

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 to The Eye on the Cure Podcast. I'm your host, Ben Shaberman, with The Foundation Fighting Blindness. And I have a guest today who is very special to me, and all my guests are special, let me make that clear. But this particular guest, Dean Bach, was one of the first researchers I heard present retinal science, and I'll talk more about that in a moment. So anyway, welcome to Eye on the Cure, Dean.

Dean Bach:

Thank you so much. It's a delight to be with you, Ben.

Ben Shaberman:

Well, it's a delight to have you as a guest. So let me tell our listeners a little bit more about Dean. He currently holds the title of distinguished research professor of ophthalmology and neurobiology at the David Geffen School of Medicine at UCLA. He earned his PhD in anatomy from UCLA. And Dr. Bach has served on prestigious advisory boards for The National Eye Institute, Research to Prevent Blindness, our very own Foundation Fighting Blindness, and the Macula Vision Research Foundation. He's won 11 teaching awards at UCLA, including the UCLA Alumni Association Distinguished Teaching Award, the highest teaching honor bestowed by UCLA. And he was awarded the very prestigious Helen Keller Prize for Vision Research.

So I met Dean shortly after I started with the foundation in early 2005. And I was at one of our science meetings in Tampa, and that science meeting, Dean, had a lot of great researchers. Jose Sahel, Gene Dewan, Alan Lady, Steve Dager. It was like an all-star group of researchers. But it was your presentation that really captivated me, and you talked about a process called phagocytosis, and we'll talk a bit more about that, that really kind of blew my mind. And it's a process in the retina. But one thing you said is that when you were young coming up through your graduate program or post-graduate program, that the retina was seductive for you. And I realized at the moment that the same thing was happening to me, that I was really getting pulled into the science and all the different functions and structures within the retina. So your presentation was very influential for me, so thank you, Dean.

Dean Bach:

And thank you, Ben.

Ben Shaberman:

So you began your career at a very pivotal time in retinal research. That was the late '60s and early '70s. There were really two big discoveries, a researcher named George Wald discovered vitamin A's role in the visual cycle in the retina. And then you were involved in the discovery of phagocytosis in the retina. And can you just tell us about that time, your role, and the trajectory that your career took?

Dean Bach:

Certainly, that was a very heady time for vision science, Nobel Prize in vision research to George Wald. That was 1967. And I finished my PhD in 1968 and was hired then by UCLA upon my graduation. When I was a student in the graduate program there, I was studying one day for a histology exam, and my

professor was Richard Young. He walked in one day while I was preparing for one of his exams, went to the blackboard, and said, "I've been studying the biosynthesis of the lens capsule." I think a lot of our listeners know what that is now if they've had cataract surgery. That's the little bag in which you put the artificial lens these days. We didn't know then who made the lens capsule. Was it an accretion from the gel around the eye, or was it produced by the lens itself? And using radioisotopes, he was able to show that the lens capsule is made by the lens, by the cells in the lens.

At the same time, he looked back in the eyes of his experimental animals using this radioactive tracer and a technique called autoradiography. He looked back and he saw this wave of radioactivity moving through the photoreceptor cells. And he said to me, "Would you like to come into my lab and work with me on this?" And it didn't take me long to say yes. I admired him from afar. I was a little intimidated by him because he was a former Marine Sergeant and he had a bearing that went along with that. At any rate, we got to be research collaborators at that point, and that culminated in the demonstration of phagocytosis of that radioactive band. This band was moving through the little antennae of the photoreceptors. Each rod and cone cell has an antenna called an outer segment. And this radioactivity would move through that outer segment and disappear. And he was working with rats at the time, and the resolution of that was kind of low, and he was working at the light microscopic level.

So we went to the electron microscopic level, applied the technique there, and showed very nicely in not only rats, but in much bigger photoreceptors in the frog, that these things were peeling off, that the ends of the antennae being eaten by the retinal pigment epithelium, which is sort of the nursemaid of the photoreceptors, providing all of its nutrients and being digested. And that was the process that we then published in The Journal of Cell Biology in 1969.

Ben Shaberman:

That was huge. And so just to sort of recap that process, our photoreceptor tips, the antennae, as you call them, they shed their tips after a certain amount of use, and then they're ingested by that single layer of cells, the RPE cells. And this is a continual regeneration process.

Dean Bach:

That's correct.

Ben Shaberman:

And you and Richard Young discovered it. That's pretty cool.

