Usher Syndrome Coalition | Emerging Cross-Cutting Therapies for Usher Syndrome

Hello, this is Ben Shaberman, Senior Director of Scientific Outreach and Community Engagement at the Foundation Fighting Blindness. Welcome to this presentation on emerging cross-cutting therapies for Usher syndrome. While most of my talk will be about actual cross-cutting therapies, the first few slides I'm going to introduce some terms and concepts that I think will help you better understand the emerging cross-cutting therapies.

So let's get started. And I think there are two important things to keep in mind if you have Usher syndrome and you're following the research for treatments and cures. First of all, Usher syndrome is actually retinitis pigmentosa with hearing loss. And as some of you know, Usher syndrome also causes vestibular issues or balance problems.

But the bottom line is you can also think of your vision loss as retinitis pigmentosa or RP. And what that means is there are many emerging RP therapies that may benefit people with Usher syndrome, specifically the cross-cutting that I'll be talking about today. So when you're listening to researchers about emerging therapies, keep in mind that those that are targeting RP and aren't genetically based may apply to you.

So what do we actually mean by cross-cutting? And the bottom line is cross-cutting therapy is designed to work independent of the mutated gene causing the disease. So when we say a cross-cutting therapy works for RP, it will generally and hopefully work for many forms of RP regardless of the mutated gene. And in some cases, a cross-cutting therapy may not only apply to RP and Usher syndrome. It may even apply to other conditions like AMD.

And a cross-cutting therapy may benefit patients whether or not their mutated gene has been identified. Obviously, if you do know what your mutated gene is, there may be gene therapies or genetically-based therapies that could benefit you.

But in some cases, your best therapy may be something that isn't gene specific. It may be cross-cutting. And that could be due to a number of factors-- the extent of your vision loss and how far along a gene-specific therapy is. There may be a cross-cutting therapy already in a clinical trial. And that might make that cross-cutting therapy more attractive to you.

And your ideal treatment isn't necessarily best because it targets the genetic cause. There may be some conditions for which targeting the mutated gene simply isn't the best approach. And perhaps a cross-cutting therapy will apply best.

So I wanted to introduce one important term that I use throughout the rest of the slides. And that is the term neuroprotective or neuroprotection. And all that term really means is that there's a molecule or a protein or some other approach that helps protect or preserve neural tissue or neural cells.

And photoreceptors in the retina are in fact neural cells. So when we say something is neuroprotective, we're basically saying it's helping save and preserve photoreceptors, ultimately to slow, and maybe even in some cases, halt vision loss.

So let's get started with the actual cross-cutting therapies. And to start off, I wanted to introduce a couple of foundation investments. The Foundation Fighting Blindness is strongly committed to cross-cutting therapies because they have the potential to help so many people of different genetic profiles and who have different diseases.

First off, there's a company that we helped get started called Nacuity in Dallas. And we're investing up to $7 and 1/2 million in their compound known as NACA. And it's a strong antioxidant designed to slow vision loss in RP, Usher syndrome, and potentially other retinal conditions. It's been studied for many years at Johns Hopkins. It's shown some promising results for efficacy. And now, it's starting to move into a clinical trial.

And an important thing to keep in mind is that for many inherited retinal diseases and AMD, oxidative stress plays a major role in exacerbating retinal degeneration and vision loss. And our bodies produce what are called free radicals when we age, when we metabolize, when we're exposed to harmful materials.

And antioxidants help mitigate oxidative stress. And again, in many retinal diseases, oxidative stress is increased and plays a key role in degeneration. So we're excited about NACA as an approach to mitigate, again, oxidative stress.

Nacuity is just announcing a phase 1/2a trial in Australia. It will enroll 48 people. And in fact, they are targeting people with Usher syndrome first. That trial is due to get underway very soon. And if all goes well with that trial, they will move their studies to the US for RP in 2021 and continue the trial for RP in Australia in 2021 as well.

Now, another major investment from the foundation I wanted to talk about is a treatment being developed by SparingVision in France. We're investing up to seven million euros in that approach.

