Speaker 1:

Welcome to the Eye on the Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome everyone to the Eye on the Cure podcast. I'm your host, Ben Shaberman, with the Foundation Fighting Blindness. And for this episode I am delighted to have as our guests Jeff Stern. He's an MD PhD and his wife, Sally, a PhD. And Jeff, along with Sally, co-founded the Neural Stem Cell Institute. And very excitingly they discovered stem cells in the human retinal pigment epithelium. And we'll be talking about this layer of cells in more detail, the RPE. It's an important layer of cells that provides support to photoreceptors and it's affected in a lot of macular conditions. So what they are going to talk about is a clinical trial that they just launched using these cells in people with age related macular degeneration. So welcome, Jeff and Sally. It's great to have you.

Sally Temple:

Thank you. We're happy to be here

Ben Shaberman:

Here. Thank

Jeff Stern:

Thank you for inviting us to help get the word out.

Ben Shaberman:

My pleasure. So just to give our listeners a little background on Jeff and Sally, Jeff's retina career began with studying early steps in vision, photo receptor cell excitation and gap junction conductance between photoreceptor cells. And after that he pursued a clinical retina practice, which provided additional valuable research direction for him. In 2013, Jeff received the Audacious Goals Prize from the National Eye Institute and in 2015 he was named the Professional of the Year by the Northeast Association for the Blind. And Sally is the scientific director of the Neural Stem Cell Institute and oversees scientific programs with the goal of understanding the role of neural stem cells in central nervous system development, maintenance and repair. And a native of York, England, Sally leads a team of 30 researchers focused on using neural stem cells to develop therapies for eye, brain and spinal cord disorders. In 2008, she was awarded the MacArthur Fellowship Award for her contribution and future potential in the neural stem cell field.

So, again, it's wonderful to have you, the husband and wife team join us. And what I'd like to start off discussing is you created the Neural Stem Cell Institute to address a broad range of conditions, including retinal diseases such as AMD. And, Jeff and Sally, can you tell us what led to the formation of the institute, what your mission is and about the different conditions you're targeting?

Jeff Stern:

Sure. A main goal in forming the Neural Stem Cell Institute was to establish an environment that not only supported discovery research, but also promoted the translation of those discoveries toward practical applications. Many environments are great for carrying out research, research institutes and universities, and many are great for bringing new therapies to patients, the drug companies and

biotechs, but few are designed to provide the bridge that's needed to translate research discovery into clinical development. This gap between research and commercialization was known as and is known as the valley of death. There's great value when scientists make a discovery, continue to contribute to therapeutic development however. So in the Neural Stem Cell Institute, we'll call it NSCI going forward, is built for discovery and involvement in downstream development. Revenues from commercialization of the discoveries are reinvested in research here to generate new discoveries. Only a few percent of reinvestment is needed to create a sustainable environment for research. We at NSCI exceed this, returning 10% of reinvestment to sustain research, called this the evergreen model.

Sally Temple:

Yeah, so NSCI is the first independent nonprofit stem cell research institute in the US. So we established now I think 14 and a half years ago, nearly 15 years ago. And we are funded primarily through NIH grants and also foundation funding and some state funding as well. And just as Jeff said, the vision here is to create a mechanism where we really could be focused on translating stem cell therapies from discovery to the bedside to get into the clinic and test in patients. Our goal is really to develop novel therapies for neurodegenerative diseases, diseases like retinal degeneration, but also tauopathies. We work on tauopathies and on spinal cord injury as well.

Ben Shaberman:

So just quickly, what is a tauopathy? And I presume you spell that T-A-U opathy?

Sally Temple:

Yes. Yeah, I should explain. So there are several diseases where the protein tau builds up abnormally in cells. It aggregates and it kills cells in the brain. This happens in rare diseases like frontal temporal dementia and in common diseases like Alzheimer's disease. So by trying to focus, understand what makes this molecule build up, we're hoping to impact neurodegenerative diseases such as those. And we have some novel ways of going about reducing those molecules. And in this case we're using stem cells not as a cell to transplant, but we're using it as a model system of disease. So then we can test our drug candidates in the model, disease in a dish mod, and we can look at safety and efficacy. And of course we're using human stem cells, so the findings we hope will be relevant to human cells in the body in patients.

