Recording:

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 I'm delighted to have as my guest for this episode, Dr. Jose Sahel. He's one of the most honored and accomplished leaders in the retinal disease and ophthalmology research space. And officially, he's the chair and distinguished professor of the Department of Ophthalmology at the University of Pittsburgh School of Medicine, director of the UPMC Eye Center, and the Eye and Ear Foundation Endowed Chair of Ophthalmology.

And Jose also founded and directed, from 2008 to 2020, the Vision Institute in Paris. And Dr. Sahel and his teams have been funded by the Foundation Fighting Blindness for decades. He's been a very active and dedicated member of our scientific advisory board for about the last 20 years, and his knowledge and experience have been invaluable in helping the foundation develop its scientific strategy.

And personally, I've really enjoyed learning about and covering Jose's many research advancements. Jose was one of the first researchers I heard present the science back, almost 20 years ago, and that was a great experience. Jose, welcome to Eye on the Cure. It's wonderful to have you as a guest.

Dr. Jose Sahel:

Thank you for inviting me. I appreciate, Ben.

Ben Shaberman:

Before we get started with the Q&A, just a little more on Jose's honors and achievements. They're innumerable, so I can't cover them all, but here are a few highlight. He's been a co-inventor on more than 40 patents, several of which have led to startup companies, including Fovea Pharmaceuticals, GenSight Biologics, Pixium Vision, Tilak Healthcare, Chronolife, Prophesee, and SparingVision. And we're going to talk quite a bit about SparingVision in just a moment.

Jose has been the recipient of numerous honors and awards, and they include Officer of the Legion of Honor in 2018, the National Order of Merit in 2014, and excitingly, last December, he was elected to the National Academy of Inventors. And I'd be remiss if I didn't mention that he received the foundation's most prestigious research honor, the Llura Liggett-Gund Award in 2015.

And one of the things that impresses me most about you, Jose, is that you have this great ability to envision the big picture, and we're going to talk about some of the research centers that you've launched with that vision. But you also work so expertly at the level of disease pathways and therapy development. And with all you have going on, are you still seeing patients?

Dr. Jose Sahel:

Yeah, I do. I used to see patients in Paris every Monday and Tuesday and, well, now in France, my role is more collaboration with scientists. And I just stopped seeing patients in France recently, actually. I still have a few patients that absolutely want to see me, but it's really a very limited activity. And in the US, I'm seeing patients twice a week. All my clinics are dedicated to retinal degenerations, but sometimes I'm provide some mild advice on complex cases, management of complex cases in retina.

So actually, I used to say that the last thing I would stop in my career would be seeing patient, because this gives me all the energy and the motivation to navigate through all the unpleasant part of the

academic life because you know why you are here, that people are expecting your work, and at least you believe that you can help them.

Ben Shaberman:

That's great. That's great that your passion for eyecare and helping patients and families remain so strong. And what actually inspired you to move into medicine and then specifically the eye and the retina?

Dr. Jose Sahel:

So the medicine was because, as a high school student, I had a real passion for philosophy, but I was also viewed as very good in mathematics and physics. So I was trying to find a field where I could focus on different aspects of science and understanding. And medicine appealed as a way to work with people and apply both philosophy and psychological thinking, but also science. So, this is why I went into medicine.

I have to say that I was disappointed for many years because it took to me quite remote from both scientific thinking and not always very humanistic. But, over the time, I discovered that you can build your pathway and try to implement as much of your energy and motivation into that. Ophthalmology came a bit by chance and I just discovered it after my medical school, and I was very impressed with the beauty of the eye, but also the extreme quality of the surgery. Surgery is amazing in ophthalmology and also the fact that it is part of a brain, the vision is a brain process. So, I thought it was an amazing combination of science, technology, and surgery. And so that's why I went to ophthalmology.

And I decided to focus on retinal degenerations mostly because, at that time, 30 years ago, 40 years ago, there was nothing. So it was so embarrassing, so difficult to talk to families and patients and having absolutely no understanding of a disease and no perspective on any therapy in the future. So, I thought I didn't sign up for something like that. I want to be on the side of a patient and the best way to be on the side of a patient at that time was to do clinical work but also research in parallel. That's why I started to, very late it in my career, to do research.

Ben Shaberman:

And thanks to all your great work and the work of many others, we now have a pretty good story to tell to patients with retinal conditions. Obviously, there's a lot more work that needs to be done, but we've come a long way. And one of the things that you did that's really monumental was founding and directing the Vision Institute in Paris, and you did that in 2008. And that's a very ambitious thing to do, to launch this really large comprehensive research center. What inspired you to do that?

