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 everybody, to another installment of the Eye on the Cure podcast. I am your host Ben Shaberman, with the Foundation Fighting Blindness. I am delighted today to have with us Steve Daiger.

Steve is the Director of the Laboratory for Molecular Diagnosis of Inherited Retinal and Eye Diseases at the University of Texas at Houston.

We're going to ask him more about what he does, but really, Steve is behind and has been behind for many years, the search and discovery of the genes, the mutated genes that cause inherited retinal diseases.

One thing I wanted to say before we actually get started, well, I guess first of all, welcome Steve. Thanks for joining the podcast.

Steve Daiger:

Thank you, Ben. It's nice to be here.

Ben Shaberman:

Great to have you. I've been with the foundation since late 2004. In 2005, my first research and science presentation was at a meeting in Tampa. Steve was one of the first researchers that I'd ever heard present.

He talked eloquently about science and genetics. I remember his one analogy, that science is kind of like a football game or more specifically, a football ground game. You just eke out a few yards with each play, and eventually you cross the finish line. You score the touchdown. That's the way science goes. It's usually a pretty long and intensive process.

That just made an impression on me. Obviously, here we are almost 17 years later, and I still remember that presentation.

Steve, you've been at this, the gene discovery work for decades now, but can you describe in a relatively succinct way, what you've done over all those decades in terms of gene discovery and research?

Steve Daiger:

Sure. I'm glad to do that, Ben. Let me start by saying, I can't completely reconstruct 2005 in my mind, but I definitely remember meeting you. I actually remember that meeting.

This really gives me the opportunity to say that your contributions to the foundation have been of great value. Your ability to understand the science and communicate it to the members of the FFB and to the general public has been very, very helpful. So, I want to take this chance while I've got it, to say thank you for your really important contributions to this field.

In general, I actually started this business back around 1985. I'll tell you a story about how that all began, in just a moment.

At that time, we were after the one or two or three genes, mutations in which cause either retinitis pigmentosa or the other forms of inherited retinal disorder, Stargardt disease, macular degeneration, so forth.

We only thought there'd be a handful of those genes. My laboratory and a couple dozen other laboratories around the world, I might note, we all actually eventually ended up knowing each other and having good, friendly, professional relationships.

We began working away, using the technology in 1980s, 1990s, to try to find the gene at the simplest level, get a DNA sample. Well, actually more practically, a blood sample or a saliva sample from somebody who's affected.

Perhaps get samples from other members of their family, so you could do family studies. Get really good clinicians to look at their eyes and determine exactly what the clinical issues are. And then do genetic studies in the laboratory, eventually with luck, finding the particular gene, particular mutation or mutations in that specific family.

Of course, all of this became much, much better by the year 2000, when the Human Genome Project was done. All sorts of virtually science fiction sounding sequencing technologies became available, certainly by 2010. So the process speeded up.

But still, in our lab, and I would say now not just dozens, but the hundreds of laboratories around the world who are working in this area, it's still done person by person, family by family. Find the cause.

As you know, Ben, as well as I do, the huge surprise, which I will tell you truthfully, looked kind of daunting, is there's not just one gene or a few genes. There are dozens, actually, hundreds of genes mutations in which can cause inherited eye diseases, inherited retinal diseases.

Even if you restrict the conversation to retinitis pigmentosa, specifically, we know of 80 different genes mutations in which can cause RP.

I always need to add... of course, Ben, for you, I don't need to add this, that in an individual and in their family, we don't expect 80 different causes. We expect one cause in that family.

In that family, the goal is always to find the gene and find the mutations or mutation in that gene, depending on the type of inheritance.

Ben Shaberman:

Right. To give our listeners some context, the Foundation Fighting Blindness was founded in 1971. We're actually just a week out from our anniversary date of September 16th, as we're recording this.

Back then, in '71, we had a sense that... well, we knew that there was probably a genetic cause, but it took 18 or 19 years just to find that first gene.

Steve Daiger:

[inaudible 00:07:04]

Ben Shaberman:

So that was about 1989, 1990. Here we are today, in 2021. Now there are more than 270 genes.

Well, it depends who you talk to, but it's hundreds that are associated with inherited retinal diseases.

While I want to get back to your gene discovery work, one of the most valuable resources that came out of your lab for me, as somebody who was reporting on the science, is your RetNet catalog of all the inherited retinal disease genes.

So if you Google RetNet, you will find all those genes listed in that catalog. You can find research papers and discussions of inheritance patterns and all kinds of helpful information.