Dean Bach:

And there's a wrinkle to that in that in mammals at least, that process is circadian and it's entrained by light as discovered by Matthew LaVail. And so whether the light comes on in the morning or not, you shed the tips of those antennae for the rod photoreceptors at least, and so that was a nice addition to the story by Matt.

Ben Shaberman:

So that happens in the morning when the light comes on.

Dean Bach:

That's correct. In the case of an experimental animal like the rat or the mouse, when the light comes on in the morning, the tips shed. However, if the animal is entrained to a light, dark cycle, let's say 12 hours

light, 12 hours dark, if you entrain them first for a couple of weeks, it doesn't matter whether the light comes on or not, they still shed. So it's circadian and it's entrained by light.

Ben Shaberman:

Wow. Very interesting.

Dean Bach:

Now in some lower animals like the frog, you need light to trigger it. If you don't turn on the light, they just get longer and longer for a while. And then when the light is turned on, they shed.

Ben Shaberman:

Very cool. And this is the very type of process and aspect of the rat that really hooked me into the science. So taking that process, can you talk about how that process is a pathway, if you will, in Stargardt disease?

Dean Bach:

Absolutely. The photoreceptor has discovered the fountain of youth. In some lucky individuals, you are born with photoreceptor cells and their antennae. You live a life of good health, and at the age of your demise, that whole process is still working normally. Now that's not the case in everyone. In the case of Stargardt one patients, those individuals have a defect in a protein that lives in the outer segments. The outer segment is like a stack of poker chips with a sausage skin around it. The sausage skin is the cell membrane, and the poker chips, we call disks. And each disk is a flattened saccule. And in the walls of that saccule lives the photo pigment called rhodopsin. That rhodopsin, as George Wald showed, uses a derivative of vitamin A in order to detect light. So this derivative of vitamin A is cocked like a mousetrap, if you will, as it's bound to a protein called opsin.

That product is called rhodopsin, which means red opsin. When a photon hits that, the derivative of vitamin A springs open like a mousetrap and comes off the protein. And now it's got to go somewhere. And in Stargardt one, the protein is called a flippase, flips that vitamin A out of the saccule into the cytoplasm of the photoreceptor, and then that gets recycled back to the retinal pigment epithelium, the nursemaid, which resets the mousetrap again. Now in Stargardt, that flipping doesn't happen, and as a result, because the vitamin doesn't get out of Dodge quickly enough, you have a double vitamin complex formed, which is toxic. And that is the poison that is then eaten by the retinal pigment epithelium in Stargardt one, and that poison produces a molecule called A2E, referring to vitamin A and the fact that it's a bisretinoid too, and that is the poison.

And it gets worse because that poison not only gets into the pigment epithelium, but it becomes oxidized. And those become more water-soluble, and then can move around the pigment epithelium and do mischief. That is Stargardt. It's a single gene mutation and one of the more common ones.

Ben Shaberman:

Right, right. And just so all our listeners know, Stargardt disease is a form of inherited macular degeneration. It usually is diagnosed fairly young in life and causes central vision loss. So what you're saying is when the photoreceptors shed their tips, there's that toxic vitamin A byproduct in those shed tips that's ingested by the RPE cells. And it accumulates in the RPE cells, and that's where the real problem begins and grows over time.

Dean Bach:

And that produce is called lipofuscin, which is a kind of general term. It's a fluorescent molecule and unfortunately, when it gets oxidized and mobilized, it activates part of our immune system called the complement system. And that then inappropriately attacks that region and causes further damage.

Ben Shaberman:

Right. And an important note for our listeners, some people take vitamin A for retina dis-pigmentosa. That can be a little controversial depending on which doctor you talk to. But for people with Stargardt disease, they should avoid extra vitamin A because that leads to more of the toxins. And in fact, some of the emerging therapies reduce the uptake of vitamin A into the retina, so there's less of these toxins that we were talking about that accumulate in the RPE cells.

Dean Bach:

Good point.

Ben Shaberman:

So you discovered this with Richard Young fairly early in your career. And how did that discovery and additional research and training, how did that propel you forward?

Dean Bach:

Well, it got a lot of attention in the field. And that's great. I think the year after we published that paper, people really got interested in phagocytosis, part of it. And I believe there were something like 35 platform sessions on phagocytosis at ARVO the next year. Consequently, some very talented people focused in on the molecular mechanism whereby this happens. It's a cooperative process. It's a dance between the photoreceptor and the pigment epithelium. They need each other for this thing to happen. A young investigator at the time, and still young, Sylvia Fenneman, who was at Weill Medical College of Cornell at the time, started working on this.