Dr. Jose Sahel:

So what happened is that when I wanted to do research as a young fellow, there was no real integration between the clinicians and the scientists. There was some limited level of dialogue, but I would say that even the mutual respect was not extremely impressive to me. So, after I came back from my fellowship and my scholarship with John Dowling at Harvard and Dan Albert, I started a very small lab, actually. Just me and a part-time technician, trying to work on the cell mechanism of cell death in the retina.

And I realized that progressively, you need to bring together people with various levels of expertise, in biochemistry, in neurobiology, in surgery. And over the time, this grew into a small laboratory back in Strasbourg. At that time, I was still combining my work with clinical and surgery. I was extremely busy surgically. And this lab grew, actually, from myself and this part-time tech to 50, 60 people. And at one point, it was very difficult to be the only surgeon doing complex surgery and to manage a laboratory.

And then I got, initially, an offer in London to join the Institute of Ophthalmology in London with all my team. But eventually, for various reasons, we ended up in Paris at the National Hospital, where I became the chair, and I had the opportunity to propose to build space for researchers in the hospital. And this was the foundation of the Vision Institute. We had to find the mechanism to raise the money to build the institute. But at that time, I was no longer alone. I was really part of a large team around me, both clinicians and scientists, and it's really almost a crowd story.

We got more and more people over time. Now the Vision Institute in Paris is more than 300 people, plus all the companies and the hospital activities. So, it's close to 1,000 people. But it really started from this idea that translational science is translating clinical question, question from the patient into scientific questions. But you need to find the right people who want to have this dialogue and to want to do a back-and-forth exchange between clinical questions, scientific answers, scientific questions and back to the patient. So, this was the foundation of the Vision Institute.

I've been very lucky, because I was really surrounded by a lot of talent, a lot of energy, and this is still happening. I now stepped down as the chair in Paris, because I moved to the US and now we just built an amazing institute in Pittsburgh. You should come and visit. It's incredible. Fully integrated clinical research, clinical research and laboratory research, teaching. We have an amazing surgical laboratory for teaching to surgeons, all in one place. So, this was the same concept, collaboration, integration, focusing on the high-quality talent, from many facets of talent, but with the common will, the common engagement to work together, because we know that none of us has the answer, but collectively, we can approach the answer.

Ben Shaberman:

That's great. It's really amazing. As if the Paris Institute wasn't enough, you moved to the US and created the same thing in Pittsburgh in 2016. And I will be there in April. We have an event there and I'm really looking forward to seeing the institute.

Dr. Jose Sahel:

It also carries a lot of humanistic approach. There is a lot of art in the building that was made by artists that understand the mission. So, it's very integrated around the patient experience. Something the older you get, the more you understand how science is not everything. You know that, but you realize that every day, when you encounter families and patients and you're faced with so many situations.

Ben Shaberman:

That's great. I look forward to seeing the art, along with the research, and I'm sure it's a beautiful facility. So I'd like to switch gears a little bit and talk about some therapies that are emerging, because I think that's what our listeners are most excited about. And I'd like to talk about the company, SparingVision, which you co-founded in 2016, and the lead therapeutic that's in development there. It's a gene-agnostic therapy that's designed to preserve cones, and it goes by the name rod-derived cone viability factor. And earlier in the episode here, I mentioned seeing you early in my career at the foundation and it was then that you talked about this protein rod-derived cone viability factor. Can you talk about when that story began?

Dr. Jose Sahel:

Yeah. So that story began, I was a young clinician, it's almost 35 years old story, so it's a long story. I'll try to make it quick. So it started with this situation that patients are facing. They lose in retinitis pigmentosa in rod-cone degeneration, they lose dark-adapted vision very fast. Actually, sometimes they

don't even notice that, but this is the first event. Then they have a constriction of a peripheral visual field, and then over time the visual field becomes more and more narrow. And eventually, they lose central vision.

A lot of this, the initial phenomenon, the loss of dark-adapted vision is a rod function. The photoreceptors that are functioning at night, rod photoreceptors, and many gene defects are expressed in rods. And this explains perfectly why these patients are losing dark-adapted function, because the protein that are underlying this function in the rods are mutated. But what I could not understand as a clinician is why patients are losing the cones. The cones don't have a mutation in many cases, not always. In several situations, they have mutations, too, but in many situations they don't have that.

And, for example, the first gene was identified, rhodopsin, very early at the end of the '80s, early '90s. And then the following gene-like phosphodiesterase and others are rod-specific genes. So I was wondering why do the cones degenerate? And I put on paper several hypothesis and started to work on that. This actually how I founded my laboratory, trying to understand why the cones die. Initially, I thought that there might be some toxic mechanisms that are connecting between the death of one population of cells and the other one. And we did work on that and this led to some pharmacological approaches that were interesting, hold some promises.