When I have patients and families that tell me what their gene is, if I don't know it, I go to RetNet. So, thank you [inaudible 00:08:06] .

Steve Daiger:

Actually, thank you for that plug. You may be interested to know, very briefly, the history on that.

Sometime around 1995, we had written a review article in which we listed the genes which were known at that time.

A very good friend of mine, who was actually a brilliant computer scientist, not working in this field, said, "Well Steve, you've got this published material. Why don't you put that on the internet?" I said, "What?" He said, "Why don't you set up a website?" I said, "What?" He said, "Well, let me introduce you to somebody who can write a website for you."

At that time, we dreamed up the name RetNet. That was the gestation of what still exists as... I think the original list was 50 genes. We're now up to 320 genes in that list. The list keeps growing.

But I always think back on my friend. If he hadn't said, "Oh, there's this thing called the internet. You ought look at it," RetNet wouldn't exist.

Ben Shaberman:

That's a great story. That's a great story. Nowadays, when you're looking to find new genes or mutations in genes we already know about, how do you go about doing that? How do you find or identify a gene as being associated with a retinal disease?

Steve Daiger:

Well, step one, the essential step is a patient, somebody who's affected, is seen by a retinal specialist. Under the best of circumstances, always by a genetic counselor or somebody else, who will collect information about the clinical problem, about other affected family members.

At that time, typically a blood sample or more recently, a saliva sample or a mouth swab is collected from that patient. It would be sent, for example, to our laboratory.

I always have to remind people that there are at least two dozen other laboratories around the world who are doing similar testing. Excellent commercial laboratories have come into existence.

A sample comes to us. We use standard methods to extract the DNA from that. Then we literally put it on a DNA sequencing machine, I suppose you might say more broadly, a set of machines. They do DNA sequencing, in our case and in many other cases, of all the 320 known retinal disease causing genes.

The sequence data comes to us. Our bioinformatics experts look at it. We use a number of computational tools. Again, this is a process being done all over the world in many, many different laboratories.

As I think you've noted before in other broadcasts, about 60% of the time we look at one of the known genes and we say, "That's it."

Why do we say that? Because there's a change in that gene, which almost certainly is likely to be a problem. The word would be pathogenic, for that change.

More often than not, it's a change seen in other families with inherited retinal disease. We may have other pieces of information relating, such as animal models and so forth.

All that information comes together based on the DNA sequence. We say, "That's it," again, about 60% of the time.

Another 10 to 15% of the time there is a hit, if you will. We look at it. We go, "We think that's probably it. The evidence is good, but the evidence is not perfect."

If I may use a technical phrase in our field, that's called a variant of unknown significance. We're not quite sure what that is.

If you do the arithmetic, then that tells you about 20% of the time we say, "We can't figure it out from the original sequence data."

Now at that point, it's no longer a standard routine diagnostic test. At that point, it becomes a research test. I won't elaborate on the dozens of research technologies available today, but there are many, many more things that can be done, than in the original process of just doing the sequencing of the 320 known genes.

If you'll bear with me, Ben... I think you're being nice to allow me to go into such detail, at the end of the process, particularly if we found something, we sit down with our clinical collaborators, confirm with the genetic counselor and the clinician that what we found makes sense, send a formal report to them.

That report then is interpreted and explained, often by the genetic counselor, to the individual who was originally tested and if the individual wishes, to their family.

If you notice, at the beginning of the process are the clinicians and the genetic counselor. And at the end of the process is the clinician and the genetic counselor.

Ben Shaberman:

Right. I will note, a little self-promotion here, is that with the podcast I did recently, I talk about the foundation's no-cost genetic testing program. That's another one of the labs that you can get. If you're a patient, you can get a no-cost genetic test.

Steve Daiger:

I'm giving you a thumbs up.

Ben Shaberman:

Okay. Thank you. Where your DNA is screened against 322 or so known genes. So that leads to the question, for those patients and families who do not have their gene identified, how are we going to advance the research so we can identify more mutations in genes, so that we can genetically diagnose more people and bump that 60 to 65% number up higher?

Steve Daiger:

As you well know, Ben, the Foundation Fighting Blindness is supporting a number of research projects in this country and actually oversees, to specifically address what are called the elusive genes, the unknown genes, the problems that haven't been solved yet.

I can describe a group of research investigators I'm a part of, but I still want to emphasize that this is just one of the many different research projects in this area, supported by the foundation.