And we often think of gene therapy as gene replacement-- replacing the mutated gene with a healthy gene. Well, in this case, gene therapy isn't replacing anything. It's helping to produce a protein that's neuroprotective that's helping keep cells in the retina healthy.

And in SparingVision's case, their gene therapy produces a protein called rod-derived cone viability factor or RdCVF. And what they've learned over the years is that cones, the cells in your retina that enable you to perceive colors and read details, recognize faces, and see things in your central field of vision, that cones depend on proteins that are secreted by rods. And one of those is rod-derived cone viability factor.

So this work has been underway for a number of years in lab studies. And they're hoping to get a clinical trial off the ground in 2021. They're targeting RP, potentially Usher syndrome, and other conditions. So we're excited about this approach because it is cross-cutting. And it's performed well in a preclinical setting.

Some other foundation investments for cross-cutting therapies include the work of Dr. Stephen Martin at UT Austin. We're investing $900,000 in his project. And he's found that there's a protein in the retina called TMEM97.

And if you modulate that protein correctly, you can help induce and produce neuroprotection and some other anti-inflammatory effects. And so he's developing a small molecule, a drug if you will, that will help modulate TMEM97 to be neuroprotective.

And he's producing this in a slow release formulation so the person receiving this treatment won't need it-- the treatment to be delivered on a frequent basis. He's had some encouraging results early in lab studies. When this project is finished fairly soon, they're hoping it'll be at a point where they can actually start translational studies and move it into a clinical trial in the not too distant future.

Dr. Clay Smith at the University of Florida is also working on neuroprotection. We're funding him for his project for $300,000. And what he's found is that if you can boost glycolysis or the processing of glycogen or glucose in the retina, you can have a neuroprotective effect. And so he's developing a gene therapy that will provide sustained production of a protein called arrestin1 that boosts glycolysis.

So the idea is with this gene therapy, you have sustained production of arrestin1. And hopefully, that provides sustained neuroprotection. This is at a somewhat earlier stage than Dr. Martin's work, some encouraging early results. But stay tuned for reports on progress as we move that forward.

So next, I would like to move into stem cells. And the first project I'd like to tell you about is using a type of cell called a retinal progenitor. Now, retinal progenitors are essentially stem cells that have almost become photoreceptors. They're not quite mature photoreceptors but very close.

And researchers have shown that these progenitors can have a neuroprotective effect in the retina for RP, Usher syndrome, and other conditions. And through the work of University of California Irvine and their startup company jCyte, they've had some impressive early results in their clinical trial, which got off the ground a few years ago.

What they're doing is they're injecting these retinal progenitors into the vitreous, into the middle of the eye. And these progenitors are releasing growth factors or proteins that are neuroprotective. And the hope is that these will save and maybe even reactivate some cones to preserve vision and maybe even restore a little vision.

In their phase 1/2, they had 28 participants in that trial. And at the highest dose of these neuroprotective progenitors, they saw that the treated eyes performed better than the untreated eye. So they've moved this into a phase 2b. 85 participants have been enrolled. And while they haven't reported any results yet, they've just announced that they've entered into a licensing agreement with the big global pharmaceutical company called Santen.

And jCyte will be receiving up to $252 million to help boost commercialization of this approach. So that's a very significant, strong sum of money to help potentially get this approach across the finish line.

And I will add that one nice aspect of this approach is that the proteins-- or I should say the cells are injected into the vitreous, which is a much less invasive administration than, let's say, doing the injection subretinally or in a different part of the retina. So it's a very safe procedure which is actually done in many outpatient settings already today.

So another approach using retinal progenitors is being developed by ReNeuron. They're a company out of the UK. Their clinical trials are underway at Mass Eye and Ear in a clinic in Phoenix. But their progenitors are being used in a different paradigm. Instead of neuroprotection, they're performing photoreceptor replacement for people with RP and Usher syndrome.

So the idea is that the cells that are-- the progenitors that are being injected into the retina, and in this case, subretina, the idea is to have these cells actually make connections with the recipient's existing retina so that vision can be restored. Again, this is a subretinal injection.

And in their phase 2 portion of this trial, they showed that many of the participants had about three lines of vision improvement, three lines on an eye chart, after 12 months of receiving this therapy. That's an encouraging result. And we look forward to additional results from more patients and additional results over a longer period of time.

