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 another episode of the Eye on the Cure Podcast,. Great to have you join us. I am Ben Shaberman, Senior Director of Scientific Outreach at the Foundation Fighting Blindness, and I'm delighted today to have as our guest, Michael Young. He's a PhD and an outstanding expert in stem cells. He is been for really since I've been with the foundation, one of my go-to guys for information on stem cell research. So, Michael is an associate professor at Harvard Medical School Department of Ophthalmology. Welcome, Michael. Great to have you.

Michael Young:

It's great to be here. I've been a big supporter and member of the Scientific Advisory Board of the Foundation Fighting Blindness for I believe 20 years or so. And even as a undergraduate, my laboratory with Raymond Lung was supported by the foundation, so we go way back.

Ben Shaberman:

Well, it's been our privilege to support your work because it's led to some pretty exciting advancements, which we're going to talk about. But to get things started, especially for our newer listeners or people who are kind of new to the field, can you give us a basic definition of stem cells?

Michael Young:

I think I can. So, it's been a bit of a moving target over the years, but the way I like to think about it is the ultimate stem cell is a fertilized egg. It can give rise to an entire organism, and we call that totipotent, something that can give rise to an entire organism. So, if we go down the spectrum of potency, we come to what are known as pluripotent stem cells. So, pluripotent stem cells. For instance, embryonic stem cells are what are known as induced pluripotent stem cells. A gentleman from Japan won the Nobel Prize for the discovery of these cells. These cells are what are known as pluripotent. They can give rise to all the tissues of the body, but not a complete organism.

So, for instance, the placenta and the extra embryonic tissues are not derived from pluripotent stem cells. But all germ layers of, there are three germ layers in mammalian species in all animals, endoderm, ectoderm, and mesoderm. So, all of those can be derived from pluripotent stem cells. One step down from that, those are the cells that we have been working with mostly for a number of years, and they are known as multipotent stem cells. They can give rise to multiple cell types, but not typically all germ layers. So, retinal stem cells are really not stem cells by many people's definition. We use that term often, but they're really progenitor cells, so they can give rise for instance, a retinal stem cell can give rise to all the retinal cell types or in some cases even restricted numbers of retinal stem cells, sorry, retinal cell types based upon for instance, their treatment and culture and the age of the tissue or the conditions of the tissue for which they derived.

And finally, there is one unipotent stem cell, and that can only give rise to one cell type. And for many people, that's really the target because you don't want to give rise to cells that you're not interested in. But typically unipotent stem cells are very different, difficult to proliferate. And so, for stem cells to be a therapy, you need lots of them. And so, proliferation is a key attribute of a therapeutic stem cell. So, that's a short definition of all the different types of stem cells.

Ben Shaberman:

That was great. And I guess just to kind of summarize the power of stem cells is you can make retinal cells for use in treatments to replace lost photoreceptors as an example, or maybe in other applications to protect the retina. And on that note, you mentioned retinal progenitors, and those are being used in clinical trials right now. Can you give us an update on a couple of those trials for RP and Usher Syndrome and other conditions?

Michael Young:

Yes. Yes. So again, there are two trials, both I would say yes, are both in advanced phase two trials. We call them phase 2B, and those are ReNeuron and J.Sight. So I can tell you most about ReNeuron because those are the cells that were licensed from my laboratory at Harvard Medical School at the Escape And Eye Research Institute. And these are cells that we worked almost 15 years on to get them to the stage where we could mount the clinical trial. And a small company, growing company now from Wales, now ReNeuron again, licensed these cells and did heroic work to get these cells in the patients. And so again, these are on a phase 2B trial and what that means is it's almost in phase three. And so, phase one is a safety trial. Phase two is an early efficacy readout, and then phase three is where the proving happens.

So, if there are successful in phase three, one petitions the FDA to get them an approved status, so then they become we still call them a drug product, but of course they are cells and we want to use them to treat retinal disease, and that's the target. So, the difference between J.Sight and ReNeuron is the site of injection. So, ReNeuron targets the subretinal space under the retina. And J.Sight targets the vitreous above the retina in the chamber between the inner retina and the lens, in the posterior chamber. And so, both of these have the potential to preserve the retina and allow the retinal cells that are sick and dying to live longer and thereby preserve vision. The difference between ReNeuron and J.Sight really comes down to the second mechanism of action, and that is the potential to replace retinal photoreceptors, and allow them to become functional photo receptors.

And that opens up the possibility of the restoration of vision, taking a patient who has either no vision or very poor vision and either restoring it or improving it. And so, that's right now, both of these companies have reported very positive phase two data. So, the phase two is ongoing, but as I mentioned, phase three is really the pivotal stage where there are blinded observations, it's larger, it's typically multi-center. And so I think that's really where we want to look. And I believe both companies plan a phase three trial for 2022 if everything goes well. So, it's very exciting times where patients with inherited retinal diseases and even potentially for patients with macular degeneration, there's a possibility that these cells can be active in that disease as well.

