

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 this episode is special for two reasons. First, I'm delighted to have Rachel Huckfeldt, an outstanding retinal disease clinical researcher from Mass Eye and Ear as my guest. But this episode also happens to be our 50th episode of Eye on the Cure. It's exciting for me. So the podcast was launched a little more than two years ago, and it has been my absolute pleasure and privilege to talk with so many experts and personalities and the vision and retinal research space. And I hope all of you listeners out there have enjoyed our guests as much as I have. And honestly, I can't think of a better guest for our 50th episode than Rachel Huckfeldt. Rachel, welcome to Eye on the Cure.

Rachel Huckfeldt:

Thank you, Ben. I'm so happy to be on. And as I was looking at the 49 people who have proceeded me, what a great selection of people that you have interviewed and I'm happy to join the crew. Thanks.

Ben Shaberman:

You're welcome. And you are keeping up the tradition of having good guests on Eye on the Cure. So let me give our listeners a little background on Rachel. Again. She's a clinical researcher and assistant professor of ophthalmology from Mass Eye and Ear at Harvard and Boston of course. And she is a member of the Berman-Gund Lab for the Study of Retinal Degenerations. That's the first ever research lab funded by the foundation. And that funding started back in the early seventies, and Rachel earned both an MD and PhD in neuroscience from Washington University in St. Louis. She received her BA in biology and psychology from Washington University and graduated summa cum laude.

Impressively, she's completed fellowships with Dr. Jean Bennett at University of Pennsylvania and Eric Pierce at Mass Eye and Ear, and today she participates in many clinical trials. We'll talk a bit about that. She's co-chair of the Foundation's clinical consortium, and she is director of the Inherited Retinal Degeneration Fellowship at Mass Eye and Ear. So Rachel, to start off, I'm just curious what inspired you to become a clinical research in the inherited retinal disease space. That is not an obvious choice for a career, but obviously we are happy you did that, but what inspired you to get into this field?

Rachel Huckfeldt:

That is an interesting question, and it's not like from childhood on, this is where I wanted to be. It was really a set of serendipitous kind of events and encounters, I think. Looking back on elementary school and middle school and science fairs, I did not like science fairs. I did not like putting together these experiments and all that stuff. But then I had a high school biology class that I think was more important in hindsight than I realized at the moment. It was an advanced biology course and it just turned me on to just how cool nature and biologic systems are. It was all of biology, not just human biology, but we got to do cool things like visit labs where people were studying why plants grow in certain directions or what it is in birds, in their brains that let them migrate. It was really cool to meet people who were studying these things and it was my first introduction to neurons, which are of course the basis of the nervous system.

So that launched me into college thinking I wanted to be a psychology major and understand learning and memory and these challenging concepts. But then in the course of my coursework, we just did a lot

of understanding the brain and the visual system and that was what led me to a PhD in neuroscience and medicine. But then I really have to thank one of your prior guests on the show, my PhD mentor, Dr. Rachel Long, who's now at the University of Washington, because I joined her lab in graduate school. Again, not thinking I wanted to make my home in the retina, but she studies the retina as a model for other things in the nervous system. And in her lab I realized how beautiful and how complicated and how important retinal biology was, and that was ultimately the launchpad to end up being an ophthalmologist. And then as an ophthalmology resident, we are exposed to every single aspect of ocular diseases, as we should be.

And I went into that open-minded, but I couldn't get over really being intrigued and fascinated by the retina and what went wrong to create blinding diseases. And this is, and Ben, I'm kind of rambling, but here's where the serendipity comes in. Eric Pierce had just arrived at Mass Eye Ear and I was looking for a research project and looking for next steps and some conversations and interactions with him led to me going to Gene Bennett's lab, which was a totally transformative experience. And then conversations with other leaders in our field over time, including people like Jackie Duncan and Mark Pennisi and Ed Stone, it just kind of set me step by step on a path that led to where I am now. So didn't grow up wanting to do what I am doing, but I am so happy that I get to come to work every day and work in this space and hopefully do things that are good for my patients and anyone with these conditions.

