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 am your host, Ben Shaberman, with the Foundation Fighting Blindness, and it is my pleasure for this episode to have as my guest Dr. Artur Cideciyan, one of the world's foremost authorities in evaluating retinal structure and function in people and animals with retinal degenerative diseases. I can't emphasize enough how critical his work and his role is in the development of treatments, cures and just the overall understanding of retinal degenerative diseases. Artur, welcome to the podcast. Great to have you with us.

Dr. Artur Cideciyan:

It's wonderful to be here. Thank you so much for inviting me and for that very generous introduction.

Ben Shaberman:

You are very welcome. Well, the generous introduction is going to continue because I'm going to give our listeners a little more background on what you do and some of your history. Dr. Cideciyan is currently a research professor of ophthalmology and co-director at the Center for Hereditary Retinal Degenerations at the University of Pennsylvania Scheie Eye Institute. He's been at Scheie since the mid-1990s. I think you're approaching your 30th anniversary at Scheie. Dr. Cideciyan holds a PhD in biomedical engineering, a master of science in biomedical engineering and a bachelor of science in mechanical engineering. Those degrees are all from the University of Miami in Florida.

Artur has received numerous awards and honors including those from the Foundation Fighting Blindness, Research to Prevent Blindness, the Association for Research in Vision and Ophthalmology, which we often refer to as ARVO, and many other prominent institutions. Most excitingly for me and I think most of our listeners, Artur, you have been an investigator on many high-profile retinal disease clinical trials, including the current Atsena clinical trial for their GUCY2D gene therapy, ProQR's clinical trial for their CEP290 RNA therapy and earlier, the University of Pennsylvania's RPE65 Gene Therapy trial.

The last thing I wanted to mention: one thing that I didn't know but I learned as I was preparing for this conversation was that you did extensive work in understanding how Stargardt disease affects the retina and vision. Artur, you published somewhere in the neighborhood of 30 papers on the topic so I think that makes you quite the expert in Stargardt disease, as well. To start off, I just wanted you to talk more about your role at Scheie and some of the work you do both in clinical studies and preclinical studies, as well.

Dr. Artur Cideciyan:

Thank you for that question and introduction. As you mentioned, I am a research professor of ophthalmology at Scheie Eye Institute. Scheie Eye Institute, for your audience, is the main home of the Department of Ophthalmology at University of Pennsylvania. We're in Philadelphia and I am the co-director of the Center for Retinal Degenerations, which provides, really, clinical care, clinical research as well as preclinical research. I share this directing responsibility with my longstanding friend and colleague, Tomas Aleman. I'm a vision scientist and an engineer, Tomas is a board certified ophthalmologist and a physician scientist and we think we make a good team with a career-long for

both of us interest and expertise in inherited retinal degenerations and tried to tackle some of the challenges of IRDs.

The Center for Retinal Degenerations was founded by our colleague, Sam Jacobson, who many in your audience may know. He unexpectedly passed away in January of this year. Over the decades, our main aim, if you will, is to provide better sight for people living with inherited retinal diseases. We take, basically, a two-pronged approach: on one side, excellence in clinical care to deal with the day-to-day problems of patients but on the other side, a world-class research program that tries to better understand their disease and then evaluating interventions such as the ones you mentioned that may lead to future treatments or cures.

What is clinical research? Different people may have different opinions, but it's understanding the details of vision loss. Also, some people refer to it as phenotype and in our case, in IRDs, that refers to understanding the details in families who have very specific genetic changes. The phenotype itself probably has two basic components, at least the way I look at it from a pragmatic point of view. One component is the severity of the disease at a specific point in patient's life. This is, of course, very relevant when the patient comes in to be evaluated in the clinic and [inaudible 00:05:39] one can talk about what is happening in their vision and their retina today at this point in time.

A very important component also is the the natural history, if you will, of disease, meaning how does the disease change over time? What was it like in previous decades that led up to this point today and how will it progress into the future in many decades? Of course, understanding this natural history is challenging because, in most cases, the visual loss develops and progresses over many, many years to decades. Our understanding in clinical research often combines what we call cross-sectional studies, which is we look at different people at different ages but with the same genetic condition and we combine that together with much more limited data where we follow a patient over time, called serial studies or longitudinal studies. When one can combine these two studies, usually, a picture emerges that allows us to estimate what is the average progression of condition or the natural history. Of course, each person often varies from this average time course.

