

Foundation Fighting Blindness
***Insights Forum* Transcript**
November 10, 2022

Amanda Bement, Chapter Engagement Assistant:

Good afternoon. My name is Amanda Bement and I am part of the chapter engagement team here at the Foundation. We appreciate you joining us for today's call. Before we get started, I would like to briefly review a few details for this call. Currently, all participant lines are in listen only mode with no video. Today's conference is being recorded and is available with closed captioning. To activate this closed captioning, please select the live transcript option located at the bottom of the Zoom interface, select show subtitles.

Please note that on today's call, our speakers do have their videos live. However, all of their comments will be provided verbally and there are no slides. If you are using a screen reader, please be aware that the controls are at the bottom of the Zoom interface. This control bar may collapse when it is not in use. If you prefer to prevent the controls from auto hiding, you can use the following keyboard shortcuts to toggle the always show meeting controls options. If you are using Window commands, you can press the alt key, and if you are using a Mac keyboard, press command and back slash at the same time.

During the call, you may ask questions through the Q and A and chat features, or by sending an email to info@fightingblindness.org. We will address questions towards the end of the call during the Q and A session, at which time additional instructions for asking questions will be provided. I would like to now turn the call over to Chris Adams, our Vice President of Marketing and Communications. Chris.

Chris Adams, Vice President, Marketing & Communications:

Thank you, Amanda, and good afternoon everyone. Thank you for joining us today. I would like to welcome everyone to our quarterly Insights Forum webcast.

We are pleased that you joined us today for our updates on a wide range of strategic initiatives here at the Foundation Fighting Blindness, and to learn more about the research and development progress within our broader community.

For today's agenda, I will provide an update on recent marketing initiatives and ways we are engaging stakeholders across our community. Peter Ginsberg, the Foundation's Chief Operating Officer, will highlight several, key corporate sponsorship opportunities and initiatives along with a summary of fiscal year '22 final audited results and fiscal year '23 financial performance through the end of September. Then, our CEO, Jason Menzo, will provide an update highlighting our new natural history study, along with a summary of recent developments in the IRD space. To conclude our formal remarks, we have a prominent clinician and researcher as our featured guest speaker today. We are pleased to welcome Dr. Marco Zarbin, who serves as Chair of the Institute of Ophthalmology and Visual Science at Rutgers New Jersey Medical School.

In addition to these speakers, we are pleased to have several other Foundation colleagues joining us today for the Q & A session, including Dr. Claire Gelfman, our Chief Scientific Officer, Dr. Rusty Kelley, Managing Director of the RD Fund, and Dr. Amy Laster, our Senior Vice President of Science Strategy and Awards. After our formal remarks, we will have a question and answer period, and then at that time, we will repeat the instructions on how to ask questions. As mentioned, this call is being close captioned and a replay and fully accessible transcript will be available on our website in the weeks ahead. We welcome your feedback or suggestions related to this webcast or the Foundation in general, and you can reach us anytime by emailing at info@fightingblindness.org. And as always, you can learn more at our website@fightingblindness.org.

Let me get started today with a snapshot of some of the many marketing and communication initiatives we have underway. We are focused on increasing outreach support and engagement within our community and beyond. We have had a very busy month in November, honoring Blindness Awareness Month. We launched a successful social media campaign called Share Your Vision, which we invited individuals affected by blinding diseases to share their vision loss journey through written word, audio or video. Participants were able to share their story

with a small select group of people they know or even share their story more broadly through social media. The response to this campaign was tremendous. We had 50 stories submitted globally from countries spanning from Germany to Lebanon to Australia. These stories are available on our website to check out, so please visit www.fightingblindness.org/shareyourvision.

The online participation increased awareness across the board. Throughout our social channels we reached over 800,000 people. Over 200,000 people engaged with our social post by sharing, liking, and commenting. We had nearly 5,000 views on our YouTube channel. We added hundreds of new users to our email database, and we expanded followers and users of our social media platforms and website up to approximately 60% from the same time last year. In addition, we supported World Sight Day, White Cane Day and Music to our Eyes through all of our social channels. To celebrate White Cane Day, the Foundation partnered with whitestickfest.org who brought together blind, low vision and sighted performers from around the globe for a virtual concert. The concert is available on YouTube by visiting the #WhiteStickFest channel.

To bring October to a close, we hosted the latest installment of our live stream music series Music to Our Eyes, featuring veteran, singer, songwriter, multi-instrumentalist, producer and touring artist Mark Erelli.

Jason Menzo sat down with Mark during the interview in the event to discuss his recent diagnosis with vision loss and how it has impacted his songwriting. Mark's next album, Lay Your Darkness Down, will come out in early 2023 and was largely written during the time surrounding his diagnosis of retinitis pigmentosa. We are so excited that within the first 48 hours, this episode had over 14,000 views.

Another important way we promote engagement is through our Chapter network. With more than 40 chapters across the country, we can reach many members of our community. At our Visions Conference this summer, we awarded our first Lulie's Light Awards, which recognizes Chapters who demonstrate leadership, commitment and dedication to the Foundation's mission. These included the community Champion Award, which went to the Bay Area Chapter, the Guiding Vision Award, which went to Jacksonville, Florida Chapter and the Path Maker Award to the Los Angeles Chapter.

Additionally, the professional outreach team had conducted an extensive training program including 33 total webinars for Chapter education and resource volunteers, so that local contacts are positioned well in their communities to educate local eyecare professionals about retinal degenerative diseases and the Foundation's resources. Some of the most popular Chapter related events are our national Chapter vision webinars. We will be hosting our next session on emerging therapies and research for inherited retinal diseases this Saturday starting at 12:00 PM Eastern. There is still time to register, so visit the Foundation website to learn more.