Ben Shaberman:

Right. Well, we're delighted that your journey ultimately led you to our world of inherited retinal diseases, and you mentioned a lot of really key names in our field, Gene Bennett, Eric Pierce, Ed Stone, Jackie Duncan. These are the all stars of inherited retinal disease research, lab research, clinical research, and I'm glad you mentioned Rachel Long because I saw her give a keynote lecture. She won an award at a big research conference called ARVO, and the way she talked about the retina, the beauty of the retina and some of the images she had, I said to myself, "I don't know this researcher, but I want to have her on my podcast." And it was a really cool episode. She's done some really great work to document the complexity and the beauty of the retina.

So we've mentioned some really important names in the field and you ended up of all places at Mass Eye and Ear and the Berman-Gund Lab, which I've already mentioned has quite a legacy. It's the foundation's first lab, really the first lab that we funded. How does that feel when you walk in every day and it's one of the foremost labs and clinics for inherited retinal diseases on the planet?

Rachel Huckfeldt:

I think I had an opportunity to meet people from the Burman family before and tell them how cool it was to walk by a plaque with their name on it every day. I'm certainly appreciative and aware of all of the milestones in our field that were reached where I'm sitting right now, and I'm also so respectful of the legacy of all of the individual scientists and researchers and clinicians who built the foundation that I get to work from today. So I hope that what we are doing on a day-to-day basis continues to honor their work and build from it. I think today my colleagues and I at Mass Eye and Ear see the Burman-Gund Lab and now what we call the Ocular Genomics Institute as this natural evolution, as molecular biology grows, as genetics grow, as our toolbox grows. So I think we are carrying on in the spirit of what started here so many years ago, and it's a great place to work.

Ben Shaberman:

So I'm curious, when you started out or when you were doing your fellowship with Eric Pierce, did you get a chance to meet Elliot Berson?

Rachel Huckfeldt:

Yeah, so even before that, so as a resident here at Mass Eye Ear on one of our rotations, we would spend a few days in his clinic. And so I had an opportunity, a few afternoons as a resident to spend time with him. And what I really admired was his respect and kindness and regard for his patients. He just only wanted the best for them and would do whatever it took. I think the chair that he used to see patients is still, what he would actually sit in when he was doing exams still in our clinic. And I try to avoid that one. It's not so comfortable for me, but his legacy is there physically and more metaphorically.

Ben Shaberman:

Right. That's great that his chair is still there. And I'm sure a lot of our listeners know who Elliot Berson is, especially people who've been with the foundation, been in our circle for a long time. But for those of you out there who don't know, he is really the researcher that brought the Bermans and the Gunds together to create the foundation. And as we've said, it was the first research lab created, so quite hallowed ground, the Berman-Gund Lab. So another thing I wanted to hear about Rachel is what your typical work week looks like, because I think many doctors spend most of their time seeing as many patients as they can on a given day. It's kind of the way our medical system works. Patients come in for a brief time, they get to see the doctor, they get examined by the doctor, and in most cases pretty quickly they're sent on their way. But you work a little differently and you do a lot more than just see patients. Can you talk about what your typical week is like?

Rachel Huckfeldt:

Yeah, I'll start with what our clinic is like because as you've already alluded to, we have a special space and I am grateful to our hospital department for allowing us to practice the way we do. We have the good fortune to not have to see as many patients as quickly as we can in the IRD clinic. And that's not to say that our colleagues elsewhere and that my department who have higher volumes don't take exceptional care of their patients, but we have the luxury of being able to slow down a little bit. I think that's really important because it gives us time to talk to patients and their families about these diagnoses. Really take the time to educate them about the testing we're doing, why we do it, what it's showing us, so that hopefully they leave our clinic knowing a lot more about their diagnoses than they came in knowing.

Part of that discussion too is what is happening with clinical research, sometimes what's happening with preclinical research, what are the types of strategies that we hope will be reaching clinical trials? So we spent a lot of time talking, which I'm really grateful we get to do. In a typical week for me, I have two days of clinic seeing IRD patients. My other three days fill up pretty quickly. I will say that until about this time last year, I had a third day of clinic every week that was primarily focused on more general retinal conditions. So that included age-related macular degeneration, diabetic retinopathy, and as part of transitioning into the leadership of the FFB consortium, I put that on hold for now. But my other three non clinic days, I have meetings with my research team, I have meetings with my clinical trial staff, a lot of administrative paperwork, finishing up clinic documentation, finding patients for clinical trials, working on manuscripts. A lot of it is computer time and zoom time, and if I'm lucky, sitting in real meetings with people. So it's a mixture of academic work and more directly clinically related work.