Actually, we, there is a long-term follow-up of that. Just recently a CHP co-division institute continued that work and he's just submitting an amazing paper. So this is still a possibility. But what we found out across many hypotheses, I had five or six hypotheses at that time, is that the roles are actually making a factor that is supporting the viability of the cones. So we started by showing that if you transplant normal rod photoreceptors in the mouse where the rods have died, you're protecting the cones.

Then we showed that there is a diffusible protein that is underlying the phenomenon. And then I recruited, more than 26 years ago, Thierry Lèveillard to join me and together we worked on the identification of a signal, a protein that brings together the rods and the cones. And this is how we cloned rod-derived cone viability factor. It was a totally unknown protein at that time, a new family of gene. Actually, it's called the nucleoredoxin-like 1.

So the name we gave is the function, but the nomenclature of genes is that it's a protein that has antioxidant and atrophic effect. Then over the years, with Thierry, but Thierry was leading a lot of the mechanistic approaches to that. The receptor was identified, it was a beautiful cell paper many years ago, and all the machinery underlying interaction between the rods and the cones, at least this part of the machinery, was identified through this initial hypothesis.

And then very, very careful, very long-term, many, many years of work to identify the factor by cloning, and then the receptor, and then demonstrate in animal models that if you bring back this signaling, you're protecting a large number of the cones. Showing also that this is underlying both glucose metabolism, which connects with some work that Kinoshita at Harvard has done, but also antioxidant, very strong antioxidant. And other groups have been working on antioxidant to protect the cone for the receptors.

So at some point, we wanted to get that back to the patient and to deliver this therapy to the patient. Because it's a gene-independent approach, it could apply to almost every single gene in retinitis pigmentosa. Not as a cure, because you are not correcting the initial gene defect, but you're preventing what is the most significant for patient, which is the loss of light-adapted vision, central vision, reading, recognizing faces, central visual field.

So, after many years and many difficulties, that I don't want to describe here, we ended up thinking that we needed to create a company to develop that. And this is why with Thierry Lèveillard, initially, we created SparingVision. The beautiful thing is that FFB was on board with that. I think this is the first

company where FFB invested a long time ago. I have to thank Gordon and David Brent for the continuous support and the trust they put in us in the work we do. And the SparingVision was founded in 2016, has now raised enough money to carry the project through the Phase 1b/2a, potentially an initial pivotal study.

And the first patients were treated in Paris, actually, which is a nice part of the story. Early this year, and this is ongoing, two cohorts of patients have been treated. So it's now moving into, hopefully, a third cohort very soon. And then these are, at this stage, as you know, the initial phases of these trials are safety mostly, but obviously you want to observe some level of efficacy. Because we are talking about neuroprotection, protecting vision, this may take time. People who are with us know that this is not going to be a quick answer. It's going to take time, but I told you the story's already moving at 30 years old, so it's a long story.

Ben Shaberman:

It's a long story and it's an important story, because it really underscores the fact that science takes a long time to move ahead. But it's so exciting that it's really last year that this moved into humans. And I love the idea that the approach is gene-agnostic, so it has potential to help so many people. And I've heard you say over the years that if we can preserve even just a small population of those critical cone photoreceptors, we can help people maintain some meaningful vision. So our therapies don't have to be perfect, but even if you can save just some of those cones, that can be really huge for a lot of people.

Dr. Jose Sahel:

Yeah. There was a beautiful work that was done by Paul Sieving and Dr. Geller, I think in the '93 they published that, so long time ago. And they showed that if you can preserve, even if you preserve 50% of the cone, patients have almost no symptoms. If you preserve only 5% of the cone, they are still able to have orientation and discrimination performance. They did work on psychophysics in patients and they showed that. So it provides the basis for not the perfect therapy, but the one that would help people to continue to live a normal life or as an independent life as possible.

Ben Shaberman:

Exactly, exactly. I wanted to hear from you about another therapy that's in development at SparingVision. So RDCVF, which you talk so eloquently about, is all about saving cones that are still working, that are still processing light. But what you and other researchers had learned is that sometimes cones go into a dormant state, at least in advanced disease. They're not completely degenerated, they're still alive, but they're not functioning, and you have a therapy in development to reactivate those cones, right?

Dr. Jose Sahel:

Yeah, that's right. So we, this is work we started many years ago, with Botond Roska, in Basel, about optogenetics. So we had a paper, we published that, I think, in Science, in 2010, showing that actually there is a stage of a disease where the cones have lost the auto-segment, the ability to regenerate the auto-segment, but the cell bodies are still there and they are still connected to the rest of the [inaudible 00:18:08] between the retina. We call that, we coined the word dormant cones at that time. I think we invented the term at that time.

But actually, there were many studies that were done in post-mortem eyes by [inaudible 00:18:19], for example, and Matt Savail, who you may remember, was a founding scientist at Foundation Fighting Blindness many years ago, centers a stack of papers from animal models, trained that at least in 13

different animal models. What we had observed was right, there was a situation where you have dormant cones, where the cones are still there, but they are not functional.