The 90-minute webinar will feature guest presentations on emerging gene therapies from Opus Genetics, a potential antioxidative treatment from Nacuity Pharmaceuticals, and a cell-based treatment from OkuloVision. I also want to mention a convenient new feature on our website. We recently added a Chapter locator on the top of the Foundation's website that helps constituents seamlessly find the local chapter as they travel or move around the US. In a great mission moment story, one of our Philadelphia Chapter leaders took advantage of this feature while visiting Southern California, connecting with chapter members from San Diego, Orange County and Los Angeles. These are the type of connections we love to help create.

In speaking of connecting, our signature VisionWalks are another important part of the Foundation's fundraising and awareness building. This fall, we hosted 13 walks in communities across the country, raising over 1.3 million with 20 more walks planned this spring. These fun, family friendly events bring together hundreds of teams and thousands of walkers. To learn more about the VisionWalk program, visit www.visionwalk.org.

Also, on the 10th of October, the Foundation hosted the 34th annual Atlanta Golf Classic at the prestigious East Lake Golf Club. We had over 120 golfers join us from all over the country for this sold out event. Not only did the players have the perfect weather for a day on the course, but they also raised over \$224,000. We were also honored to have Mark Curley, son of national trustees, Tom and Joyce Curley share his positive experience participating in a Foundation funded clinical

trial during the award ceremony, which moved golfers knowing that they were making a difference for someone in our community.

And finally, we also hosted the Fountain Cup golf tournament presented by Titan Advisors on Monday, October 24th at Oakwood Country Club in Kansas City. Despite it being a rainy day, the event raised over \$85,000 thanks to our generous sponsors, donors, and dedicated committee.

To learn more about the many events that we host, visit the Foundation's website. I am now pleased to turn the program over to Peter Ginsberg, our Chief Operating Officer, Peter.

Peter Ginsberg, Chief Operating Officer:

Well, thank you, Chris. I would like to begin a discussion of our funding sources and financial snapshot by recognizing our corporate sponsors that provide critical funding for important initiatives. We actively connect with leading and emerging companies in our field and beyond, that help fund various Foundation programs. Along these lines, I'd like to highlight key sponsorships with Editas, Novartis and Parexel. Editas is a gene editing company that's running a Phase 1/2 trial for EDIT-101 in Leber congenital amaurosis 10, otherwise known as LCA10. Editas also has earlier stage programs for autosomal dominant RP and Usher syndrome 2A. We much appreciate Editas' recent renewal of our Outreach partnership.

Novartis is a leading global medicines company with a focus on ophthalmic disease and a gene therapy and clinical development for dry AMD and an optogenetics program for IRDs in late preclinical development that was obtained through the acquisition of RD fund portfolio company Vedere Bio in 2020. It's excellent to have Novartis on board as a new Outreach partner.

And thirdly, Parexel is one of the world's leading global CROs providing services from decentralized clinical trials to regulatory consulting services. We're excited that Parexel is now a Foundation Fighting Blindness Outreach partner as well.

In addition to these companies, we just announced this morning several more partnerships supporting our new and largest natural history study to date. This

Uni-Rare study will improve the clinical understanding of more IRDs and boost development of potential therapies by enrolling 1,500 people with inherited retinal diseases caused by rare mutated genes. Jason will talk a bit more about this exciting study, but I'd like to recognize the following partners who are helping to fund the Uni-Rare study. And oh, by the way, we did put out a press release this morning launching the Uni-Rare study. You can learn more about the Uni-Rare study in that press release.

The first of the three partners for Uni-Rare is Opus Genetics, which is a gene therapy company for inherited retinal diseases founded by the RD fund. Opus is targeting numerous orphan retinal diseases with its gene therapy portfolio that tackles some of the most neglected forms of inherited blindness while creating novel orphan manufacturing scale and efficiencies.

The second new partner for Uni-Rare is at Atsena Therapeutics, which the gene therapy company developing novel treatments for inherited forms of blindness. The company's ongoing Phase 1/2 trial is evaluating a potential therapy for a form of LCA, one of the most common causes of blindness in children. And Jason will share more information on that trial as well later in the call.

Also, Cove Therapeutics is focused on developing non-viral, non-lipid, nano particle gene therapies for orphan and chronic prevalent indications. The company's nano particle technology enables cell-specific tropism, scalable manufacturing, re-dosing and packaging of large genes while maintaining a favorable safety profile. We're really grateful to Opus and Atsena and Coave for being corporate sponsors, for their support and collaborative relationships.

Now, I want to shift gears for a second to our financial update. We completed our fiscal year 2022 on June 30, and our audited financial statements are now available on our website in the About US section under Financial Reporting. There's a lot more data there, but I'll give you a quick overview. As noted during our insights, our last Insights forum, our FY22 net revenue and net fundraising surplus exceeded our budgeted expectations and that enabled us to spend \$27 million on research and \$3 million on public health education plus more than \$10 million we invested in RD fund companies developing treatments for inherited retinal diseases and dry AMD. So just to emphasize here, that means \$40 million

in total research and education spending in FY22 from the Foundation Fighting Blindness.

Looking ahead to the fiscal of 2023, we're targeting \$31 million in unrestricted revenue against \$18 million in expenses for \$13 million net fundraising surplus, which will support new research funding. I can report for the first quarter of Fiscal 23 that ended on September 30th, our unrestricted revenue was \$43.5 million versus expenses of \$3.9 million for a net fundraising deficit of \$0.4 million, which is slightly ahead of budget. Keeping in mind that our seasonally strong donation months lie ahead.

I will end by expressing our sincere appreciation for the commitments and support from our donors, sponsors, and Foundation partners, which make it possible to continue to drive the research that leads to treatments and cures for inherited retinal diseases and dry AMD. I will now turn the call over to our CEO, Jason Menzo. Jason.