As you mentioned, of course, an important part of clinical research is not just understanding but also performing clinical trials, which are novel interventions performed very carefully in small groups of patients to determine whether they're safe or efficacious. My expertise in all of this in the clinical research is to use functional and structural measures, some of which are standard methods like everybody will know the acuity chart. Some are state-of-the-art methods, some of which we have developed in-house over the years and only exist in our center. That gives an overview of clinical research. We perform with many of the similar tests, at least from our point of view, preclinical research, also, trying to understand the disease in naturally occurring animals such as dogs, which have blindnesses that overlap with humans, as well as genetically engineered animals such as mice, but using similar functional and structural methods.

Ben Shaberman:

I don't think we can emphasize enough how important these natural history studies are. It's not just about watching people or animals and seeing how their disease progresses, but you can better understand which subjects are best for clinical trials of emerging therapies based on where their vision is at and what's likely to happen down the road. Extending from that comment, you talked about the different measures that you use, the functional and structural measures. What are some examples of the tests that you typically use? I realize this is going to vary based on the disease and where a person is at in their disease progression.

Dr. Artur Cideciyan:

Before I mention the examples, generally, to explain to your audience, structural measures looks at the anatomy of the structure of relevant parts of the organ, in this case the eye, and in the case of inherited retinal diseases, the most relevant cell types that are affected primarily are the photoreceptors and their neighboring cells, called the RPE, or retinal pigment epithelial cells. The structural components of the cells, how many of the cells are remaining, how many of the cells are degenerated and have died and then, among the remaining cells, what condition they're in while being retained are some of the questions we ask in terms of structural measures. Functional measures usually measure some aspect of what we call vision. Of course, vision starts in photoreceptors, ends in the brain where we perceive certain differences in our environment and anything that goes wrong in that whole complex pathway can cause vision loss. In inherited retinal diseases, we are often mostly interested and directed towards the function of photoreceptors.

To answer your question, some examples of these kinds of tests is ... in terms of the structural tests, I find optical coherence tomography, OCT, as the most informative, if you will, the most available and thus most powerful in evaluating IRD patients. This is a test that can evaluate major sections of the retina as opposed to one little area of the retina. It is usually a very comfortable test to measure and depending on the aims of the testing, it can be as quick as a few minutes for simple questions in stable eyes, or it can take in our hands a few hours of testing to answer much more detailed questions, especially in eyes that are not ... they can't hold a steady gaze. Of course, then there is other things to consider: once the OCT image is acquired, the analysis of what's acquired can be done in stages also. That's one of the advantages of using OCT. It can be a very quick visual instantaneous evaluation by a physician, for example, for diagnostics. On the other extreme, it can be highly quantitative analysis requiring dedicated experts who have spent their lives thinking about this, custom software that's written for purpose to ask much more specific scientific questions.

Probably another reason I like OCT is because it can be what's called platform-neutral. What that means is there is more than a dozen different companies that provide commercial instruments and the reality is what they produce is more or less comparable. That allows us to compare across centers, across what other people have recorded or reported. We can collaborate and use data across different instruments. There is another reason, a historic reason, if you will, why we love OCT. Even though OCT is in every clinic these days, some 25 years ago, our center was really one of the earliest adopters of this technology to evaluate specifically photoreceptors. This approach has been very successful these days, 25 years later.

In terms of functional tests, the most powerful test I believe evaluates what is the purpose of the photoreceptor and the purpose of the photoreceptor, as the name implies, photoreceptor, is to catch photons of light and generate a signal that is transmitted to the next cell and eventually to the brain. One of the ways of doing that, to measure its light sensitivity, is using a method called perimetry, which allows measurement of light sensitivity as a map across the eye. A related matter or related test is something called an FST, which we like a lot also. This was invented by my colleague, Alejandro Roman about 20 years ago at our center. It is now used around the world. It is similar to perimetry. It measures light sensitivity, but it measures it at the most sensitive locus in the retina and thus, it can be very useful.

