:

Thank you. It's always great talking to you. I always enjoy it.

Ben Shaberman:

Same here. It's a pleasure for me and listeners as always, thanks for joining Eye on the Cure. Glad you could be with us for this episode and stay tuned for the next one. Catch you later.

Speaker 1:

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