Jason Menzo, Chief Executive Officer:

Awesome. Thank you so much Peter, and thank you everyone for joining us today. It is so great to be with you all on another one of our quarterly Insights Forums. As you've heard so far in this call, the pace of activity here at the Foundation Fighting Blindness is unbelievably high. There is so much going on, not only across the inherited retinal disease field, but specifically here at the Foundation Fighting Blindness. As I look back over the last several months, I've really enjoyed the opportunity to travel across the country and get to meet with so many different members from our community. I've had the opportunity to meet with donors and Chapter members, researchers and clinicians, companies from industry, Foundations who support our mission, and many other types of constituents as well. It's really energizing to witness the strong support that the Foundation has throughout the entire global inherited retinal disease community. And on today's call, along with members of the community here in the United States, we're actually joined by members of our community from all over the world, which is truly inspiring for those of us who are passionate about driving this mission forward.

I want to spend a few minutes today and talk a little bit about some of the recent activities that are happening in the inherited retinal disease and dry AMD field and really focus on one specific event that occurred just a couple months ago, actually last month, in October, and that is the American Academy of Ophthalmology or the AAO Annual Meeting. It took place in Chicago and every year the AAO is the absolute pinnacle of new activity that is happening in the entire ophthalmic marketplace and it was amazing to see the breadth of innovation and research that was presented at this conference specifically to our field, which is a great, great and inspiring fact that we want to share.

There were a number of noteworthy announcements, data presentations on emerging therapies and many other pieces of news that have come out in the last couple weeks. I'd like to take a few minutes now to share some of the highlights with you all.

First off, RD Fund portfolio company, Atsena Therapeutics, which we've talked a lot about on these Insights Forums. They reported positive results from their Phase 1/2 gene therapy clinical trial for people with Leber congenital amaurosis Type 1 or LCA1, which is caused by mutations in the gene GUCY2D. Overall, the gene therapy, which is called ATSN-101, was very well tolerated. The nine patients that were receiving the highest dose of the treatment had clinically meaningful vision improvements as measured by the full field stimulus test, or FST, which measures the patient's ability to respond to different levels of light and by their ability to navigate over a mobility course under varying lighting conditions. That was great news.

Next, Apellis Pharmaceuticals reported 24 month data from two different Phase 3 trials of their program called pegcetacoplan. Pegcetacoplan targets geographic atrophy associated with dry AMD. The company continued to report meaningful reductions in the growth rate of the geographic lesions that are the regions of cell loss from advanced dry age-related macular degeneration in eyes that were treated with the therapy. Apellis filed a new drug application, which is also called an NDA, with the U.S. FDA and after a recent amendment to the NDA that they announced last week, we all now expect a response and potential launch early in 2023 for this novel treatment.

Another company focused on a similar area of our space, called Iveric Bio, presented results from their second Phase 3 trial for Zimura, which is another emerging treatment aiming to slow the progression of geographic atrophy associated with dry age-related macular degeneration. At the 12-month mark, monthly intravitreal injections of Zimura reduced the growth rate of these lesions. Iveric Bio has announced that they planned to file an NDA, new drug application, with the FDA soon and actually announced the beginning phase of their filing with the FDA just last week.

Another exciting update came from a company called Belite Bio. They presented encouraging one-year interim results for their two year Phase 2 clinical trial of an emerging oral treatment targeting Stargardt disease. This Phase 2 trial is ongoing currently in Australia and Taiwan and is designed to reduce the uptake of vitamin A into the retina, thereby reducing the accumulation of the toxic vitamin A byproducts, which are really the hallmark of Stargardt disease.

Another update came from a company called MeiraGTx, along with their partner Janssen, and they presented results from their Phase 1/2, X-Linked retinitis pigmentosa gene therapy clinical trial targeting the RPGR gene. In this Phase 1/2 trial, improvements in retinal sensitivity were measured using full field static perimetry and microperimetry and walk times improved for patients navigating a low light mobility course. The company's Phase 3 Lumeos clinical trial is currently underway. Janssen also reported encouraging data from the Phase 1 clinical trial for their geographic atrophy associated with dry age-related macular degeneration gene therapy, which is delivered through a single intravitreal injection. The low, intermediate and high doses of the therapy were safe over a two-year follow up period and the company also reported continual decline in growth of lesions, which again are the regions of cell loss associated with dry age-related macular generation.

Opus Genetics, which we've talked quite a bit about on these Insights Forums for the last year or so announced plans to submit an investigational new drug application, also known as an IND, which is the step before entering into a clinical trial. They announced their plans to submit this IND to the FDA for their gene therapy trial in LCA-5. The IND, if authorized, would enable Opus to launch their

planned Phase 1/2 clinical trial for an emerging treatment next year. The company is also in pre-clinical development for gene therapies for LCA13, which is caused by mutations in the RDH12 gene and LCA9, which is caused by mutations in the NMNAT1 gene. Opus is another RD Fund portfolio company and we're very excited about the prospects as they continue to mature and move programs into the clinic in the next couple of years.

And then finally, I'd like to mention one other very recent update in our space that happened just a week or so ago. In late October, the company, AGTC, agreed to be acquired by a larger company called Syncona Limited, which is a leading healthcare company focused on founding, building and funding global leaders in life sciences. As many of you know, AGTC is focused on AAV, adeno associated virus, based gene therapies for the treatment of rare diseases, including inherited retinal diseases such as X-linked retinitis pigmentosa. And they're actually currently in clinical trials here in the United States for a program in X-linked retinitis pigmentosa targeting the RPGR gene.

Through the course of this acquisition, which is not yet finalized, the company has committed to continue to proceed with this clinical trial and X-linked retinitis pigmentosa. More details of the transaction and any impact on the rest of their portfolio will follow in the months ahead after the deal closes.