Ben Shaberman:

Sometimes, perimetry is referred to as microperimetry. Is there a difference between just regular perimetry and microperimetry? Maybe the overall question is, "What are the different kinds of perimetry?"

Dr. Artur Cideciyan:

There are indeed very many different kinds, but there's two examples you mentioned: the so-called perimetry by itself, which refers technically to what's called free viewing perimetry. What that means is the person is asked to look at a dot in space and it's presumed that they're using their fovea to look at that dot and everything else, the mapping is based on that assumption that they're using their fovea. That sets the whole coordinate system, if you will. In microperimetry, which is probably a misnomer, a better name would be retina-controlled or retina-imaging perimetry, no assumption needs to be made as to which way the patient is gazing. Retina is imaged in real time and exact locations in the retina are probed in real time as the eye moves. There are advantages and disadvantages for each technique. They are relevant for certain disease stages and not relevant for other stages.

Ben Shaberman:

Right but, as you said, what's so powerful is you can see changes in sensitivity or the relative sensitivity of different points within certain regions of the retina, which I think is really powerful. Now, perimetry is being used in several clinical trials as a potential endpoint. Speaking of clinical trials, you've been at this for a long time and you've worked on a lot of clinical trials. Can you tell us about some of those trials you've been involved in and some that are most memorable or where there were results that were particularly surprising?

Dr. Artur Cideciyan:

It has been absolutely a long run with clinical trials. My first clinical trial that I was involved in was soon after obtaining my PhD in the early 1990s. Some of your audience will remember was a very exciting time because initial molecular discoveries were being made in terms of IRDs and at the time, the clinical trials were based on nutritional supplements independent of molecular causation. Our center, led by Sam Jacobson, on the other hand, was very interested in these emerging molecular mechanisms and we were very interested in testing novel hypotheses, if you will, based on these very specific mechanisms.

For my first clinical trial ever, we concentrated on a disease called Sorsby fundus dystrophy caused by TIMP3 mutations. In this disease, very unusual, thick deposit forms between the RPE cell layer and blood supply [inaudible 00:16:21] capillaries. This can be seen as a block that stops from vitamin A products moving in from the bloodstream into the stores into the RPE, which is where they're needed for all vision. We hypothesized that if we could just increase the bloodstream content of vitamin A, we could go, if you will, by mass action through this deposit and increase vision. Indeed, that's exactly what happened. It was very exciting to be part of this. Indeed, to my knowledge, it was the first time ever where a humongous increase in vision, about four log units or 10,000-fold, was recordable upon days following oral vitamin A, high-dose vitamin A. That was the first time in a genetic disease that you could show such a large magnitude of an improvement in a matter of days.

As you mentioned, over the next 20 years, I got involved in about a total of a dozen, almost all early-phase clinical trials, some as a co-investigator, some as principal investigator, including electronic chip implants and other gene augmentation and gene-based therapies. Always memorable was the operating room. As a non-physician vision researcher, I was excited and happy to be, basically, a fly on the wall in the operating room in every one of these clinical trials in some 30-odd number of times I've been in the operating room. Each time, it's very, very informative because it tells us something about what is happening in that individual patient at the time of the injection and how that relates later to some of the visual functional changes that we are seeing. That has been very memorable and continues to be very memorable. I appreciate the surgeons allowing me to be part of that.

In terms of most surprising, probably ... you did mention the CEP290 trial. That was with the antisense oligonucleotides in the LCA10 form, which is caused by SEP290 mutation. We had a long history before that trial started for about a decade before 2017 where we had tried to understand that the phenotype of this disease, which was quite distinct, really, from any other inherited retinal disease. Specifically, they had a mound of foveal cones that survived for decades but with reduced function in many but not all patients. Thus, one can think of them as perfectly ready to receive a treatment if there was an efficacious treatment and all of a sudden start functioning.