In our group, working with Harvard and with UC San Diego, we will basically do more advanced genetic testing than the simple 320 genes.

There's a technique called whole exome sequencing. There's another technique called whole genome testing. There's a third technique called long read sequencing.

There are additional kinds of genetic testing I haven't even mentioned. I'd say there's at least another half dozen potential methodologies, if you will, in the laboratory, for doing testing.

In addition, our lab and other labs are particularly interested in looking at multiple affected family members in a given family, because if we find something suspicious in the first affected person and that suspicious thing is present in the six other brothers and sisters, that's a very strong piece of evidence that what we found is in fact a new gene, potentially or a new kind of mutation within the known genes. So, family studies become an important part of this.

You'll have to bear with me on this, Ben. I'm not even mentioning a number of additional technologies which are in use all over the world now, to try to go further.

Almost sounding like a tangent from the actual laboratory procedures, what I just described really focuses on that 20% of, we don't know what it is now. We hope to figure it out.

But remember, I mentioned those variants of unknown significance, now ranging anywhere from five to 15%. Where you go, wow, we think we've got it, but we're just not sure. Now what do you do?

That's a different domain of research. It's called functional studies. Again, the foundation is invested very, very heavily in supporting that kind of research.

We might go to an expert who can grow cells from, say a skin cell from the patient and use the skin cells to say, well, did that variant of unknown significance affect the cells growing in culture?

There might be an animal model that could be developed. So, there's a whole area of research, separate but overlapping with DNA testing, which is functional testing of the variants of the cells from the patients. That's another way of going forward, specifically to look at the variants of unknown significance.

Ben Shaberman:

Right. Just help me clarify something. When you're talking about somebody's genome, you talked about whole genome sequencing, that's looking at their entire collection of DNA. Aren't you looking at literally billions and billions of pieces of information?

Steve Daiger:

Amen. A reminder, you get about three and a third billion base pairs from your mom and 3.3 billion base pairs from your dad. So, your whole genome is actually 6.6 billion base pairs, half from your mom and half from your dad. Whole genome sequencing looks at as much of that as is possible in 2021.

We've got ways to go before we can go beyond looking at small snippets. But yes, there are hundreds of millions of small snippets done in doing whole genome sequencing.

I don't know any other way to say it, but massive computers and massive computer programs are now involved, to try to reassemble all of those small pieces into your personal genome or my personal genome.

Ben Shaberman:

You're really just looking for one change, at the end of the day. Is that right?

Steve Daiger:

You're looking for one affected region of the DNA.

Ben Shaberman:

Okay.

Steve Daiger:

We sort of abbreviate that by calling it a gene. There's some technical definitions. But the best way to think of a gene is just a very small region of your DNA, representing 0.01%.

Within that, you may have one tiny change. You might have two bigger changes. You might have three or four even bigger yet changes. But we still are looking at a very local specific spot, a gene.

That's why, Ben, I make the distinction between finding the gene which causes the problem in a given person, versus the specific mutations within that gene.

Ben Shaberman:

Okay. Yeah. Thanks for helping to clarify that. You've been at this for several decades. I know it's a slog.

The sciences, as we were talking about earlier, doesn't usually move too quickly. But can you tell us perhaps, a moment or two during your career, where you had an aha moment or a surprising moment, a discovery or just something unusual that you weren't expecting?

Steve Daiger:

At the beginning of our discussion, I mentioned my first contacts with the Foundation Fighting Blindness in 1985.

The very quick story there is, we had just begun looking at the technologies which would've been called advanced in 1985, gene mapping, linkage, testing. This was long before the completion of Human Genome Project.

A graduate student of mine came in and said, "There's this disease, Retinit ID, Retin IDC, something like that, piggy bee." We finally looked it up. It was retinitis pigmentosa. Literally never heard of it before.

She said, "We might just have a handle on this." I said, "Well, let's look for a grant."

At that time, the Foundation Fighting Blindness was then called the National Retinitis Pigmentosa Foundation. They had a address. I literally wrote a two-page proposal to a completely unknown address. I think it was in Baltimore at that time.

48 hours later, my phone rings. Then a leader of the Scientific Advisory Board, Alan Laties was his name, called me up and said, "Steve, you've never heard of me, but I saw your letter and we'll give you a grant."

That was literally the fastest, most improbable grant I've ever gotten in my entire life. I remember I said, "Alan, let me sit down and think about this."