As Peter mentioned earlier, another very recent development actually just announced earlier today, just a couple hours ago, is the launch of our Uni-Rare study, which is the first of its kind. It's a new type of natural history study for people with one of the more than 300 genes associated with inherited retinal diseases, including retinitis pigmentosa, LCA, Usher syndrome, and the broad range of other conditions affecting our space. Because the more common IRD causing genes have been the subject of other clinical trials, this specific study focuses on the less common or the rare IRD genes. That's where the name Uni-Rare comes from. Pretty clever, right?

The study, which is due to begin recruitment in December, will help clinical researchers gain a better understanding of the course of progression of retinal degeneration and vision loss for people with mutated genes that have not been well-characterized in the clinic up until now. The study will also help IRD research

and therapeutic development by identifying more people who can participate in future clinical trials for therapies that are in development. We are thrilled to launch this highly inclusive study. I would like to specifically thank one of our colleagues here at the Foundation, Dr. Todd Durham, for his leadership on this initiative. The study will affect and benefit a large segment of the population of our IRD community, which is so genetically diverse. Stay tuned for more updates on this study and how you may be able to participate.

I know that in the last few minutes, I covered a lot of information and these topics that we talk about on these calls are very detailed, they're technical in some cases and they can be very complex. The good news for all of you who are on the call today is that all of this information that we covered on this call can be found on our website @fightingblindness.org. And of course, a replay of this webcast will be available to re-review anytime you'd like in the weeks ahead. And of course, if you ever have any questions, no matter how technical they might be or how simple they might be, about any of the information that we present, please feel free to reach out to us directly @infofightingblindness.org or via our social media channels. We're on Facebook and Instagram and I guess Chris told me we're now on TikTok and we're all over LinkedIn. We try to be as accessible as we possibly can for members of our community so you can reach out to us via any number of ways, and of course we'd love to hear from you, including today.

If you have questions, we're going to get to those in just a few minutes. But first, to provide a big picture look at the development landscape, we're very pleased to have one of the leaders in AMD and IRD research with us here on the call today as our guest speaker. I'm very pleased to introduce Dr. Marco Zarbin, who serves as Chair of the Institute of Ophthalmology and Visual Science at Rutgers New Jersey Medical School. Dr. Zarbin is an expert in the field and specializes in vitreal retinal surgery and research with an extensive educational background, including an undergraduate degree from Dartmouth and an MD/PhD from Johns Hopkins University School of Medicine. We're especially honored to have Dr. Zarbin serve as Vice President on the Foundation's Scientific Advisory Board. And Marco, I'd just like to extend a warm welcome to you here on this call, and thank you for being with us today. I'm pleased to turn the call over to you and again for our

audience, we'll take questions after Dr. Zarbin's comments. Marco, the floor is yours.

Dr. Marco Zarbin:

Thanks and thanks for inviting me. Thanks for the kind introduction. It's a pleasure to be here with you virtually. I don't have any earth-shattering news for the audience. I want to make that very clear, and I know you all have somewhat diverse interests, so I thought I would try to make some general comments about the pathway for developing treatments for blinding disease. And I would like to spend most of my time answering questions to the degree that I am able to.

Generally speaking, this is going to be, I think, obvious to most if not all of you, there are two broad branch points in treating retinal blindness. One is prevention and the other one is vision restoration. In principle, prevention ought to be the better path because we're talking about neural tissue and reorganizing something as complex as the retina is going to be challenging biologically. It'd be easier to stop it from degenerating.

And this is true both for age related macular degeneration and for inherited retinal diseases like retinitis pigmentosa and the syndromic diseases associated with RP. Now, there's some problems with prevention though, if you think about it from an operational standpoint. One, suppose you do have a treatment that prevents blindness. Well, how do you prove that you have such a treatment? Out of necessity, you're going to have to have a control group in which you follow one group that's treated, one group that's not, and you show that there's a difference in the visual outcome. The only way you could get away without having such a control group is if you have a disease which is very rapidly and universally progressive to blindness and in that case, you could just have a treatment group alone. But the point I'm getting at is that in general, prevention trials are going to require more patients and last for a longer time and therefore costs more money and that's of course, a barrier that needs to be addressed. Now, one of the virtues of prevention though, is that prevention doesn't have to be a 100% effective to be highly cost effective.

For example, if you have a treatment that reduces the risk of progression by 15%, that's actually quite valuable, even though it doesn't sound like it, because what you're really reducing is the number of irreversibly blind patients.

When we think about reversing blindness, the challenges of the clinical trial design is much simpler, but the challenges to having an effective treatment are much more complex and let me illustrate what I mean by that. Let's suppose that for example, you have a gene therapy for a particular mutation that causes blindness, and you verified that this gene therapy is effective in preclinical animal models. Well, the problem is that the preclinical animal models are just models and genetic modulation is a highly complex process. The fact that it works in an animal model in no way means that it's going to work in a human patient, although one hopes that it will. So there's a certain amount of uncertainty in that.

Then, beyond that, if you have degeneration of the retina before treatment is administered, how do you undo the degenerative changes? And for those of you who don't understand what I'm getting at, the way the retina is wired, it's not like a circuit board. Say you have a light bulb that's burnt out and now you want to get the light back on, all you have to do is replace the light bulb, right? Because all the circuitry in your house is still intact, you're just missing the light bulb. That's not how the retina works. When the photoreceptors die, it's not like that light bulb socket that's missing the light bulb because what happens in the retina is it rewires itself to accommodate for the loss of the photoreceptors and now when you put in new photoreceptors, even if they could connect in principle to the retina, the question is, are there any empty light bulb sockets for those new photoreceptors to plug into? And if there is, how do you get it to plug into it? So these things are quite complicated.