Ben Shaberman:

Right. And I want to talk a little bit more about clinical trials in a minute, but what is a visit like for one of your inherited retinal disease patients, especially somebody who may not have gotten a really good workup ever before?

Rachel Huckfeldt:

Yeah. So we do our homework before a patient comes in to understand as best we can from the paperwork available, who's referring them, what testing has been done. Sometimes that means looking at a one page note. Sometimes that means looking at a stack of documents, because we really try to start our discussions and start our planning acknowledging what has already been done. But with that in mind, when a patient comes to clinic, either myself or our clinical fellow who is a trained ophthalmologist, just getting extra training in retinal dystrophies, we'll start most visits by sitting down with a patient and just talking, hearing about the history of their vision over time, whether that is something was noticed six months ago or they've been having difficulty for years or decades. We talk about the diagnoses they've been given over time, what information has been made available to them.

And we also make sure we understand somebody's greater medical history because sometimes there are clues that might be related to their retinal condition. And we also spend a lot of time talking about family history. With that discussion under our belts, we finalize a plan of what clinical evaluation makes sense for that person on that day. And for someone who is brand new to us and hasn't had much of a workup before coming, our standard battery looks at how vision and the retina function and then what is the anatomy of the retina. So we start with pretty standard stuff, measuring vision on the eye chart. Then we move into assessing a visual field. So that's a map of how well and where people see straight ahead versus in their side vision. We do a test called an electroretinogram that measures the electricity that the rod cells we use for nighttime vision and the cone cells we use for daytime vision generate in response to flashes of light.

And then we move on to taking different types of pictures of the retina that show us different but complimentary things. And that usually gives us a pretty good sense of structure and function and how they're related. Sometimes there's a few extra tests we might add in. At that point we sit back down with a patient and do our own exam and start talking about what we found, how we put it together as a clinical diagnosis, what we think next steps are, what our recommendations are. And we make sure that through that process we answer any questions that a patient or their family have. And I keep saying we, because we, as you alluded to in the introduction, we have a clinical fellowship training program. So my colleagues, Eric Pierce, Jason Commander and I, when we're in clinic, we work very closely with a clinical fellow who again wants to develop expertise in taking care of patients with retinal dystrophies. So it's an interactive process.

Ben Shaberman:

That's great. And how long is a typical visit?

Rachel Huckfeldt:

It can be lengthy for a brand new patient to us. It can take three to four to five hours to get through everything. Not that all of that time is spent talking or examining or testing. Just sometimes there's little waits for different steps in the process. And I should have added that often after seeing me, the next step is to see one of our clinic's genetic counselors, either to review genetic testing that had already been done or perhaps to start the process brand new. So a new patient will spend a good chunk of time with us. A patient who has seen us before and maybe is coming back for just periodic follow-up can be a shorter visit.

Ben Shaberman:

Right. And I know a lot of patients may have visited many doctors and been on a pretty long journey by the time they reach you. Do you find that many patients and families have a sense of release or affirmation after they've spent so much time with you learning about their condition and helping them understand what's going on?

Rachel Huckfeldt:

I sure hope so. If they do, we're doing our job well and we're communicating well. I think it's really hard as a patient to not get concrete answers or definitive answers and to not understand what is being measured and checked and looked at. So I hope it's useful. Of course, always situations where we do everything we can, but we may not have a definitive answer just yet. And that's where it's nice when I'm sitting in my third floor clinic to refer to the fifth floor of Mass Eye and Ear, the home of the Berman-Gund Lab, the home of the Ocular Genomics Institute, and give nice call outs to some of my research colleagues who are working on improving the outcomes of genetic testing or working on studying disease pathology. It's nice that there's often a next step, even if the timeline for achieving that is a little ambiguous.

Ben Shaberman:

And what are some of the common recommendations that you make to patients and families? Obviously it's going to vary based on each case, but what are often the things you suggest people do moving forward?

Rachel Huckfeldt:

Yeah, so I will say that I talk about the foundation a lot and I talk about the foundation's website a lot as a source of rigorous and legitimate information, whether it's just a reference for information about a person's condition or if they want updates on clinical trials. Thank you for what you do in terms of giving us a place to send people. And there's some other disease specific patient groups that I am grateful for because when I can, I point people in the right direction in that regard.