Ben Shaberman:

That's really cool and exciting. Thanks for explaining that. So when you created NSCI, you both brought your own areas of expertise. And in reading your bios, Jeff, it seems like you have a little more of the clinical expertise and, Sally, you bring a lot of lab research expertise. Is that how you collaborate? Can you tell us more about what each of you brings to your efforts, to your mission?

Jeff Stern:

Well, I can give you some history of how it evolved, which perhaps will explain the roles.

Ben Shaberman:

That would be great.

Jeff Stern:

Sally and I met, I won't say how long ago, but it was too long ago at the Woods Hole Marine Biological Laboratories. I had a small lab studying very primitive retinas in horseshoe crabs and squid and Sally was enrolled in the neurobiology course, which was a very well respected course that attracted young scientists from around the world. After we met, Sally returned to London to hear studies with Martin Raff at University College and I returned to postdoctoral research with Peter MacLeish and Chorston Weasel at the Rockefeller University in New York City. One year later Sally moved to New York to work with Tom Jessell at Columbia University. We married the next year. The practical challenges around forming a family in New York City with two science careers led me, I think Sally may have led me, to the PhD to MD program in Miami. While we were in Miami, Sally discovered that there were neural stem cells present in CNS and that launched her career to a new level while I was now in the trenches learning clinical medicine.

Over the next decade, I was focused on retina practice, ophthalmology practice, while Sally worked on defining the neural stem cell niche and breeding her great career. We joined forces about 15 years ago working in the RP stem cell and I continue to practice to this day. I'm part-time now, but working with Sally full-time. And as you mentioned, Sally is the scientific lead while I am the clinical one, but we work together in all the aspects of the research.

Sally Temple:

It's really great to work together because I think our skill sets really compliment each other. I'm mainly a cell biologist, molecular biology. So I'm really interested in studying the cells and the mechanism whereby cells die and how stem cells can be used to regenerate. And Jeff has really focused on biophysics in his research background, but now has this added perspective of knowing clinical practice in retina. Knowing not just how to treat patients, importantly talking to patients about what they want and need. I think that that's really crucial to bring that into any study, like the ones that we're doing. You're developing something for patients, you've got to talk to them and bring in that understanding. And of course in his office Jeff had been involved in running several clinical trials. So as we moved to our own clinical trial design and thinking all of that through, his skillset was really, really important to develop that design.

Ben Shaberman:

That's really cool how you each bring your own set of experiences and skills. And there's a little overlap because, Jeff, you obviously have some lab experience, as well, but let's move into AMD. Let's talk about this retinal therapy that you just moved into at clinical trial and there are a lot of organizations targeting replacement of RPE cells. And can you talk about why that's such a common therapeutic strategy, at least for now?

Jeff Stern:

Thank you, Ben, for a great question because there's a really simple answer. Our RPE cells are lost as AMD progresses. And this, as you mentioned earlier, decreases support of overlying neural retina, feeding to loss of vision. Since RPE cell loss is central to AMD, an obvious strategy to treat AMD is to replace the RPE cells that are lost, very simple. Molecules or biologic drugs could slow the loss that's ongoing, but will not revive dead RPE cells. So RPE cell replacement is needed to reverse the disease. Transplantation of RPE is a direct way to increase the number of RPE cells to reverse the RPE cell loss that occurs during AMD. So the answer is almost totally logical. It's very simple. RPE cells are lost, we found a way through the RPE stem cell to generate many RPE cells. Others, as you mentioned, have been using pluripotent stem cell sources to generate RPE and then simply transplanting these under the

macular to increase RPE cell number to counteract the loss of RPE cells in AMD is the strategy that others and we are following.

Ben Shaberman:

Right. And what's interesting is other groups are using RPE that are derived from maybe human embryonics stem cells or developed by a process known as inducing pluripotent stem cells, but you, meaning you and/or Sally, actually identified RPE stem cells in the human eye. And that's what you're transplanting. That's what's so novel and innovative. How did you identify these cells in human eye? How did this happen?