In terms of visual restoration. The therapeutic approaches that are being followed at the moment are, first of all, let me back up, what are the therapeutic approaches for prevention of vision blindness? Well, oddly enough, in the case of retinal degenerative diseases, gene therapy can be a preventive therapy depending on the rate of progression of the blindness. You might think we're replacing genes for gene therapy and that's one way, that's DNA supplementation, which has limitations because depending on the mutation, you

may not have a vector that can carry a gene of sufficient size that would help the patient in question. But apart from DNA therapy, there's also RNA therapy and the beauty of RNA therapy is that it also can prevent degeneration. It's because you can do something called antisense oligonucleotide therapy where what you're modulating is not the patient's DNA, but actually their RNA.

You don't need a virus to deliver the therapy. In fact, you can inject the antisense oligonucleotide intravitreally without any virus, and it can last a long time and it can, in principle, prevent retinal degenerative disease. So gene therapy can be a preventive strategy.

Another type of preventive strategy in the case of macular degeneration is to reduce the inflammation that causes macular degeneration. I'm going to spend a couple minutes talking about the pathogenesis of age-related macular degeneration in a minute.

Another strategy is to replace damaged mitochondria that are part of the early changes that occur in age-related macular degeneration. And then there are things like nutritional supplements.

Preventive therapy can range from taking a vitamin pill to having something injected into your eye, either to modulate gene expression or to modulate inflammation, or it could even involve some type of injection on the outside of the eye, within the eye wall itself, which is another way to deliver medications.

In terms of visual restoration, we have of course gene therapy, which I'm sure you're all familiar with to some degree. There's also cell-based therapy where you try to replace the cells that are lost. There's even a way of doing cell replacement that doesn't involve a transplant of the cells that are lost. And to understand why that is, it turns out that there are certain animals like zebra fish, where if you damage their retina, they will spontaneously develop a new retina. It turns out that they can do that because there are cells in the retina that remain pluripotent that can differentiate into, say, damaged photo receptors.

Well, it turns out that even humans seem to have such pluripotent cells and under the right circumstances with the right exposure to chemicals, it might be possible

to induce the regeneration of photo receptors from cells that are endogenous in the recipient in the patient. And of course, that could be very powerful in terms of the issues of invasive surgery and also immune rejection of a transplant.

And then of course, there are the electrochemical biological device versions of trying to restore lost vision and that involves things like implanting a chip, which is light sensitive, and which creates an electrical current that stimulates the remaining cells in the retina to provide vision. Or taking cells in the retina that normally are not light sensitive and making them light sensitive by transfecting them with viruses that induce the expression of proteins that are light sensitive and that create electrical currents that then stimulate our brain, that's called optogenetics.

So to recapitulate, there's preventive therapy, there's replacement therapy or visual recovery therapy. Preventive therapy can range the gamut from vitamins to gene therapy. Visual recovery therapy can range from gene therapy to cell-based therapy to electrical chips to photo transduction where we make cells become photoreceptors that are not normally photoreceptors. There's eve, a chip that doesn't get implanted in your eye, but gets implanted into your brain, which could be useful for people not only with retinal blindness, but also optic nerve blindness.

Now, as far as age-related macular degeneration is concerned, there was a question that was posed that I thought might be a good one to discuss before we get to the specific questions. And it has to do with the different types of macular degeneration and how one distinguishes them. I think the best way to answer that for age-related macular degeneration is to think about what the pathogenesis of the disease is. This is my version of history - my version of the pathogenesis of age-related macular degeneration. Not everyone would agree with what I'm going to say, but I think many people would. Age-related macular degeneration basically starts out as a chronic, low grade, inflammatory response in the back of the eye. And as a result of this inflammatory response, there's damage to the blood vessels that supply oxygen and other nutrients to the photoreceptors in the retinal pigment epithelial cells and as a result of this impaired nutrient transfer, the cells begin to behave in an abnormal fashion.

They begin to produce abnormal material which builds up, which creates a diffusion barrier to receiving oxygen and nutrients. The abnormal metabolism results in death of the photoreceptors and as the damage to the circulation to the back of the eye proceeds, it's like having a micro stroke in the back of the eye. And so in the early phases of this inadequate nutrient production or delivery, we get the manifestations of drusen, those yellow flecks in the back of the eye, and the pigmentary changes. As the inadequate nutrient delivery proceeds, we get the development of the death of the tissue, which is what we call geographic atrophy, typically not involving the center of the vision initially, but typically in about two and a half years, it will involve the center of the vision with associated central visual loss.

Then, as a result of this inadequate blood flow, we get what is called a homeostatic response, which is a healing response. And the healing response is to grow blood vessels to replace the blood vessels that have been damaged from this inflammatory reaction. While these abnormal blood vessels unfortunately, typically, do not behave well, not in all cases, but in most cases, they do not behave well because they leak fluid and blood and this induces scarring and further loss of vision, unfortunately. But there are occasional patients, maybe 10% of the patients, where the abnormal blood vessels actually behave quite well. And as a result of that, the progression of visual loss actually is attenuated or stopped completely. That's what we're talking about now is the wet form of the disease and that's why not 100% of the people with the wet form of the disease go blind, although close to 90% of them do, if they're not treated.

When you see that as the pathogenic sequence, then you can understand what the available therapies are and why they have been developed. When you think about the nutrient issue, that's where the vitamin and mineral replacement therapy comes in. It's intended to supplement the defenses against oxidative damage. When you think about the most recently approved or about to be approved treatment for geographic atrophy, which Jason mentioned, those are actually anti-inflammatory treatments. We could argue that those anti-inflammatory treatments ought to be provided even earlier in the disease than they were in these trials. But for very good reasons, the trials were not designed that way. And then when you think about the treatments for wet AMD, they are

treatments that are essentially intended to stop the leakiness of these abnormal blood vessels. And the good ones do, and as a result, they do help preserve vision for a long time.