In terms of other recommendations, I like to make sure that everybody has a good general eye provider, whether it's an ophthalmologist or an optometrist who's maintaining or helping me in terms of just routine eye checks. Or those who have any type of visual impairment that is getting in the way of their daily activities, like to make sure that they know who their resources are, whether it's for a local patient, our vision rehabilitation clinic, trying to help people in other states find the appropriate resource where they are. And then we make a lot of what I think of as my mom advice to people, which is don't smoke, be in the habit of wearing sunglasses. We talk about a healthy, balanced Mediterranean style diet. Just ways that any of us can help protect and promote our retinal health.

Ben Shaberman:

Right. That's great. So let's move into clinical trials a bit because we're really at an exciting juncture in our history. We have so many trials underway, and I know it's something that keeps you pretty busy as a clinical trial investigator. What's it like to do that, to play that role as a clinical trial investigator?

Rachel Huckfeldt:

Oh, I think it's pretty awesome. And this is where I'm mindful in the sense that so many of our current clinical trials are gene specific, that I'm grateful for all the work that the folks before me have done to

identify these genes and develop vectors and develop technologies because it's pretty great to come to a family or patients who have been hoping for just an opportunity to participate in something or get a treatment for so long and say, "Hey, there's this trial that you might be eligible for. It's investigational, right? I can't promise you it's going to work. We need to think about the safety." So we are very deliberate in that discussion. But it's exciting that there are so many things on the horizon, and I am a worrier. I am such a chronic worrier, so I don't take clinical trial participation lightly. Obviously, we would not participate in something if we didn't think that the benefits outweighed the risks, but it is a responsibility. It's a responsibility to oversee these trials and make sure that we're maintaining patient safety. But it is also just a really exciting part of my day-to-day.

Part of enrolling patients in trials is, as I've already said, making sure they understand that anything we're trying is going to be founded on or based on rigorous science and rigorous preclinical evaluation. But it's always a big jump to take something to people. So we all have to be cognizant that we don't know what's going to happen in terms of what is the outcome going to be for vision. Another reality of being in a clinical trial, an interventional trial in particular, is that we really ask for a big time commitment from patients and families. So that's something that we talk about too. But because of that time commitment, we really get to know people well. So I always enjoy having these individuals come back time after time because we look to see what's changing. We of course do all kinds of testing to see what a trial or what a therapy might be bringing, but I really like getting to know them in the process as well.

Ben Shaberman:

That's great. And I think on one hand, clinical trials are so exciting for patients, families, for you, but as you've said so eloquently, it's still research. We're still learning about these therapies, and that presents a challenge. And I know I have a colleague at the foundation who participated a few years back in a trial at Mass Eye and Ear. Ultimately, the therapy did not move forward, but he was so grateful for the experience and the attention he got from the Mass Eye Ear research team. So hats off to you for the great patient care you provide. And one thing I'm curious about is there are so many trials underway and you at Mass Eye Ear, you and your colleagues are conducting so much research. Briefly, we could spend a whole podcast episode talking about this, but what do you think the challenges are right now in clinical research for IRDs? What are some of the opportunities as well?

Rachel Huckfeldt:

And I think challenges come in a few different flavors. One is always being respectful of what we are asking of our participants. I hate the phrase guinea pig because I think it implies a lack of respect and just ignoring that your participant is a human being with dignity and all these things. But as we've been talking about, trials, they are research. They are carefully controlled research and people. And as researchers and as scientists, we want every data point that we can try to get. But sometimes that means doing. We have to be mindful even as we want that, of how much testing we're asking someone to do and where's the line between what is really a value and likely to show us something and where is what is testing that's going to be less useful. So I think any of us involved in conducting or designing trials have that in the forefront of being respectful of participant time.

I think another challenge gets into how do we prove something works? I think this is a big one, Luxterna the first FDA approved gene therapy, as many of us know, it showed that those who received the gene therapy had improved ability to navigate in dim lighting on a mobility course. It clearly improved this aspect of visual function. And I can't stress enough. The important proof of concept Luxterna has showed us, has given us in so many ways, but it also set a high bar to demonstrate success. The clinical

trials for Luxterna were pretty revolutionary in moving away from visual acuity or vision on the eye chart as an outcome measure. Because for many clinical trials in ophthalmology, the outcome measure has always been getting 15 letters or three lines better on the eye chart. And that's not a relevant outcome or goal for many retinal dystrophies.