So the idea was to express in these cones a protein that is sensitive to light that could be activated with a large amount of light, and then could elicit responses to light. And the beauty of targeting the cones is that you are driving both the on and the off pathway, a dark pathway and the light pathway, and you are able to have almost physiological responses. And this paper in Science really showed that you could do that. And I credit Botund for this amazing collaboration we have had for many years.

At that time, we tried to translate that into a clinical development and actually Foundation Fighting Blindness supported us, but we faced a lot of complexities, especially the level of expression of a protein and the level of light we would need was close to be toxic. So we decided to explore another avenue and we moved towards the ganglion cells. And this is what led to the clinical trial, successful clinical trial, we had with GenSight, where we showed actually that you could reactivate the ganglion cells in this patient who lost all vision.

And in initial patient, we published in Nature Medicine almost three years ago now, and now we have more patient that we are reporting upon. They have some responses, they're able to detect object, they're able to counter-object, to orient themselves. This is not normal vision, but these people were totally blind. We continued that and this is still ongoing. And as you know, other companies are now doing that, too, like Ratio Therapeutics and others. But we continued also to explore the idea of activating the cones, because we believe this could be a very nice cell target.

I have to say that other targets have been explored, like bipolar cells, by us, but also John Flannery, Botund Roska. Also, cells are currently being explored by going back to cones. Our group, and this is led by Deniz Dalkara, in Paris, got this ideas of using a protein that would benefit from the remainder of a transduction in the cone for the receptors, and would be responsing to much lower levels of flighting, so that you may not need a huge amplification of the light.

Botund Roska is doing a similar work in Basel, and I think this is also very promising. So SparingVision, to cover this technology from Deniz Dalkara, she had created the startup company and the fine vision to cover this project, it's called GS20. They are moving it, it's in the preclinical stage currently. They hope to be able to treat patients, I think, 2025. So this would be in compliment to the, actually the rod-derived cone viability factor, because now you are reactivating the remaining cones.

And we believe, actually, and this is a project that we have, but we could combine the two approaches, protecting the remaining cones from dying and reactivating the ones that are no longer functional. So it could then target a large number of patients at many stages of a disease. Of course, this is a long, it's still farfetched to say that this is going to work, but this is something that sounds very promising at this stage.

Ben Shaberman:

Well, it's very exciting that the cone reactivation approach, at least you plan to move into patients in 2025. And again, that's designed to work regardless of the mutated gene causing the RP or the other disease causing dormant cones. And it's really designed for people with really advanced vision loss, and we know those are the people who really need answers more than anyone. So that's very exciting.

I really appreciate, Jose, you talking about what's going on at SparingVision, and you mentioned some of the optogenetic work at GenSight. I'm just really excited about all the things that you're involved in that we don't have time today to really cover. But, before we close out, I really can't imagine that you have a whole lot of time to relax and recharge, but maybe you get a few moments here and there to do so. What do you like to do to relax, to recreate, and just enjoy some downtime?

Dr. Jose Sahel:

Well, I think I'm very fortunate, because I have a wonderful relationship with my patients, and this is something that is really giving me a lot of fulfillment via relationship. Also, my collaborators. I am someone who needs to relate to people and I'm very fortunate that this is happening. I've also wonderful family, have children, grandchildren. My wife is wonderful. She has always been extremely supportive. So I don't have, when I come back home, I find a very constructive environment that I've always enjoyed.

As you may know, also, I'm an observant Jew, so I don't work on Saturday. So every Saturday, I have time for meditation, praying, being with my family, and this has been a very important component of my life. I am also very fond of music. I'm a big lover of music, and this is a big source of joy for me, listening to classical music, especially.

I'm a big fan of Bach, and anytime I'm listening to his music, I feel energized and I feel the harmony of the world, which we forget how beautiful the world is. We are living in such terrible times, and this can be extremely distressing, but there's also a lot of harmony that is hidden behind everything. There's a silent music of the world, and I try to recharge to this silent music all the time.

Ben Shaberman:

Well, that's wonderful and very well put. We have to remember, there's a lot of beauty in the world, while a lot of crazy things are going on. Thank you, Jose, for again, taking time today to talk about your career and some of the great therapies and development. And most of all, to your unwavering, so strong commitment to patients and families and helping people potentially save and restore their vision. We're all so grateful for your commitment. It's really wonderful.

Dr. Jose Sahel:

Well, thank you for your support and trust. It means a huge lot for me.

Ben Shaberman:

You're very welcome. Thank you again. And listeners, thank you, as always, for tuning in to Eye on the Cure. Always great to have you, and we look forward to having you back for the next episode. Take care.

Recording:

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