There are some problems with those treatments, which we can discuss if people are interested, but that's the way of thinking about it. I wouldn't characterize AMD as dry or wet, that's an inadequate characterization, which reflects an inadequate understanding. There's early AMD and there's late AMD. Late AMD, both the geographic atrophy and the neovascular form, both arise as a result of chronic inflammation with damage to the blood vessels to the back of the eye and early AMD also is due to that chronic inflammation. It's just that the story starts out with chronic inflammation and damage to the blood vessels, but it doesn't end up there. The way it ends up is either this inflammation induces permanent damage and visual loss in the form of late dry AMD or geographic atrophy, or it induces the reactive growth of abnormal blood vessels, which causes wet AMD. And of course, there's no reason that these two late manifestations should be mutually exclusive, and they're not. You can have geographic atrophy and wet AMD both in the same eye.

Those are my prepared comments, and I'd like to focus the rest of the time on answering questions if I can.

Jason Menzo, Chief Executive Officer:

Excellent. Well, thank you so much, Marco. And not only thanks for joining us today, but for the valuable information. I know that for our audience, we've got, some 300 folks that are on the call here today, most of which are coming from the patient community and they have many questions. There's some that have been chatted in already, some that have been emailed in. We've got some that were emailed to us before the call today. We'll get to them in a second. We've got 15 minutes for questions, so we can keep everyone on the line here for a little bit. But let me turn it over to Amanda to talk about how to ask questions if you haven't asked your question yet.

Amanda Bement, Chapter Engagement Assistant:

Thanks, Jason. There are several methods for asking questions. First, you can ask using the Q and A or chat features that Chris has been sending through the chat. They're located at the bottom of the Zoom control bar, and you can type in your questions there. Second, you can ask questions verbally. To do so, select the hand raising function on the menu bar at the bottom of the Zoom interface, and we will provide you with instructions to unmute yourself. And third, you can submit your questions via email to info@fightingblindness.org.

Please note that if there are any questions that we aren't able to answer it on today's call, we will follow up directly with you via email over the next week or two if you've sent in your questions.

Jason Menzo, Chief Executive Officer:

Awesome. Thanks, Amanda. And that last point is critical because we've got 30 questions in 10 minutes. I don't think we're going to get to them all.

Dr. Zarbin, I'll pose a question to you. You did an excellent job distinguishing the difference between dry AMD versus geographic atrophy and wet AMD. I actually really liked the way that you posed the early versus late, rather than the distinction between wet versus dry, which I think most clinicians would appreciate. I appreciate that distinction. The question, and it's not just around AMD, but it's I guess around IRDs as well. But for folks that are on the call today that are curious about how do I get involved in a clinical trial? You mentioned that there are clinical trials for dry AMD treatment, so what do folks do if they're interested in learning more about a clinical trial?

Dr. Marco Zarbin:

This is a very “me specific” answer to that really important question. In my opinion. The first thing to understand is that a clinical trial is an experiment. Anyone who thinks that it's not an experiment needs to become very deeply reeducated. And when I say an experiment, that means nobody knows if their treatment works or not. And another corollary of that statement is, it could be

worse to be in the experimental treatment group than to be in the control group. And there are many examples in medicine turned out that the best thing to be was in the control group and not in the treatment group. I know that's hard to get your head around because these things are so derisked. I mean, there's basic science experiments, there's preclinical experiments, there's animal model experiments, there are panels of experienced clinicians who serve as experts, all critiquing whether a molecule should go into clinical trials and how the clinical trial should be designed. And despite all of that effort, only 16% of the products that make it into clinical trials actually end up with an approval.

The reason is, there's a difference between models and reality. Human diseases are simply, generally more complicated than the models we use in which to develop treatments. So how do you proceed with that kind of caveat? In my opinion, the only way to do it is by having, if we're talking retina trials, having a retina doctor who takes care of you, give you advice on what you should do. Why? Because there's two parts to the advice. The first, is the trial crazy or not? Is it run by lunatics? Has it passed all the appropriate levels of judgment that are required for it to be a reasonable experiment? Unless you have quite a bit of time on your hands and a lot of technical knowledge, it's probably best to rely on a retina surgeon to give you advice about that.

The second thing is, are you an appropriate candidate for that trial or not? You may not be because of how the medicine's supposed to work or because of an allied health condition or because of your personality and what your risk tolerance is. There are just as many variables to determine whether a particular patient should enroll in a trial as there are, whether the trial is any good or not. And only really someone who's an experienced clinician who knows you well, who knows your disease well, who knows where you are in the phase of your disease progression, that's the person who's best qualified to engage you in a conversation, to think with you basically about whether a trial's appropriate for you and whether it makes sense for you at this point in your life to become enrolled in the trial. And the same applies if you're talking about enrolling your children in a trial.

Jason Menzo, Chief Executive Officer:

Thank you, Dr. Zarbin. It's such important advice, and particularly around ensuring that a clinical trial is really only an authorized clinical trial if the company or the sponsor has filed an IND with the FDA and that IND has been cleared. There are times where we hear about, and I'm using air quotes, a quote-unquote "clinical trial", but it has never been actually authorized by the FDA. And unfortunately, that does happen sometimes, and I think it is great advice. Obviously, at the Foundation Fighting Blindness, our stance is always to advise patients to get medical advice from medical professionals, including clinicians who are experts in the field.

Let's shift gears. I'm going to actually bring on, and we've got several members of our team, Claire Gelfman, our Chief Scientific Officer, Amy Laster, Senior Vice President of Scientific Strategy and Awards, Peter Ginsburg, Chief Operating Officer, Rusty Kelley, Managing Director of the RD Fund, so you've got a powerpack group of professionals here from the Foundation.