Ben Shaberman:

That's a great explanation. Thank you for sharing that. And one thing I want to emphasize about both of these approaches, J.Sight and ReNeuron is that their gene agnostic, so they potential to help a broad range of people with conditions like RP, Usher Syndrome and as you said, maybe macular degeneration and other conditions.

Michael Young:

Yeah, so and I would say that with a small caveat, there's the possibility as we go into a larger study that they will be more effective in one particular, for instance, mutation in RP. So, that's a possibility. But to say they're agnostic, again, contrast them with gene therapy where it's one therapy, one disease, every disease is going to need a new vector. Or again, the technology is so rapidly advancing there are

different words that can be used for CRISPR and CRISPR Cas9 is maybe some of your listeners have heard about. But I just want to say that my feeling all along has been that if there is a gene therapy available that's effective for you, that's probably going to be your best option. But many patients either have diseases which are not yet targeted by gene therapy or their disease has advanced to the place where there are no retinal photoreceptors remaining, and that means that they need to have new cells. And that's where, for instance, ReNeuron especially comes to the rescue.

Ben Shaberman:

Right. Good. Good points. Excellent points. So, let's move on and talk about the work that you're involved in, what your latest efforts are?

Michael Young:

So, our latest efforts involve a new technology that uses a special process of cells sorting and purification that will allow us to generate pure populations of progenitor cells. And we have targeted cone photoreceptors and we target cones because those are really critical cells in almost all retinal diseases. One can lose all of their rods in their eye and still have central vision. The most important bit of vision that is for recognizing faces, reading, watching television, all those attributes come from cones. So, we have isolated cone photoreceptor progenitor cells that we can grow in large numbers and again, graft under the subretinal space where the hypothesis is that they will become new mature cone photoreceptors, make connections with in this case, the retinal ganglion cells. And the hope is that they'll be able to restore vision.

Ben Shaberman:

That's great. That's great. Exciting work, Michael. Exciting work.

Michael Young:

Thank you.

Ben Shaberman:

So, just one last question. Obviously you're working on these new purified cones. How do you see the field advancing perhaps over the next decade or so?

Michael Young:

Oh, that's a very good question, and one must be careful. I'm mindful of that many patients, particularly patients and families of people with inherited retinal diseases have perhaps early on, especially in the stem cell era, been promised too much. And so, I think we have to be very careful in terms of timelines because they're unknowable. And the only thing that we know is they often take longer than they should or longer than expected I should say. But I will say if you give me a 10 year horizon, my hope is that progress will continue to advance and that at that time patients will be presented with an array of potential therapies and gene therapy, stem cell therapy, another field called optogenetics that you may have spoken about, certainly retinal chips, devices that can connect to the central nervous system and relay information about vision to the central nervous system for the patient to make use of improve their quality of life.

I believe that in 10 years there will be many approved therapies. Right now there are really two second site implant and the work out of Philadelphia and Gene Bennett's group in RPE65 Leber congenital

amaurosis. So, those are approved therapies. I can't promise you that there will be many more, and that will change the quality of life for hundreds of thousands of patients. And again, if we can make these work also in macular degeneration, millions of patients in the US alone. So, I think that's a certain true fact, and we just have to work very hard and get as many of those into patient's eyes as we can and improve their lives, that's what we think about every day in the laboratory.

Ben Shaberman:

That's a great perspective, and I think it's not only hopeful, but it underscores the fact that we're going to need a multitude, a portfolio of therapies to help everybody. Stem cells is one promising approach, but gene therapies and some of the other approaches you talked about will be important as well.

Michael Young:

Yes. And I think you have to also consider the potential that some of these are not mutually exclusive in that one can imagine using gene therapy or even neuroprotection to preserve your retina, and then coming in with a different gene therapy or optogenetics or stem cells, and improving their vision with multiple therapies. Many diseases that are complex require multiple drugs. Think of HIV and the triple antiviral cocktail that was needed to move us to the stage we are now where HIV is no longer a death sentence. We get to the point where a mutation in your retina is no longer a blindness sentence. And so, we are very close to that and just know that we're working very hard.

Ben Shaberman:

Well, thanks Michael, and we really appreciate all the great work you've been doing for decades to advance these therapies into clinical trials and get them out to the hundreds of thousands and millions as you said that need them. So, 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. Michael, thanks for taking time out of your busy day to tell us what's happening in the stem cell world. This was a lot of fun and informative. Any closing remarks before we go?

Michael Young:

Yes. I would say that just keep in mind that as few as maybe five years ago, there were no therapies available and there were almost dreams that someday there would be... the number of potential therapies, the number of clinical trials ongoing. And so, we are advancing very rapidly, not as rapidly as many parents, for instance, would hope. And so, I just want to tell them that help is on the way.

Ben Shaberman:

Well, thank you again for such hopeful comments to conclude our podcast. Thank you, Michael. And listeners, stay tuned for our next episode. Glad you could join us for this one. Take care.

Speaker 1:

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