

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 this episode of the Eye On the Cure Podcast. I am Ben Shaberman, Senior Director of Scientific Outreach at the Foundation Fighting Blindness. I wanted to let you know that today's episode is sponsored by Apellis Pharmaceutical, so thank you Apellis.

I am delighted today to have, as our guest, Dr. Nancy Holekamp, and she will be discussing therapies and emerging therapies for age-related macular degeneration. She's also going to give us some insights and perspectives on what's in therapy development for inherited retinal diseases. Welcome to Eye On the Cure, Nancy, it's great to have you.

Dr. Nancy Holekamp:

Thanks, Ben. It is my pleasure to be here.

Ben Shaberman:

Before we get into the discussion, I wanted to let our listeners know a little more about Nancy. She has some impressive credentials. She is the director of Retina Services at Pepose Vision Institute in St. Louis. She is also a professor of clinical ophthalmology at Washington University School of Medicine in St. Louis, and a principal investigator at Lifelong Vision Foundation in St. Louis. Now, her educational credentials are impressive as well. She got a BA in molecular biology, summa cum laude, from Wellesley College, her medical degree from Johns Hopkins, and her internship and residency from Washington University School of Medicine, again in St. Louis.

I think what should be most important and most impressive to our listeners is that you've been involved in a number of clinical trials for the retina, for AMD, retinal vascular occlusion and diabetic retinopathy. The count that I have is 35 national trials, is that pretty accurate still ?

Dr. Nancy Holekamp:

Accurate and growing, Ben.

Ben Shaberman:

Okay.

Dr. Nancy Holekamp:

I do a lot of clinical trials.

Ben Shaberman:

That's very exciting, thank you for your work there. Before we start talking about some of the emerging therapies and therapies for AMD, I'm curious what actually drew you into the retinal research and retinal care space?

Dr. Nancy Holekamp:

Well, I was a medical student at the Johns Hopkins University School of Medicine in Baltimore. As a second and third year medical student, you're really going on numerous rotations and trying to decide what area of medicine you're going to specialize in. I went to the Wilmer Eye Institute, which is world famous, and I had the great privilege of working under a retina specialist there by the name of Stuart Fine. Stuart Fine then went on to become chairman at the University of Pennsylvania, but he really was a clinical trialist. He organized clinical trials, he participated in clinical trials, and he made not only caring for people with retinal diseases look meaningful and interesting, he made being a clinical trialist look important and meaningful and it would move the field forward. I think when you have good mentors at an early stage in your career, I think it matters. I think there's no surprise that I became not only a retina specialist, but also a clinical trialist.

Ben Shaberman:

That's a great story. For us, Wilmer has a special place because the Foundation was founded in Baltimore and we've been working closely with Wilmer really since our early days. One of our original scientific advisory board members, Mort Goldberg, was director at Wilmer for quite a while. That's really cool that you have that deep connection to Wilmer. Clearly you have a pioneering spirit, because I don't think you get into clinical research without wanting to venture forth and make new discoveries and get emerging therapies across the finish line for patients.

Dr. Nancy Holekamp:

Well, I will say that the practice of medicine is really doing the same thing over and over again. It really depends on your training, so it's so important to train at the very best places. But doing clinical trials is creating something new, it's breaking through new frontiers. Thanks to all the research that's done in my field, there's nothing I do today that's the same as when I trained about 27 years ago. It just shows you how exciting our field is and how many smart people we have bringing innovation, new technology and new treatments to patients. It's one of the reasons why I've loved being a retina specialist for the last 27 years.

Ben Shaberman:

Well, again, thank you for doing what you do to get more treatments hopefully through the pipeline and out to people who need them.

Let's start off, when it comes to reviewing some of the therapies that are out there, talking about wet AMD. If you can briefly tell our listeners what wet AMD is, just so we have that basic understanding.

Dr. Nancy Holekamp:

Sure. Wet age-related macular degeneration, or wet AMD, used to be the leading cause of legal blindness, not total blindness, for Americans over the age of 65. Age-related macular degeneration, although it's age related, you don't get it just because you're older, you actually have to have the bad genes. It's not like blonde hair or blue eyes, it's where 19 different DNA variations come into the right mix to create this disease we know as AMD.

Age-related macular degeneration always starts off as dry, but then anyone who's dry can, out of the blue, without pain, without warning, develop wet macular degeneration. Wet is where abnormal blood vessels grow underneath the retina and they leak fluid in blood, that's why we call it wet, wet is just a descriptive term for this leakage, but it's that leakage that can destroy your vision. It first shows up as distortion, where straight lines suddenly become wavy, and then it causes blurred vision. If left

untreated, again, it leads to permanent legal blindness, defined as not being able to see well enough to read or drive in that affected eye.

That's what macular degeneration is, but what I can say is that we've decreased the rate of legal blindness by 50% over the last 15 years because of the advent of injections into the eye. These injections are really nothing more than an anti-leakage protein. If you're wet and you have wet AMD, you have these blood vessels that are leaking, and we inject an anti leakage protein into the eye. It's really been a paradigm shift and it is now possible to prevent legal blindness for the majority of patients if we catch it early enough.

Ben Shaberman:

That is very exciting. I'm really glad you mentioned that we've decreased the rate of legal blindness by 50%. That's a really impressive figure and that really shows how effective these treatments are.