Ben, I almost want to say, turn the microphone off, but of course I don't mean that.I told my graduate student this. Then she and I went over to the library, and we spent another two or three hours trying to figure out what it is that we're actually talking about, even after we'd actually written a potential proposal.

So the first big surprise, if you will, in my field for RP, was that the foundation said, "Do this."

One of the stories that I remember... This ties in with graduate students. I might add that graduate students and postdocs have been the bread and butter, if you will, of our laboratory, making things happen again and again. It's still true.

We were in a meeting, this would've been in the late 1990s, had studied a lovely family in California for years, made no progress. One of the graduate students said, "Well, maybe this is an X-linked problem."

We all said, "Nah, we've looked at that. We don't think that's it. Come on. That doesn't make any sense."

But in fairness, we went out of the lab, and we all went to our own areas to study. Sure enough, there was a real possibility that it was X-linked. So, we did the actual test. Sure enough, it turned out the student was a hundred percent right.

We gave full credit to her. She was the author of the paper. We felt it was a major breakthrough. It gave us some information about X-linked disorders that we hadn't known before.

But the funniest part of this story to me, is there were at least six people in that room, and every one of them thought it was their idea. If you asked them now, 20 years later, they'd say, "No, I had that idea."

You'll go, "Well, no, I don't think so. I think the graduate student had it." "Well, no, no, no, that was my idea. She just took it from me."

Everybody's real polite about this, don't misunderstand me, but it tells you about disparate memories of a major event. This is true in all our lives.

Ben Shaberman:

Right. That would make a good podcast as well. I'm curious, do you know what happened to the graduate student?

Steve Daiger:

Oh, yeah. She went on and she went to NIH. She has been very successful in looking at other disorders.

The technology that we used for retinitis pigmentosa discovery is applicable to all other human inherited diseases. So, that goes in two directions.

Number one, that means that students, graduate students, postdocs, young faculty members who are trained in inherited eye diseases, can move into inherited kidney diseases or inherited brain diseases. That's wonderful. We've had students who cross over into other disorders and made major contributions.

The subtlety, which is really important, is that works in the other direction too. If you make a profound discovery on kidney diseases, we in the inherited retinal disease field can look at that discovery and go, "Wait a minute. How does that apply to my field?"

So it's easy to think of the study of inherited eye diseases, a little, small domain that just only talks to each other. That's not true. The entire community of people working on inherited diseases in humans is all talking to each other and sharing ideas.

So, the fact that a student of ours may leave our field and go to kidney disease or somebody who studied kidney disease may come into the retinal field, is a wonderful power of synergism, if you will.

Ben Shaberman:

That's a good point. We're not in an isolated world. We interact with a lot of other branches of science.

One comment I want to make about your grant submission process and how easy and quick that was, things have changed.

The foundation has this thing called the Scientific Advisory Board. We review grants over a process that lasts the better part of a year.

The reason I'm bringing that up is to thank you for your service on that scientific Advisory Board, because in addition to being a researcher and a professor and whatever else you do in your professional life, you have given countless hours to the foundation, to help us review grants. That's an important role as a scientific advisor. But also guide our strategies for funding future science. So, thank you for all you've done.

Steve Daiger:

Thank you for that, Ben. I will add that part of the pleasure of my relationship with the foundation, has to been able to work with other people.

There's actually some real satisfaction of sitting down with a group of other experts, people, all of whom I know by first name, are all professional friends, and going through the grants and saying, "This is what we think about it."

It's actually been deeply satisfying for all of us who have worked with the foundation on grant reviews, to see that grants go out to young people who years later, become brilliant scientists, making fundamental contributions to the field.

The foundation has a huge roster of young investigators that started their career with support from the foundation, have gone on to be glorious scientists, making enormous contributions to inherited retinal diseases and other fields.

So, there's a personal satisfaction in being in these committees, but there's a little secret, and everybody who does research knows this. There's a selfish reason, which is that it forces all of us to learn the latest science, to learn the best ideas, to be able to take that information back to our laboratories or to our research facilities.

So, I've taken pleasure out of working with the foundation. It's been highly informative. The secret sauce is, it really helps my own research too.

Ben Shaberman:

That's great. We greatly appreciate the collaboration. We really try to do all we can to foster that.

What is next on your agenda, looking forward, after all these decades of very productive and innovative work?

Steve Daiger:

We are part of a group funded by the foundation, to look at what are called the remaining elusive causes of inherited retinal diseases.