Sally Temple:

So I can tell you a little bit about this history because when things are difficult I like to remind Jeff that really this was his idea. Also, he needs the credit for this because way back thinking about how the RPE layer plays a role in retina repair in model organisms, the sort of animals that Jeff used to work on when he was doing his PhD in postdoc. So in salamander, for example, the retinal pigment epithelium can regenerate the entire neural retina as well as the RPE layer. It's really quite remarkable. And I think that Jeff had in the back of his mind, right, Jeff, that maybe in the adult human there was some residual regenerative property. And so he said, "Let's look for this." And that was when we started. We actually started getting cadaver donated eyes. They donated to eye banks, as you know, which is a wonderful and generous thing that people do to help research.

And we got those cells, those eyes in, we learned how to get very pure RPE cells out of them and to culture them. And what I had done previously was develop assays for identifying stem cells in the nervous system, things like plating single cells to see if they would grow into a very large colony, demonstrating that these cells could actually grow in a floating non-adherent culture and produce again these little spheres, or we made movies to show that some cells had truly much larger self-renewal potential than others. And that's a cardinal feature of stem cells. And what we found was there's a subpopulation of cells in the adult RPE, about 3% to 5% of the cells, that have features of self-renewing stem cells. That most of the cells in the RPE layer, if you plate them, they really don't divide. Maybe they divide once, but this small subpopulation divides and just takes over the whole culture.

And it can expand to give billions of cells. And, really, that was the starting point. We realized if there's an adult stem cell and we can grow it up and make billions of cells, we can use these to help replace the cells that are lost in patients with RPE degenerative diseases like AMD.

Jeff Stern:

If I can jump in, thank you, Sally, for giving me full credit, the husband wife team for this discovery. And perhaps there were parallel pathways to the discovery because my recollection is that the entire group was involved in discovery of the RPE stem cell. That we had been working, if you recall, to bottle drusen formation to describe changes in the RPE cell phenotype that led to production of drusen proteins, which are in the early stage of AMD. And we hadn't known that RPE cultures can proliferate extensively. It's been known for many decades and we use that to generate the RP cells that we were studying. And you, Sally, if I recall, notice or brought to the forefront that a few of the RP cells in these bulk cultures divided a lot while most of them divided very little. And that led to the isolation of the highly proliferative subpopulations. And we found that the progeny of these cells also proliferated extensively, i.e. they self renewed using your method, Sal, and defined these cells as stem cells that can self-renew and differentiate.

The original work was published in 2005 and then the stem cell itself in 2013. And we continue to work on it to characterize its properties and better define the RPSC and its role in AMD.

Ben Shaberman:

So let me try to understand something. When you extract these cells from the donor cadaver eyes, are you expanding these before you transplant them? Are you making a lot more stem cells or are you just transplanting them "as is" from the donor eyes?

Sally Temple:

No, that's really critical to understand. We do a lot of expansion. So we get one donor eye. The stem cells that we get out, maybe one to two million stem cells, those cells are highly proliferative and we end up generating a bank that can provide hundreds of doses for patients. So from one donor we can get hundreds of doses through that expansion.

Ben Shaberman:

That's great. And why do you feel the cells that you're deriving this way and expanding, why do you think these are going to work better than some of the other RPE cell replacement strategies that other groups are trying?

Jeff Stern:

Another great question, Ben. Thank you. And we don't want to get trouble. We're very supportive of each approach. We should make clear and carry out a lot of the pluripotent stem cell derived RPE research here, as well, but our preclinical work using animal models show that progenitor stage RP cells are more effective in grafting and rescuing vision after transplant than our mature RP cells. And most of the approaches with pluripotent stem cells, they're differentiated extensively into mature RP prior to transplantation. The use of progenitors makes a lot of sense on a few levels. We all know, quoting Darwin, that developmentally younger cells are generally more effective at repair. Younger tissues we all know heal faster than old ones. And in retrospect, it's no surprise that younger cells at the progenitor stage of development are more reparative. We found the four week progenitor stage is more effective than older or younger cells in fish and rescuing animals. And so we focused on that.

We call it the goldilocks stage of development and we hope that the clinical trial will follow a similar course, that the younger cells can graft and repair more effectively than fully differentiated or less differentiated cells. The adult RPSE does not form tumors. It's purpose built to make RPE, so it is a way to get this progenitor stage of differentiation.

Ben Shaberman:

And just to clarify, progenitor, or an RPE progenitor, is an RPE cell that is almost a mature RPE cell, but not quite?

Jeff Stern:

Committed to produce RP progeny, but not there yet. Sal, you could probably expand on it.