Of course, that was theoretical until there was a treatment and then there was a treatment, this was the sepofarsen, which was an antisense nucleotide that was supposed to bypass this molecular defect. The first patient we treated was a 41-year-old who had lost his vision over the previous four decades and I remember like yesterday, six weeks after the injection, him calling on a Sunday night, very excited, saying that right out of his injected eye, he can see lights with increased brightness and clarity. When we made measurements later on, we showed that he had changed from light perception to 20/400 vision, which was very exciting for him, very exciting for us.

At the same time, excitement didn't stop us from thinking, "What is exactly happening in terms of the science behind this?" What we realized is that, even though the magnitude of the change is quite dramatic, but the time course of the change, of improvement, was really slower than what we expected. We expected in a matter of days and instead, it took three to five months to peak. Indeed, we expected it to go away in about two to three months and instead, when we measured it, we realized that it's lasting for two to three years. We had a whole bunch of hypotheses as to what may be happening, both in the treatment side of things as this new protein is being formed and moving to the cone-ciliar transition region, as the disease is primarily affecting. Also, we had some hypotheses as to what may be happening that the diseases or the treatment is so durable that it can last two to three years. Those ... they stand out over the years.

Ben Shaberman:

Right. I remember a few years ago you and Sam Jacobson were keynote speakers at ARVO, the big research conference that we all go to every year. I remember you and Sam presenting in front of hundreds and hundreds of other researchers about how some of these conditions like LCA caused by CEP290 mutations ... how despite significant vision loss, there's a lot of structure that's surviving, even if the structure isn't functioning as well as it should, and these patients are great candidates for therapies. Sepofarsen, as you just talked about, from ProQR is a really great example of that. That was exciting for me to see you and Sam as keynote lecturers at ARVO. I think you won the Proctor Medal, if I remember correctly.

Dr. Artur Cideciyan:

That's correct.

Ben Shaberman:

That was an exciting moment because those researchers are interested in a lot of different conditions, but it was LCA that really was on the forefront for those talks. The other thing I wanted to update our audience on ... you mentioned sepofarsen, which is a treatment that was developed by the company ProQR. Not so long ago, ProQR announced that they were getting out of the ophthalmology business and that was disappointing news for many of us who were excited about treatments like sepofarsen. They recently announced that they're in final negotiations or just coming up with the final terms and conditions with another company called Thea, or Théa, to move those treatments forward, both

sepofarsen for CEP290 mutations and also an RNA therapy for people with USH2A mutations in exon 13. It looks like those treatments are going to continue to move forward with this new company. I think that's exciting news.

Dr. Artur Cideciyan:

I certainly hope so. Disappointing to see the phase three trial results, at least as it has been reported in press releases. No publications have come through yet describing the details. Without a question, in my mind, in my obviously biased opinion, in the right patient, sepofarsen without a question improves vision in the fovea region. However, in CEP290 as well as in any other inherited retinal diseases, even though patients may have exactly the same gene change, they may have very different expressions of disease, so capturing or enrolling patients with treatment potential, meaning that they have a measurable and often large dissociation between the amount of anatomy of photoreceptors remaining, which being much more than the amount of function then opens up the door for a functional improvement. Not all patients have this dissociation and not selecting the correct patients of course dilutes the results and makes findings more difficult to interpret.

Ben Shaberman:

Exactly, and because so many of these conditions, really all the inherited retinal diseases, are rare, it's hard to find enough patients for these trials that fit the criteria for potentially responding to the treatment. The other challenge is determining which endpoints, which measures are going to, A, show that the treatment works and B, are acceptable to the FDA. That's been a big challenge in our space. Can you talk about that a little bit? Is there an emerging endpoint or endpoints that you think are likely to be most acceptable to regulators?

Dr. Artur Cideciyan:

It's clearly challenging. As you know and your audience knows, there is at least 300 different gene changes that causes IRDs and thousands of different mutations on these 300 genes. I do not believe one, two or three endpoints will be applicable to not only such a wide range of molecularly distinct diseases with different phenotypes, but also very different natural histories that are treated at different stages of their disease. That's important to consider, and the other thing that's important to consider is the aims of the intervention. For example, regenerative therapies that attempt to add new light receptors are very different than therapies to aim to improve the function of existing photoreceptors and in turn, those two are very different than therapies that aim to arrest the future progression of the disease. One has to think that through carefully.