And leading this trial is a young clinician, Jason Comander. That's the smiling gentleman on the right part of this slide. We've provided a lot of career development funding for Dr. Comander. And we've also provided significant funding for this project as well. So stay tuned for further results from ReNeuron.

And then finally, the last treatment I wanted to present is called optogenetics or optogenetic therapies. But before that, I want to explain what happens to people's retinas when they have advanced vision loss. That'll help you understand how optogenetics applies.

So in the graphic on the right on this slide, I show a side view of the retina. It's blown up tremendously. But in the top part of this image, you can see vertical cells, including cone-shaped cells. Those are the photoreceptors. And those, as we've discussed, are the cells that make vision possible.

Now, I have a big, black, ominous x going through the photoreceptors on this image to represent somebody who's lost all their vision, i.e. they've lost all of their photoreceptors to a retinal disease like RP or Usher syndrome or even age-related macular degeneration.

So by definition, you lose all your photoreceptors, you've lost your vision. And any type of gene replacement therapy won't apply because you don't have any photoreceptors to receive new DNA.

But what some very clever researchers in lab studies determined is that there are other cells in the retinas of both animals and humans that survive after photoreceptors are gone. And those are called ganglion cells. And in the bottom half of this image, I have an oval around those ganglion cells.

And what they've done is they've delivered a gene, copies of a gene, to these ganglion cells to bestow light sensitivity to them so they could operate in some fashion like photoreceptors. So the idea is instead of using photoreceptors for vision-- obviously, if you've lost all of them, you can't-- but to instead use ganglion cells with this light-sensitive gene being administered to them.

In lab studies, they did demonstrate that animals who were completely blind had some vision restored. Obviously, you don't exactly know what an animal sees. But there were some encouraging results. And what's very exciting is that in a short amount of time, this approach has been moved into

human studies, into clinical trials.

And there are now three studies underway for optogenetics in the clinic. Allergan has a study at Retina Foundation of the Southwest in Dallas. A French company called GenSight has a study underway in the UK. And our partners AGTC are teaming up with Bionic Sight to get this approach underway in Long Island.

So optogenetics can often benefit from the use of eyewear that either helps amplify the signal coming into the ganglion cells, or it actually enhances and makes that signal more sophisticated. And in the GenSight trial and the Bionic Sight trial, there is special customized eyewear that helps amplify and enhance the signal so that hopefully the user's vision will be that much better.

So optogenetics is still relatively new. No one has actually reported efficacy just yet. We're still learning. I think it's OK to be cautiously optimistic. But this is still at an early stage. And there are other optogenetic approaches in development, including those funded by the foundation, that are more sophisticated and we hope to move into clinical trials in the not too distant future.

So stay tuned. Again, this approach shows promise for people who have lost all of their vision. And it's designed to work across many diseases independent of the mutated gene that caused the vision loss.

So to close out, I just wanted to give you some resources that you can use to learn more about many of the approaches I've talked about, as well as clinical trials. The Foundation Fighting Blindness' website fightingblindness.org has a plethora of information on diseases and many of the studies that I've highlighted here today.

You can go to clinicaltrials.gov to learn about the latest clinical trials that are under way across the United States and even many in Europe and other locations overseas. Clinicaltrials.gov has all of the exclusion and inclusion criteria and also contacts for these different trial sponsors so you can reach out and start communicating with those contacts and see if a clinical trial-- specific trial is right for you.

And then finally, we strongly encourage people with all inherited retinal diseases to enroll in our My Retina Tracker patient registry. By uploading your human data, your personal and disease information, in My Retina Tracker, you can get on the radar screens of researchers who are conducting important research and companies and researchers that are recruiting for clinical trials.

So this is a great way to get on the radar screen of the research community and companies that are doing human studies. We never give out personal information. When these companies are looking at

the data, they never see personal information. It's a free service. It's highly secure. So again, it's a great way to stand up and be counted and let the research community know you're on the radar screen for potential studies.

So thank you for taking time to learn about emerging cross-cutting therapies for Usher syndrome. And stay tuned for more updates on research as the research moves forward. Thank you.