Welcome to Eye on the Cure, a podcast from the Foundation Fighting Blindness, providing science research, news, and insights about the world of vision and blinding diseases.

Welcome everyone to the Eye on the Cure podcast. I'm your host Ben Shaberman with the Foundation Fighting Blindness, and I'm pleased to have Dr. Hema Ramkumar as my guest for this episode. I've known Dr. Ramkumar for a few years and I've always appreciated her commitment to caring for patients with inherited retinal diseases and age-related macular degeneration. And I'm also very impressed with her work on a therapy for intermediate AMD, which we'll talk about in a few minutes. But what caught my attention recently was her work to put mice into space to create models of retinal degeneration. So welcome to the podcast, Hema. I look forward to hearing about your mouse-tronauts as I call them, as well as your emerging therapy for AMD.

Thank you so much for having me, Ben. It's really a pleasure to be on the podcast today and I've always been so excited about the work the foundation's doing and it's just a great opportunity to speak with you. Thank you.

Well, it's our pleasure to have you. So a little more background on Hema. She received her Bachelor's Degree in economics and developmental neurobiology from Northwestern with distinction in research, and she also received her medical degree from Northwestern. She has 17 years of translational research experience in retinal diseases, especially macular degeneration. She's been an investigator in multiple phase two/three clinical trials for novel retinal therapeutics, and Hema has authored more than 30 papers on retinal diseases in peer reviewed journals. And, Hema is a Thrasher Foundation Early Career Award recipient for retinal research and was a Howard Hughes research scholar at the National Eye Institute. So Hema, you've taken a somewhat non-traditional path professionally. You're a retinal specialist in private practice, but you make it a point to see inherited retinal disease patients, and that's really important to us. We're grateful for that. But you've also decided to launch a company, Oculogenex, to advance a dry AMD therapy. Tell us a bit about your journey and how you reached this point in your career and tell us why you do what you do.

Sure, Ben. So I grew up watching my mother, who's a community pediatrician, take care of the people in our town when they were in need. And so that was always inculcated in me of being there for someone, helping them get through a difficult spot and seeing the reward with their health. And so that has been the reason why I wanted to become a doctor. But throughout my medical training, I completely fell in love with retinal biology and I just was amazed at the way the retina can repair and improve function when we're younger and how those same processes just completely change and turn off as we get older. And I've been chasing that switch in my research both at Northwestern and also at the NIH. Throughout this time, I've been really interested in changing the natural history of retinal diseases. As you mentioned, in my residency I was one of the lead investigators, principal investigator, in an interventional trial for retinopathy of prematurity, and since then I've been an investigator in multiple trials for geographic atrophy and wet AMD.

And while we had many successes for my patients with wet AMD and now also some successes for patients with geographic atrophy, there's still this big gap. And so that gap in caring for my independent patients with intermediate AMD that want to keep their license or those patients that drive by themselves and are afraid to drive home because once it gets dark they can't see. That's the gap that I see in private practice. And having my conversations with them led me to believe that we have to do something more as a community. And from my understanding of the biology of the disease, I know that it's very difficult to emulate intermediate macular degeneration in the lab. And so this is part of the reason why I am challenged to help patients with this disease. It has been both addressing lifestyle modifications, epigenetic factors that they can control, and then also trying to find a better model of their disease and then ultimately a better therapy.

And so that's really me coming the full circle to coming back to trying to help my patients with intermediate macular. So once I've been in practice now for about six years, I'm ecstatic about the therapy we can give our patients with diabetic retinopathy and advanced AMD, but I'm focused on really making life better for my intermediate AMD patients and helping them get more security. And so you mentioned the mouse-tronauts, that's such a cute name. I've never heard of that.

Before we continue on, I wanted to have you explain a little more about intermediate AMD and the therapy that you're working on to address it, because I think we spend a lot of time talking about advanced AMD, geographic atrophy, that's the advanced form of dry AMD. And we also spend a lot of time talking about wet AMD, but what is intermediate AMD? Do people have vision loss if they have intermediate AMD?

I'm going to just speak very broadly before I get into the categories for your viewers. Macular degeneration, or AMD, is when the eye is aging faster than you, than the patient. And so in intermediate AMD, there is some signs of retinal dysfunction and the retina is not working at 100%, so you have some symptoms but you don't have retinal tissue loss. So symptoms patients can have are when they go from outside to inside, they feel like they're blind for a couple minutes and it takes time for their vision to come back. That's one of the early symptoms. And the other symptoms is in low light conditions they're not able to see clearly. So that's the beginning, so they do have symptoms. Their retinal photoreceptors are not working at 100%. They may be shortened or changed, but you still have them.

And also at this stage you're losing mitochondria, and we can see that on retinal scans, and the mitochondria are supposed to be keeping the retina healthy. And so if you start losing them you start getting more and more dysfunction of the retinal cell. And so advanced AMD is in two categories, geographic atrophy, where you have areas of retinal damage and retinal tissue loss, so you have nerve thinning in geographic atrophy. And wet macular degeneration where your body sprouts new blood vessels that leak or bleed. So our therapy is focused on helping patients with good vision but some symptoms of the disease to have better vision and preventing the advanced stages of the disease, broadly speaking.

Right, and your therapy targets mitochondria. You mentioned mitochondria a few moments ago. Why is that a target?