I am most experienced, most interested and excited about those kinds of therapies that can in the short term improve visual function, and for those subset of therapies that include what we talked about, CEP290, LCA10, but also LCA1, which is guanylate cyclase, LCA2, which is RP65, and some other conditions also, the largest signal, if you will, are measured in the dark with light sensitivity measures. That's somewhat my bias, if you will, but that is a fact. Those can be measured by, we talked about previously, perimetry or FST. Perimetry is already acceptable as an endpoint to regulatory agencies in the US because of all the glaucoma work that preceded it. However, the typical perimetry done, for example, for glaucoma is more difficult to get a very large signal in patients with IRDs. Much more easier in IRD patients is dark-adapted forms of perimetry. I would love to see more and more forms of dark adapted perimetry evaluating both rod and cone vision, but in the dark being used as primary outcomes.

Somewhat related to that, as I mentioned earlier, is the so-called FST, which has a lot of similarities to perimetry, but it can be used in patients who do not have a good way of stably fixating or gazing at a

dot, if you will. It has been ... at least we have heard from US regulators that they don't view FST very positively. However, I have heard through the grapevine that regulators in other countries and regions may be much more open to using the FST as a potential outcome measure. Currently, about a dozen of us vision scientists are working on what's called an FST standard, which currently doesn't exist. We hope that not only helps clarify some of the technical and practical aspects of this test but also gets more and more people familiar with it, and with greater familiarity hopefully comes a greater acceptability in the future, considering the very large magnitude of signals that are available and occur in FST as we originally showed in the RP65 gene therapy trials, but since then in CEP290 trials, LCA1 trials and others.

Ben Shaberman:

Thank you for that perspective on endpoints. I want to shift gears a little bit and hear about from you what it's been like to be at Scheie. I want to preface that with when I started at the foundation quite a number of years ago in 2005, it became very obvious to me early on that University of Pennsylvania, the Scheie Eye Institute, was one of the most focused, committed and passionate group of researchers and clinicians for IRDs in our space. I've just never come across a group of investigators that's so committed and again, so focused on good science and doing the right thing. Now, you've been there, as I mentioned earlier, for nearly 30 years. What's it been like to be a part of that team?

Dr. Artur Cideciyan:

It has been an incredible pleasure and I've been very lucky to be part of this knowledgeable, committed and hardworking colleagues that really stimulate scholarly research that has had really quite lasting impact. At the Scheie Eye Institute, there's a large cadre of physicians and scientists interested in IRDs, but beyond Scheie Eye Institute, across the university, there is also a lot of strength not just in basic science of vision, but specifically in inherited retinal diseases.

The one incredible example that comes to mind is the School of Veterinary Medicine, which is basically the world's foremost center for understanding naturally occurring blindness in dogs, which more than 20 now, and many of the dog blindnesses result in a near exact duplicates of the human blindnesses when they're matched to the same gene change. This has been performed over many decades by my longtime colleagues and collaborators, [inaudible 00:30:32] and William Beltran. They have spent their careers on the canine blindness as we have spent our careers on the human blindness. These collaborations, for example, include treating a range of canine diseases such as RP65, RPGR, rhodopsin, bestrophin, NPHP5.

Of course, none of this, as you said, would occur without supportive leaders. The strength of the IRDs really initially was forged in 1990s by Stuart Fine, who was the department chairman. He brought on Jean Bennett, Albert Maguire, Sam Jacobson, and myself, and soon thereafter, Tomas Aleman joined the department and through the 2000s, there were some incredibly productive results in basic and clinical science. That was well beyond just the RP65 studies that many people are familiar with associated with the University of Pennsylvania. The next department chairs after Stuart Fine was Joan O'Brien from about 2010 until last year and then, as of last year, we have a new chair, Bennie Jeng. Both Joan and Bennie have been incredibly supportive in terms of the growth of this very strong IRD program, with new hires and clinical and basic sciences that continue to make it very exciting with new ideas and new people coming in, working with them and hopefully doing some good.