Sally Temple:

Yeah. No, you explained it perfectly. And what we found that a progenitive stage cell is better at rescuing vision, at least an animal model. We see this with other cell transplants, too. Dopaminergic

neurons, astrocytes, oligodendrocytes. The more mature, fully differentiated cell in each of those cases does not integrate and does not move into the tissue and combine in the tissue as well as a progenitor stage. So I think there's something very fundamental here, actually, about the ability of a progenitor stage to be more reparative.

Ben Shaberman:

Right. So, Jeff and Sally, tell us about the clinical trial that you just launched through this newer company, Luxa. And this is for AMD. Tell us about the trial and what you're hoping to observe.

Jeff Stern:

Well, Luxa is a partnership between NSCI and Y2 Solutions, which is a Korean technology company. NSCI brings scientific and clinical expertise while our partner at Y2 brings business and financial skills to Luxa. And the combination is working out very well, combining the science, clinical and business at Luxa, an ideal to advance the RP transplantation for dry AMD. The study is very simple. We're transplanting three doses of RPESC, derived RPE at progenitor stage cells, into two groups of patients. We call them the worse seeing, better seeing groups, legally blind and on the way to blindness. Our major outcomes will be vision, visual acuity. We're also measuring microperimetry and some anatomic aspects for safety. We're in phase one still, so safety is our goal. Of course we're hoping to see efficacy. We're off to a good start. The trial's going very well.

We've just started, so the enthusiasm is probably ramping up as we speak. It will take a year, year and a half before interim results are available for public consumption. I should add that with the stem cell field in general is struggling right now with questionable treatments for shoulders, for the eyes. There's women in Miami that were blinded just recently and a few years ago. So we're in partnership with the NIH, National Eye Institute and also with Kellogg Eye Center aiming to make an example of how to properly do the study. So the study's going to be relatively formal, very careful at analyzing outcomes and the statements that we're able to make about it.

Ben Shaberman:

Right. And I think it's important for our listeners to know that there are some bogus stem cell treatments out there. And a sign that a treatment or a trial might not be legitimate is when you're being charged thousands of dollars to get the treatment or be in the trial.

Sally Temple:

Yes. And another red flag, Ben, is if the people who are doing that say things like we don't need FDA approval. That's another red flag. They try to make arguments that they don't need regulatory approval for what they are doing, but in fact they're really operating in an environment where they should have regulatory approval. And these have caused devastating damage, like Jeff said. They've blinded individuals and it was really awful to read that this is still going on. It's been going on now several years, so called stem cells being injected into people's eyes in these so-called clinics and blinding people. So let's urge people not to do that. And there's actually a great website called A Closer Look at Stem Cells. It is run by the International Society for Stem Cell Research, ISSCR, and they give information in lay terms. They have a patient booklet, they talk about the red flags and the questions that you should ask if you're thinking about a stem cell therapy. So I can send you the link to that, Ben.

Ben Shaberman:

Sure, that would be great. And if any of our listeners have a question, they can always send an email to info@fightingblindness.org and we're happy to follow up. Jeff, you had a comment.

Jeff Stern:

Yeah, I would just add to Sally and Sally was involved with writing the guidelines for patients to avoid unscrupulous trials or, as you say, bogus treatments. And we've discussed this a lot, Sally, I'm convinced that one of the best ways to counter the snake oil salesman is to make an example of how to do the trial properly. And the NEI has been invaluable, our colleagues at Kellogg Eye Center, and we're working with a CRO to administer trial MS corporation that has a lot of experience working with the NIH and NEI. I'm all on board. Part of the mission of this trial is to carry it out properly, ethically and set an example against the unscrupulous trials that are charging patients money and so forth.

Sally Temple:

Yes, and thanks for mentioning the way that our clinical trial is organized is that the cells are being manufactured at the Cedar Sinai Biomanufacturing Center. They're doing an awesome job. The generating GMP grade cells that have to meet all of the criteria that are important to achieve before we can even transplant them. And those cells are then shipped to the Kellogg Eye Institute in Michigan. And [inaudible 00:25:44] is the lead surgeon on that and this is a whole team and they're doing a fantastic job.

Jeff Stern:

And we are recruiting subjects, so legally patients with dry AMD. I should specify our trial's not addressing wet AMDs, so the dry form, geographic atrophy. And contact Kellogg directly, so we are recruiting you.