So Luxterna reminded us that there are different ways to measure success. I think a challenge in IRD research though and IRD clinical trials compared maybe to other areas of ophthalmology, is that, as I've already said, visual acuity may not be the best outcome and we may achieve success even without hitting a huge degree of improvement in visual function. So what if a therapy doesn't make somebody a lot better right now, but what if it slows down progression and changes the slope, the slope of disease? That could be a worthwhile therapy if it's safe and if there's enough change from the natural history.

We've seen the FDA accepts this as an legitimate outcome or an approvable outcome for a drug that was approved this year for geographic atrophy in dry age-related macular degeneration, where this drug that's injected into the eye doesn't help people see better right now, but it slows down the expansion rate of the area of atrophy that contributes to poor vision. So the FDA has shown us that for a safe drug in the right clinical context, slowing down the rate of disease could be an approvable outcome. So now our challenge in the IRD space is always being mindful of outcomes that are disease relevant and trying. If we need to rely on outcomes that show that we're slowing down the rate of disease, make sure that that still is somehow clinically meaningful to somebody. A little bit of rambling there, but I hope you took home the points from that.

Ben Shaberman:

Oh, I did. And I'm sure our listeners will as well. And I'm glad you talked about endpoints because we've had a few clinical trials that have shown some efficacy but haven't met the endpoint to get approval. And we as an organization and the research community in general are working with the FDA, so we can come up with better endpoints so we can get more therapies across the finish line. And I know you and your colleagues at Mass Eye and Ear are very involved in that effort, so we appreciate that. And I want to add, you mentioned Luxterna, and I believe it was your colleague Jason Commander who did the first injection, post FDA approval injection of a Luxterna patient.

Rachel Huckfeldt:

Yeah, that's correct. And others were right behind him. But it was a really exciting moment, and I think of some of the things we heard from that patient afterwards, and what is this, six years later, it still kind of gives me chills. So a very impactful, exciting day.

Ben Shaberman:

Agreed. So to finish out, I want to shift gears a little bit, and I think you might've answered this question a little bit, but who are some of your heroes both in your professional work, your field, but also maybe some personal heroes?

Rachel Huckfeldt:

Yeah, I might reframe how you ask that and say, who do I aspire to be like? Because I hear heroes and I think capes and boots or whatever, but who do I aspire to be like? And I think professionally, I've already mentioned a lot of names of people in our field who, to me, they really exemplify having a long-term goal and having the creativity and flexibility and perseverance to get there. Curing blindness, that's not a linear path. That's something where you're going to have setbacks. You're going to realize there are new technologies that you can pull into use. And so I look at so many people in this field, and if I named

names, I would leave people out. But people who over the arc of their career have really adapted to what science is giving us, if not being at the forefront of that science, with this goal and this destination of helping people with vision problems always in mind. I am not quite brand new in my career, but I'm still early enough that I have a long time ahead of me.

So as I think about what I want my trajectory to be, I'm mindful of all these folks as role models for that. I think personally somebody who, if I am a fraction of what he is, I'll be doing good. But I think about my dad who, he's retired now, but he full throttle pursued his career and his life outside of his career without compromising either half. And so if I can do even a little bit of what he managed to do, I'll be happy. And then I also just think about my mom, who is just the strongest person I know. So I think I'm lucky to have people in my personal life and in my professional life who model so many things that I would love to successfully emulate.

Ben Shaberman:

That's great. And not to make you blush at all, but you're a hero for many of us. Not only those of us at the foundation who are so excited about what you do, but for so many patients and families, this is not an easy path to take, inherited retinal diseases, they're challenging, as you've alluded to. It's a long haul. We don't cure these conditions overnight, but the commitment that you're making to moving the research forward and helping patients means so much. So again, thank you for being a hero for so many of us, and thank you for a great discussion. I can't think of a better way to celebrate our 50th episode than to have this conversation about the great work you're doing and how you got into this field. So thank you, Rachel, for sharing so much about what you do and how you got here.

Rachel Huckfeldt:

Well, thank you so much, Ben, and congratulations on 50 episodes and creating such a great program with so many interesting and diverse guests.

Ben Shaberman:

Thanks again. And listeners, thanks as always for joining Eye on the Cure. It's great to have you and come back soon for episode 51. Thank you.

Speaker 1:

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