She had a good biochemical background. And she's not at Fordham University, but she's played a major role in the molecular mechanism whereby this process takes place. However, early on, Matt LaVail and Dick Mullin did a classic experiment in order to try to figure out where this mutation in this process is expressed. And there happened to be an animal model for that, which I had studied with Michael Hall. And we showed there was a phagocytic defect in that animal called the RCS rat. And Matt LaVail and Dick Mullin cleverly fused the embryo of an RCS rat with the embryo of a normal rat. And the RCS rat has an albino pigment epithelium, very little if any melanin, whereas the control rat had melanin. So they mixed those two embryos, now they had a rat that had four parent. And they could tell where the process was going awry. And it turned out that it was in fact the pigment epithelium that was defective, not the photoreceptor. It wasn't like the photoreceptor had a bad taste to it. It's because the pigment epithelium wasn't eating it.

And then Matt went on and collaborated with Doug Vollrath and discovered the gene called MERTK. Very, very important work. So there have been a lot of really talented people focused on this, and we're still mystified by the signal that arises in the outer segment that says, "Eat me." We know that there's a flipping of a phospholipid that takes place at the tip of the outer segment in the plasma membrane that says, "Eat me." Then a whole bunch of molecules spring into action and the phagocytic process takes place. But we don't know what it is that tells the photoreceptor or motivates it to say, "Eat me."

Ben Shaberman:

So do you think by identifying that process in a little more detail, we can come up with better targets for treatments?

Dean Bach:

Absolutely. Any time you know the molecular mechanism of something, you now have a rational approach to the therapy, and that's why genetics is so important. As Randall [inaudible 00:15:33] always likes to say, "It starts with the genes." And of course, he's right. And once you know the gene that's involved, then you can have a rational approach to treatment and intervention.

Ben Shaberman:

Right. Listening to you talk, Dean, and also looking at your bio, which I did in preparation for this interview, clearly you've done a lot of research and you've played an important role in advancing research. It seems like you really love to teach.

Dean Bach:

I do.

Ben Shaberman:

Won all these teaching awards. Can you talk about that a little bit?

Dean Bach:

Certainly. The teaching awards at UCLA are given at the university level, and that's the one that you mentioned, the UCLA Alumni Association Distinguished Teaching Award. I would have to say that's my proudest achievement there as a teacher. But awards are given out at other levels as well, at the departmental level, even at the clinical level. And those 11 awards are from the university, from my department, which is now called Neurobiology, having changed its name twice since I first started there. And then I'm proud to say that I got an award from the Jules Stein Eye Institute from the residents for the teaching that I'd done over the years. I have a daughter-in-law, who is a teacher. And now I have a granddaughter, who's at UCLA, who's going to become a teacher. And I'm very proud of that.

Ben Shaberman:

That's great. So your teaching chops are getting passed down through your progeny.

Dean Bach:

Yes.

Ben Shaberman:

That's great. Well, what's so great about teaching is the influence that you're having obviously on so many other people, not just your own family, but all those students at UCLA and beyond. And it had a big influence on me.

Dean Bach:

Thank you.

Ben Shaberman:

So just more of a general question, but you've been in this field for decades. What surprised you most as your career has moved forward?

Dean Bach:

Well, I guess it's a mixture of surprise and pleasure. One of the great leaps forward was the molecular genetics of inherited retinal disease. And that really started when Pete Humphreys localized a mutation to a particular chromosomal region and shortly thereafter, Ted Dryja discovered that it was rhodopsin that had a mutation. Now there's an interesting history there because one of the first meetings between the RP Foundation and the Canadian RP Foundation, as we called it in those days, we were locked up into a building and told that we were not allowed to escape until the white smoke puff from the chimney. And there was a brilliant young fellow there by the name of Richard Cone, what an interesting, appropriate name. Right? Cone, photoreceptors.

He said, "I think it's got something to do with rhodopsin, retinitis pigmentosa." And we all kind of smirked. Brilliant guy from Johns-Hopkins, physical chemist, but he doesn't know anything about clinical stuff. Well, it turned out that the very first gene mutation was in rhodopsin. And Pete Humphreys had mapped it in Ireland, but this family had moved to the United States and produced a lot of progeny over the years. And that's still the most common rhodopsin mutation in the world, I think. But it's very prevalent in the United States. P23H, we call it.

Ben Shaberman:

Right, right. That's a great story. And thinking about your career trajectory, that discovery didn't happen until 1989. That's almost 20 years into your career until the first retinal disease gene was found. The progress has accelerated since then, but those were some challenging times.