Sure. So the cell has many parts and the nucleus decides what to do and the mitochondria has to do all the work. The mitochondria is the workhorse of the cell. And so in macular degeneration, patients have less mitochondria in the retina compared to patients who don't have them. So you have a genetic predisposition to disease and then you have less basically workers taking away all the oxidative stress and damage. So the reason why we need good mitochondria is because they need to fight all the oxidative stress and prevent the cell from dying. The mitochondria is responsible for making antioxidants and for turning the cell death switch on. There's something called programmed cell death or apoptosis that is triggered by the mitochondria. So it's both the cell defense mechanism and the cell death switch, so that's critical. What our therapy does is deliver a protein that is concentrated on the mitochondria and its main effect is to increase the production of multiple antioxidants or cellular defense proteins against oxidative damage and it stabilizes the mitochondrial potential preventing cells from going into cell death in the setting of a lot of cellular stress.

And so what we've done in the laboratory is emulate various methods of cell stress with chemical stressors, light stressors, UV stressors, and we've found that retinal cells treated with our therapy had more antioxidants, preserved function, and did not go into cell death. So this was very exciting in vitro and in vivo work. And we worked with very harsh stressors that basically burnt through retinal tissue, but that's not what macular degeneration is. It's not one hard blow, it's death by a thousand small blows. And that's how it works over years and years. There's small amounts of DNA damage, small

amounts of oxidative stress, and then you have high cholesterol, high blood pressure that add a little more lipid, and this combination of many small blows is what leads to dysfunction and death.

So our therapy, while we showed that we can protect against harsh stressors, I wanted to find for both us and for everybody who's looking to get a therapy for intermediate AMD, a better model of this disease. And so that kind of is what led us to the whole mouse-tronauts topic. And when we were in the mass challenge accelerator, the International Space Station National Lab approached us and said they were excited about the therapy we were developing and wanted to partner with us in technologic development and future commercialization of our therapy. And while I was excited to have NASA and the space station come to us, I said, "What does this have to do with anything? I'm trying to help patients with AMD right here on the earth not in space." But the review of the literature showed that a one-month trip to low earth orbit actually activated oxidative stress pathways and induced apoptosis and mild cell death, and it activated those chronic oxidative stress pathways, not the acute stress pathways that we can generate in our lab.

So Ben, you know as well as I do that the macular degeneration models are really a gap and we don't have any good model of intermediate disease. While we can develop transgenic models, those aren't representative of our general population. And so this mild chronic stress that we can generate in just a one-month trip to space I thought would be a very interesting thing to study. And so what they have supported us with is a grant to evaluate the validity of this low earth orbit as a model of dry macular degeneration. So we'll be looking at biomarkers of dry AMD to really see how well this space flight emulates dry AMD. We do know that it reduces ERG function, causes increased oxidative stress markers, and causes 10% thinning of the retina, but beyond that there's limited data on activation of pathways such as complement and other ocular inflammatory pathways. So we're going to be at that and then we'll see if our therapy has a protective effect.

That's so cool. And when do you anticipate the launch of this experiment? When will the mice go into space?

Mice are slated to go into space next week, March 14th.

Wow, that's very cool. So our discussion is very timely. I seem to recall that humans who have spent a lot of time in space have some retinal abnormalities as well. Have you heard that? Are you familiar with that phenomenon?

Yes, Ben. It has been shown in astronauts that they develop pigment epithelial detachment, and that is a finding that we see in dry macular degeneration as well. And the OCT scans have been generally analyzed in these astronauts, but they haven't shown macular degeneration, thankfully, in long-term follow-up. And that's because we're dealing with a really fit healthy group of people that are going to space. And so based on their lifestyle choices they can control many factors on retinal gene expression. But we did see some signs of dry AMD and that may be due more to the fluid shifts, but we can't say it doesn't exist.

Right. That's so interesting. So the mice will go into space, and after that, what are your next steps for developing your therapy? Do you have a hope or a schedule for a clinical trial, a hopeful timeframe?

Yes, Ben. So we're having our pre IND meeting with the FDA this year. Soon we'll be doing our IND enabling studies and then hope to have our IND next year and treat our first patients toward the end of next year.

Okay, that will be awesome. And just to close out, you're targeting intermediate AMD, which I think is such an important target because all of our therapeutics right now are really for the advanced form of AMD, but in your discussion of your approach targeting mitochondria it sounds like this approach might benefit people with other retinal diseases. Do you think that could be the case?

Absolutely, Ben. So the difference between our approach and other mitochondrial targeting therapies is that it's a gene therapy, so it's a single therapy that can last for years. And the way many of the inherited and age-related retinal degenerations go is that you have some signs of dysfunction in the beginning and then it progresses. So this therapy has the potential to prevent progression of any retinal disease associated with oxidative stress, and I think it has the most potential for stargardt, however, it would be exciting to see what the effects would be in other IRDs as well.

Definitely. Well, Hema, thanks for taking time out of your day. I know it's early there in southern California where you reside and provide care for patients, and I'm really excited about the work you're doing. You've done a lot, but you're still relatively early in your career so I look forward to a lot of the great work you're going to do down the road for patients in therapy development. And we'll look forward in the next week or so to hear about the mice in space and see how they do.

Absolutely. Thank you so much, Ben. I appreciate it and I hope to give you an update soon.

Okay. Thanks Hema. And listeners, thanks as always for joining the podcast. It's great to have you and we look forward to having you back for the next episode. See you later.

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