Remember the equation, as I sort of set it out a few moments ago, is using what are now the standard laboratory approaches, diagnostic testing.

You can find the cause from 65 to 75% of people. There's another, say, 10% where you may or may not have the cause. And if you do the arithmetic correctly, that leaves roughly 15 to 20% where you go, "Wow, we've used contemporary standard diagnostic techniques and we can't find it."

So all of us who are still pursuing this genetics, and there's hundreds of laboratories around the world who are doing this, are trying to figure out that remaining 20%.

I mentioned a whole series of new technologies which have come along. We're just near a technology called telomere-to-telomere sequencing. That hasn't yet gotten off the ground. I hope to see that in the next five years.

One of the big problems we have is, we find what we think may be a problem in one of a patient's genes. We need to prove it actually causes a disorder in that patient. That requires animal studies and functional studies.

So for us, funded by the foundation, I work with a group of people. Again, I mentioned Harvard and UC San Diego, along with the University of Texas in Houston. We're trying to nail down that remaining 20%.

We anticipate that some of this will be the kinds of mutations, big changes that we couldn't recognize with the technology we used, up to this time.

We admit that there will be new genes and new kinds of changes. I will virtually guarantee you, among that 20% will be the kinds of changes that we just hadn't anticipated. Completely new biology.

I see that working its way out over the next five to 10 years. My hope is, whether I'm still a participant in this field or not, 10 years from now, we'll be able to say in 95% of cases, here is your problem.

Of course, I need to add, the goal of foundation is to be able to say, and here is the solution to your problem, which of course, is the long term goal of all of this.

I'm going to predict that 10 years from now, we'll be able to figure out the cause in 95% of people. There'll still be 5% of people where we go, "Wow, we just don't get it. We don't understand it." Human genetics is a lot more complicated than anybody wants to admit.

Ben Shaberman:

Well, it's great that you're pursuing these elusive genes. That's providing hope to people who still haven't had their gene identified. I'll just make the comment that, an important focus for the foundation, also, are gene-agnostic therapies.

So even if somebody's gene is never found, there are therapies that are designed to work, regardless of what the gene is.

Steve Daiger:

I think that's an extremely important point to make. What's a tactful way of saying this? Typically, if you don't know what's broke, it's hard to fix it. But sometimes it's possible to work around it, even if you don't know specifically the problem.

Because I've spent my career and many, many other people supported by the foundation have spent their careers looking for the underlying genetic cause, I still believe in the long run, that's the way forward.

But at the same time, the foundation has made, I think, very substantial progress in... What would you call it? Broad-based treatments that don't require you to know the specific cause.

In the long run, I think we will know the specific cause in at least 95% of people who are affected today.

Ben Shaberman:

Well, thank you. Thank you for all you've done over all these decades, to get us closer to that number. Yes, there's still work to be done.

Steve, this has been a lot of fun. Whether I'm in the audience, listening to you present or we're having a conversation like this, it's always a lot of fun and I learn something new.

So, thank you for sharing this with me and of course, our listeners. I want to remind our listeners that if you have questions, you can email them to podcast@fightingblindness.org. Again, that's

podcast@fightingblindness.org. Steve, thanks for taking time out of your busy day to have this conversation with me.

Steve Daiger:

Could I get a quick last word in Ben, which is-

Ben Shaberman:

Please.

Steve Daiger:

I have been incredibly privileged to work with the Foundation Fighting Blindness since the 1980s. I've had the privilege of working with you since early, mid, what, 2005 I believe it was.

I cannot tell you how valuable it is to have had a foundation that have people like you, who have pushed this field forward.

The reason so much has been accomplished by 2021, in not only knowing the cause of these disorders, but providing treatments and gene therapy, is because of the Foundation Fighting Blindness and people like you, who represent the foundation.

So, I give you a very sincere call out to thanks. You and the foundation have done remarkable things in pushing this field forward.

Trust me, you ain't seen nothing yet. This is going to really explode over the next 10 years, in a positive way.

Ben Shaberman:

Well, thanks for concluding this on that positive note. Thank you, Steve, for all you've done for the field and most important, our patients and families who are waiting for these treatments and cures. The genetics work is helping make that possible.

That concludes our Eye on the Cure Podcast. Please stay tuned for our next episode, and thank you for joining us.

Steve Daiger:

Thank you, Ben. I appreciate it.

Ben Shaberman:

Thank you.

Speaker 1:

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