Ben Shaberman:

And do you know offhand what the email might be? I know if somebody goes to clinicaltrials.gov and searches under Luxa they're probably going to find your trial and have the contact information for that.

Jeff Stern:

I don't have that handy. Sorry, Ben.

Ben Shaberman:

Well, again, if people are interested, they can reach out to us, info@fightingblindness.org, or go to clinicaltrials.gov and search on L-U-X-A. That's the name of the company. And thank you for that overview of how your cells are being produced and how your trial is being run. We do a lot of funding and work with Kellogg and they are an excellent clinical research outfit.

Jeff Stern:

If someone interested in the trial wants, they can email me directly. Just my name, Jeffrey Stern, at neuralsci, N-E-U-R-A-L-S-C-I.org. And I'll pass them on to the Kellogg recruiters.

Ben Shaberman:

So one more technical question about the cells, I know there are other macular conditions besides dry AMD where the RPE are significantly affected. Stargardt disease, Best disease, perhaps some cone rod

dystrophies. Now, I realize you're focused on AMD now, but if you have success, are these other conditions potentially on your radar screen?

Jeff Stern:

I think RP transplantation is a straightforward strategy to increase RP cell number to address any condition that involves RP cell loss such as AMD, Stargardt's and et cetera. All of our resources right now are committed to AMD, but of course in the future we hope to add other diseases, like Stargardt's, where there's great patient need.

Ben Shaberman:

Right. And I'm not asking for a bold commitment to these rare conditions, but I know some of our listeners have an interest in those. So finally, to conclude, I think it's very interesting that you two collaborate scientifically, clinically. I think it's interesting that you're husband and wife. And so I was wondering if you'd share how you spend some of your nonscientific time. What do you do for fun? Do you have favorite restaurants, movies, concerts? What do you guys do on date night?

Jeff Stern:

Well, date night for us consists of writing grants, presentations.

Sally Temple:

No, Jeff.

Jeff Stern:

No, on a serious note, we do get away. We walk in the woods. We're in a beautiful location surrounded by countryside and we enjoy de-stressing through a walk in the woods. And that's probably our most common activity, but we visit children. We have children, a grandchild now. So we visit or take vacations. We were in Paris earlier this month visiting museums. For a week we went and I can recommend a few restaurants later if you want to discuss.

Sally Temple:

Yeah, we did have fun. We do talk science a lot. We do talk about this even when we're walking in the woods, but we love it. It really is a wonderful thing. Very privileged to be involved in this whole process. And from discovery, now we're in the clinical trial. Remember, Jeff, after we transplanted the first patient, I think we were out for a walk and saying did we really get through to this point? It was just so exciting and it's fun. We enjoy doing this together.

Ben Shaberman:

And we're fortunate that you share the passion and work together to move this research forward. And I remember, Sally, I want to say it's about six years ago the foundation hosted a pre-ARVO summit and that's where I first learned about these RPE stem cells. And I thought this is interesting. Hopefully they can move these into treatments for people. And so it's exciting for me to see after a few years that you've actually done that and that's what it's all about. The science is really cool, but ultimately we want to save and restore vision for people. And thank you so much for getting to the point where there's hope that you can do that and you've moved these into a trial.

Sally Temple:

Thank you. And this is such an exciting point in science research, what we can do with stem cells and with gene therapy, gene editing. It's truly a new era and I'm very hopeful that there will be lots more clinical trials and hopefully lots more successful therapies coming to help people with blinding disorders.

Ben Shaberman:
Well, we're working hard at the foundation to do that and work like yours is making a huge difference. So, Jeff, Sally, this has been fun. It's been informative and I appreciate you taking time out of your busy days to be here and share what you're doing. And I'm sure our listeners greatly appreciate it. Thank you.

Jeff Stern:

Thank you, Ben.

Sally Temple:

Thank you.

Jeff Stern:

It was a great interview.

Ben Shaberman:
My pleasure. And listeners, thank you again for joining another episode of Eye on the Cure and stay tuned for our next episode. Have a great day. Bye-bye.

Jeff Stern:

Bye.

Sally Temple:

Thank you.

Speaker 1:
This has been Eye on the Cure. To help us win the fight, please donate at foundationfightingblindness.org.