Claire, I want to come to you first. There's several questions that were chatted in about, I have rod cone dystrophy for a particular gene that has been identified, but there's not a gene therapy that's targeting this gene that I'm aware of, treatment that's being developed, or many questions, which happens all the time, I have RP, for example, and my gene has not yet been identified. And so we talk a bit about gene therapy, but maybe you can talk a little bit about gene agnostic approaches and what that means.

Dr. Claire Gelfman, Chief Scientific Officer:

Thank you Jason, very much. This is Claire Gelfman. You bring up a great point because through the Foundation we offer free genetic testing and free genetic counseling to our constituency through physician ordered tests. Sometimes that information does not tell you the genetic cause for this clinical diagnosis that you've received from our ophthalmologist. And so there are, as Dr. Zarbin described, gene specific therapies when you know your causative gene. But what about when you don't? And that's really where these agnostic approaches come in. If you think about it, regardless of the gene that's causative, the fact is that

your photoreceptors are not doing their job right. And that inability to capture light coming in and send a message to your brain what it is that's in front of you, when that process is compromised, there's vision loss regardless of the causative gene.

One way to think about treatments beyond the level of the gene, the causative gene, is to think about therapies that help restore the ability of the photoreceptor to respond to light. And it's agnostic in that it doesn't matter your genetic cause. It's more about restoring a functional photoreceptor so your vision will improve. I'm happy to say that there are actually a lot of clinical trials in progress that are using that exact mechanism. Dr. Zarbin talk about optogenetics, so this is for late-stage photoreceptor receptor degeneration where there's very little vision loss left, where that ability of the photoreceptor to respond to light is actually given to a different part of the retina that's not degenerating. And there are companies in our space, Vedere Bio, Sparing Vision, GenSight, that are utilizing optogenetics as a way to think about not just treating, but restoring vision to late-stage photoreceptor degeneration.

Now, there are also other ways to think about treating in a gene agnostic way. One of the things we know about vision loss is that a pathway known as oxidative stress can really wreak havoc on the retina. And it's not only in the ophthalmology world, but really all over the body, that our ability to respond to stress over time gets worse and worse as we age. And if you have a retina that's not functioning properly anyway, oxidative stress can really exacerbate that pathology. So no surprise then that there are companies in our space, for example, Nacuity Pharmaceuticals out of Fort Worth, working on an antioxidant approach.

What's interesting about the Nacuity trial is that unlike a lot of other clinical trials for ophthalmology indications, the treatment is not directly into the eye. It's actually a pill. It's an oral therapeutic to inhibit oxidative stress and those trials are currently in progress. So that's a way to treat your photoreceptor degeneration, your vision loss, regardless of the genetic cause and in fact, the trial and progress is actually looking to treat retinitis pigmentosa from a population of individuals with different types of Usher syndrome. So really, regardless of your genetic diagnosis, it's wonderful to know that there are therapies in development

that can target the pathways that cause blindness and we are supporting a lot of those companies in those mutation agnostic ways.

Jason Menzo, Chief Executive Officer:

Great, Claire, that's awesome. Peter, oftentimes we will hear from constituents, so as a Foundation, how much of the investment that we put into the field is being targeted to strategies like what Claire just described, gene agnostic strategies versus gene therapy, which we talk a lot about as well. Maybe you could talk a little bit about our portfolio analysis.

Peter Ginsberg, Chief Operating Officer:

The portfolio analysis that Jason referred to was an evaluation we did in the recent months. We looked back at our funding over the last five years to make sure there weren't any significant gaps, any areas that we should be funding that we haven't been funding recently. And one analysis that we did was to compare, is too much of our funding going into gene agnostic approaches or too much going into gene specific approaches?

What we found was that actually our funding over the last five years was really well balanced between gene agnostic and gene specific approaches. And in the last five years, in terms of our grants and RD Fund investments, those that we could clearly say that's a gene agnostic approach or that's a gene specific approach, we've put \$61 million into projects focused on gene agnostic technologies and \$55 million focused on gene specific technology. So really well balanced between those two fields and we feel good about that because we do feel there are gene specific approaches that will work well for some patients and gene agnostic approaches that will work well for other patients and we want to make sure that our funding is balanced in those two areas.

Dr. Marco Zarbin:

I think one of the things that the patients in the audience may not appreciate is the idea of why gene specific approaches might not work. And furthermore, why from a business perspective it's much better to have gene agnostic approaches,

they're actually related factors. When we find a mutation that we know is associated with the disease, that actually isn't the end of the story because it turns out that there could be other mutations that influence the severity of the disease manifestation, the rate of the disease progression and so forth. In fact, for example, there's a gene called the ABCA4 gene, mutations of which create clinically, what look like completely different diseases. And the reason is it's not just the mutation in the ABCA4 gene, that's the issue. There are other mutations that act in concert with it.

When you go in with a specific gene therapy, it's like shooting with a silver bullet. It's got to be the only thing that's really wrong and you just really can't count on that. Furthermore, from the point of view of return on investment, all these trials are incredibly, I mean, what is it a quarter of a million dollars to just get through the trials. So from a business perspective, you'd like to be able to treat as many patients as possible once you develop a therapeutic that actually works. That's why I think it's really important that the Foundation has recognized the value of investing in mutation agnostic therapies. I think that's really the way of the future.

Jason Menzo, Chief Executive Officer:

That's great. Thank you so much. Dr. Zarbin. The question for you, and actually in follow up to that, we had a few folks, and it actually comes up pretty regularly when we talk to our constituents, in light of what you just shared around the limitations or the potential pitfalls with gene specific approaches but individuals, we still encourage, of course, strongly encourage folks to be genetically tested to understand what their gene is. Many times we can identify the specific mutation, but there are times obviously where a mutation is not identified in variance of unknown significance come back on the genetic report. And the question is, what do you recommend to your patients in terms of frequency of being retested if their specific pathogenic mutation was not found? How often should you be retested?