Dean Bach:

I can give you an example of the acceleration when I had the privilege of collaborating with Michael Redman on the knock out of the gene that's involved in the setting of the mousetrap for vitamin A. It's called RPE65. Mike knocked that gene out in 1998. And we published that paper then and it smelled of the isomerase, as we called it. And it was only 10 years before there was gene therapy in a human being for that, so that's pretty fast.

Ben Shaberman:

Right. And that's the gene therapy that became Luxturna.

Dean Bach:

That's right.

Ben Shaberman:

Well, in 2017.

Dean Bach:

Yep, virally based delivery of the correct gene into the pigment epithelium.

Ben Shaberman:

Right. And that in many ways changed everything when you look at all the clinical trials that are underway for gene therapies.

Dean Bach:

I think vision science can take some credit for really being ground breakers. Certainly, the discovery by George Wald was unique in that prior to that, no one really knew the molecular mechanism for vitamin A. We knew it was important. We knew it was a vitamin. You had to take it in through your nutrition. But no one knew how it worked, and that was the first demonstration of it. And also, I think in the context of gene therapy, vision science has really, really been a leader.

Ben Shaberman:

Right. Especially the retina, it's such an easy, small target, easy to access. And most of the conditions that we're interested in, the inherited retinal diseases are caused by mutations in one gene, so it's a fairly clear target. So you've mentioned a lot of personalities. Are there any other people, researchers, really anybody, that you would consider your heroes?

Dean Bach:

Yes, and some are outside the field of vision, of course. One of my heroes is Francis Collins, erstwhile director of The National Institutes of Health. He really saved the genome project in my view. It was sort of on rocky soil for a while. Jim Watson, the Nobel Laureate, was in charge of it initially. But he didn't get along very well with the director of the NIH, and he stepped down and Francis Collins took over and really brought that to fruition. So that human genome project has been so, so valuable for our understanding of inherited diseases. Of course, I have to mention Richard Young, my mentor. Had he not been my mentor, had I gone on to marine biology, which I thought I was going to take up, I would never have gotten into this field, so I have to give him credit. He used to sit in this tiny little lab, which was about the size of this office I'm sitting in. He had one technician and three graduate students. And he would hammer away on his typewriter. And at the end of the day, he'd say, "I can't believe they're paying me to do this." And he'd go home and come back again all juiced up for the next day.

So I really have to tip my hat to him, and of course, people like Ted Dryja and Jeremy Nathans. My goodness, Jeremy was a medical student at Stanford, and he solved rhodopsin and all the cone photopigments as a graduate student. And the insights that he gave to us regarding the mechanism of color blindness is just extraordinary, so those are some of the people. And I've collaborated extensively with people like Gabe Travis, who discovered the RDS gene. We did a lot of working knocking that out and actually doing gene correction therapy in animal models. And Bob Randall at Harvard, I would not have gotten involved in the cloning of some of these enzymes involved in the visual cycle, as we call it, the rhodopsin cycle had it not been for him. So those are just a few people I really, really enjoyed working with and who I admire very much, but there are many more.

Ben Shaberman:

Well, thanks for sharing that. And I want to add in case you didn't know, in case our listeners didn't know, just to clarify, the RDS gene is also called PRPH2. Correct?

Dean Bach:

Yes, Peripherin-2, it stands for.

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Ben Shaberman:

Right. So we're actually collaborating with a family. They're called the Nixon family. They have a foundation. And along with UC San Diego are investing pretty substantially in development of, well, first getting a better understanding of the PPHP2 gene, how it causes retinal disease, and also, therapeutic target. So that's a big effort for us right now because PPHP2 is actually a pretty common gene. I think it's the second or third most common IRD gene.

Dean Bach:

That protein is a glue really that holds the outer segment together. And if you don't have that, you've got chaos in terms of its development.

Ben Shaberman:

Right, right. So Dean, thanks so much for sharing the stories and more research. I learned a lot from you so many years ago, but even fast-forwarding 18 years to today, I'm still learning from you.

Dean Bach:

Thank you.

Ben Shaberman:

Thank you. Thank you. And I just appreciate you taking time out of your day to share your knowledge and the stories and history. And we appreciate all you've done to advance research and teach so many people about all the cool stuff that happens in the retina.

Dean Bach:

Thank you, and the respect is mutual.

Ben Shaberman:

Okay. Listeners, thank you as always for tuning into Eye on the Cure. And come back in a couple of weeks for our next episode.

Speaker 1:

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