Looking inwards, in our center, we have about eight people who are simply the best, this is the Center for Retinal Degenerations, that include electrophysiologists, engineers, physicists, coordinators and multi-talented people that span many responsibilities. They've been with us for more than 10 years, and

they absolutely love working towards the goal of treatments for IRDs, and Tomas Aleman and I love working with them with that level of excitement.

Ben Shaberman:

Your passion and your colleagues' passion really come through and all the constituents at the foundation really appreciate that. You mentioned a lot of key figures in our space and I want to go back to Sam Jacobson. You mentioned early in our conversation that he passed away unexpectedly earlier this year. I know a lot of people listening to the podcast know Sam from being his patient or have just come across him in being affiliated with the foundation. He was so beloved for his care and commitment to good science. I just wanted to hear from you what it was like for you to work with him. Didn't you follow him from the University of Miami when you moved to Scheie back in the '90s?

Dr. Artur Cideciyan:

Yes, indeed. He was a legend. He was a ophthalmologist and a scientist who, as many of your audience will know, spent his whole career trying to help and support patients. I first met him in 1989, for the record, and that was a summer of 1989. I was a year into my PhD studies in biomedical engineering and, within a few weeks working for him over a summer, I knew two things. One was that I liked his personality. He had an incredible clarity of thought, attention to detail, but awareness of the big picture all at the same time. He had a constant desire for perfection, but he balanced it well with a dose of pragmatism and the fact that you have to get the information out and you can't do experiments for eternity.

The second thing I realized very quickly was that the retina and the photoreceptors were just a totally different ballgame compared to any of the other previous research I was involved with, which was heart and arterial circulation, kidneys and the brain. That was a very exciting time where new molecular findings were coming through in inherited retinal disease field, so we could have an attempt to bridge from the molecular to the clinical with relative ease, and we could do this in an organ that was accessible to electrophysiology, imaging and perception, which was just absolutely a beauty in terms of for a biomedical engineer to work with. I switched dissertation subjects, concentrated on inherited retinal diseases studying with Sam Jacobson, and that was one of the best decisions I made.

I absolutely loved working with Sam. He was tough. He expected a lot from others, but the reality is he expected much more from himself. I was used to putting in many hours in the lab but, with him, that came to a different level, where we would put in five days a week, the regular days in the clinic with the patients, and we would spend the weekends with animal experiments. The amount of learning was exponential and I absolutely loved it. Over the 35 years that I got to know him, he became a friend, a colleague, a mentor who would guide my career. In 1995, him and I moved together to the Scheie Eye Institute from the Bascom Palmer Eye Institute and remained here at the Scheie.

Since he passed in January, I've heard from many of his patients. They were very generous with their praise and very generous also with their donations towards a Samuel Jacobson memorial fund that was started by his widow, Jean Jacobson. At the center I co-direct, we hope we are working tirelessly to find treatments and honor his legacy to the field of IRDs.

Ben Shaberman:

Well, thanks, Artur, for telling us about your relationship with Sam and your experience with him. As I mentioned earlier, he was so beloved by patients and families because of the time he spent with them and his commitment to doing as much as he could to help them. I think talking about Sam is a great way to conclude the podcast. This has been a wonderful discussion. I've learned a lot and I appreciate you

sharing your wealth of knowledge about imaging, vision measurement, how important these approaches are to helping patients understand their diseases, helping understand the natural history of diseases and perhaps as important, getting therapies through clinical trials. Artur, thank you for taking time out of your day to share your wealth of knowledge and information.

Dr. Artur Cideciyan:

Thank you very much, Ben, for inviting me to this podcast. It is really my pleasure to contribute and to think through some of the things that we spend our days thinking about and let people know what we are thinking.

Ben Shaberman:

Well, it's our pleasure to hear about this several decades of knowledge and experience that you've gained, and sharing it in 30 or 40 minutes. We've covered a lot of great ground. Listeners, thank you as always for joining the Eye on the Cure Podcast and come back soon for our next episode. Great to have you, as always.

Speaker 1:

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