Dr. Marco Zarbin:

My answer is totally related to what the therapeutic opportunities are. If progress were to stop completely and there were going to be no more gene therapy trials

than there are right now, I wouldn't see a deep value in additional genetic testing. But that's not the case. The fact is that just over the past five years, there's been more than 50 gene therapy trials in retina and most of them are for inherited retinal diseases. As new trials come online, there then is a recurring value in retesting because what may have been an untreatable thing before, is now actually enrolled in a clinical trial and now you have an opportunity to retest and see if this patient in question actually has that particular mutation for which the new trial has been established. My template isn't based on every six months or every one year, it's actually based on what new trials are out there that weren't there before, where discovering the gene in this particular patient might have some value for this particular individual.

Jason Menzo, Chief Executive Officer:

That's excellent. Thank you so much. Let's shift gears. Amy, I'm going to come to you next. Many folks typically think of the Foundation Fighting Blindness, rightfully so, as being laser focused and a global leader, I would say the global leader in the field of inherited retinal disease. But we spent a bit of time today talking about dry age-related macular degeneration, maybe you can share with the audience our programs in funding dry AMD research and how we're emerging as a leader in that field as well.

Dr. Amy Laster, Senior Vice President of Science Strategy and Awards:

Thank you, Jason. Across all of the Foundation's research funding programs, we do support proposals on dry AMD and very specifically with one of our funding partners, the Free Family Foundation. About four years ago, we entered into a very specific initiative to address AMD and specifically as Dr. Zarbin spoke about earlier, what causes dry AMD, those early stages of disease? And so we have been specifically funding researchers, actually pairs of researchers, to come together with different expertise to try to answer that question.

Currently, in our portfolio we have a pair of researchers looking at developing animal models because we need really good animal models that recapitulate human disease to test different therapeutic options. So they're looking at that as well as potential genetic risk factors that can cause AMD. We also have another

pair of researchers looking at developing and exploring a gene therapy for one of the key factors in AMD called complement. Our other programs are looking at what goes wrong with the disease. What are the pathways that might be targets for potential therapies as well as gene therapy strategies? Can we develop gene therapy strategies if there are genetic risk factors? Those are some of the kinds of projects that are currently in our research portfolio. But I will reemphasize that for all of our research focus programs, we always invite researchers to help us to explore and develop treatments and understanding of dry AMD.

Jason Menzo, Chief Executive Officer:

Awesome. Thank you so much Dr. Laster. And just for everyone at home, it is about six minutes after two o'clock here on the East Coast. And as always, this is the fastest hour of the quarter I feel like, because this hour that we're with you all on these Insights Forums always seem like they go by so fast so we are a few minutes past the hour. We're going to stay on for two more questions. I do want to thank everyone for, certainly all of our panelists, for joining us today and all of you for joining us today.

I want to bring Dr. Rusty Kelly into the conversation. Rusty is the Managing Director of our RD Fund, which is the venture arm of the Foundation Fighting Blindness. You've heard us talk about the RD Fund quite a bit on these calls, but I want to pose two questions to you Rusty. One is related to what we're familiar with EYS. There were several questions that were emailed to us in advance around EYS and then also USH2A, particularly with the news that we spoke briefly about on the last Insights Forum as it relates to ProQR. Could you address both of those and anything else related to the fund you want to share?

Dr. Rusty Kelley, Managing Director, RD Fund:

Yeah, thanks Jason. Happy to, it's great to be with you all today. To borrow a line from Dr. Zarbin, to the degree I can answer the question, is the preface. We are bound by confidentiality with a lot of the companies that we speak with, including within our portfolio, so the best answer as to what the interest out there for EYS and USH2A is that we're aware of a number of companies that are interested in

these targets, but we are not aware of any of these companies that have disclosed their interest in EYS. For USH2A, of course, Jason just mentioned ProQR.

Outside of ProQR, we have, as Dr. Gelfman and Dr. Zarbin discussed earlier, the gene agnostic approaches, we have Nacuity in the RD Fund portfolio that's going after a gene agnostic approach. And this is an oral antioxidant called NACA, N-acetylcysteine amide. It's in clinical trials in Australia and it's open to all Usher patients and many of those are USH2A patients. And then the other company that has disclosed their interest in USH2A is Prime Medicine. They have a form of gene editing and they're going after a specific high frequency mutation that they're correcting. Those are the two companies for USH2A. And of course there are another handful of companies that have expressed interest as well, in USH2A, that have not disclosed their interest.

Jason Menzo, Chief Executive Officer:

Excellent. Thank you so much Rusty, and thank you to everyone for joining us today. I will close by saying that, as we said at the very beginning, and I should say, if anyone sees me looking different directions while on this call, it's because I've got questions being texted and chatted on three different screens so if you notice, that's the reason why.

We mentioned at the very beginning of my remarks, how much activity is happening here at the Foundation Finding Blindness and how much momentum and how many different initiatives that are ongoing at any point in time. I did want to come back to a plug for this Saturday where we've got two key webinars that are occurring. One related specifically to the gene CRB1. There are usually many questions about the CRB1 gene on these calls, so anyone who's on the call today that would like to learn more specifically about our efforts around that gene, please join us on Saturday for that webinar. And then we have another one of our national Chapter webinars immediately thereafter on Saturday morning. So Saturday's going to be a busy day for us here at the Foundation, but all of the information that we covered today on these webinars, other events and things of that nature are all available at our website @fightingblindness.org. Thank you everyone for joining us today. Have a great rest of the afternoon and we'll see you all real soon.