Now, sometimes the challenge with these treatments, as I understand, is they have to be injected into the eye on a fairly regular basis really for the life of the patient, sometimes it's monthly, I guess it depends on the doctor and the patient, sometimes it's more on an as needed basis, but there are emerging wet AMD therapies, and actually some newly improved therapies, that reduce that burden. What I'm thinking of both happen to be from Genentech and one is called Susvimo and the other is called Vabysmo. I was wondering if you could talk about those and give us your perspectives on those approaches.

Dr. Nancy Holekamp:

Oh, absolutely. These are two very exciting treatments for wet macular degeneration and each just got FDA approval. Susvimo got FDA approval late in 2021 and Vabysmo just got FDA approval early this year, I think it was January or February. Very exciting that these are brand new treatments, and we'll talk about them in turn.

Let's start with Vabysmo, this is an injection. Ben, you're right, the problem with our first generation anti-leakage protein injections was that they're not magic, they're pharmacology and they have to be given as often as monthly to a lot of patients. Boy, those months come around pretty fast and it's hard for patients to get back to the doctor's office. Vabysmo is an anti-leakage protein plus an additional molecular entity. It has two targets, not just the leakage, but it helps stabilize normal blood vessels. It targets something called Ang-2. With this single injection, we can prevent leakage and we can also stabilize normal blood vessels. Stable blood vessels don't leak, so it's an added bonus.

I've just started giving my patients Vabysmo and I am explaining to it to them as an anti-leakage plus a bonus injection. I'm trying to give it to patients who are coming in every four weeks or every six weeks, very, very frequently, because the clinical data showed that we could improve and maintain vision with far fewer injections, maybe on average just five injections the first year and maybe three injections in the second year for some patients with diabetic macular edema. We don't have a second year data yet for AMD, but that will be out soon. It decreases the number of injections without losing vision, so Vabysmo is very, very exciting. I call it injections 2.0. it's the second generation of injections.

Now, the other treatment you mentioned then is called Susvimo. This is a complete paradigm shift. This actually requires a surgery of a drug delivery implant into the eye. Patients who have been used to getting shots, they'll say, "Oh, now you want to do surgery?" Well in age-related macular degeneration, a lot of patients have already had implant surgery, it's called cataract surgery. Cataract surgery is taking your cloudy lens out and putting a clear lens implant in. Here, we're just putting a drug implant in, but it

sits inside the eye, it's made of the same types of material. Once it's inside your eye, you never know it's there.

But what this implant is, is a drug reservoir. It holds 20 times the concentration of an injection and it's got a special filter that releases its slowly over six months. It's a sustained delivery drug implant. Patients who have this initial surgery just come back to the office and get the implant refilled every six months, but they don't need monthly injection. Again, the clinical trial data that led to FDA approval showed that vision was maintained and the leakage was controlled with just getting this implant refilled every six months.

These are two very exciting innovations that move our field forward, and I'm happy to say that I was part of those clinical trials.

Ben Shaberman:

That's really cool, you were part of both of those trials. Well, obviously you did some good work, so thank you.

One more question about wet AMD. I know there are at least two, maybe three, gene therapy trials that are ongoing for wet AMD. Can you give us an update on what's happening in those?

Dr. Nancy Holekamp:

I am very excited about gene therapy, but it has a longer runway, we're not quite there yet. I want people listening to understand that this gene therapy is a way of creating bio factories within the eye to produce these anti-leakage proteins we've been talking about. The whole idea is they have a gene that encodes for this anti-leakage protein, they put it into a virus that can infect some of the cells inside the eye called retinal pigment epithelium cells, then the virus unloads that DNA in the cellular machinery of that retinal pigment epithelial cell. It goes to work and it starts manufacturing these anti-leakage proteins.

It's a great idea. In early phase clinical trials, it is working, but gene therapies have a fairly long runway. I still see this being at least five years out before we get FDA approval or clinical use. Very, very exciting, I really am hopeful for it down the road, but it's not here now.

Ben Shaberman:

Right. I think what's exciting about gene therapies, if we can get approval for something, is that they are one-time injections and, as you say, sets up a bio factory in the eyes so you have a continual sustained release of the protein to prevent the growth of those leaky blood vessels. That is an exciting potential there.

Let's switch to dry AMD. As you pointed out, which I'm glad you did, everybody starts out with the dry form. Many people may have early stage dry AMD and never have a problem with their vision, but for some people the dry can advance to the point where they have some pretty significant vision loss. We call that geographic atrophy. Therapy development in that space is a little further behind the wet AMD space, but what's going on for dry AMD, especially the advanced form that you're excited about?

Dr. Nancy Holekamp:

Well, Ben, you're right. The science in this area has lagged behind because we didn't understand it well, and we probably still don't understand what causes geographic atrophy completely. Just a word about geographic atrophy, it's the end stage or the late stage of dry macular degeneration. Atrophy means

that the cells die off of old age. If you lose enough cells, you're going to lose your vision, particularly if that area of cell death, that area of atrophy, is in the center of the macula.

When you look at what causes cell death, again, we've had numerous really smart scientists from all over the country, and even all over the world, all arrive at the same conclusion, that it involves something called the complement system. Complement is part of our immune system, it helps fight invading bacteria or illness or disease, but it's very, very complicated. We're having to dissect the complement system, look at it closely, examine it, and see if there are things we can target in the complement system that could turn into a therapy.

We have proof of concept that targeting complement factor 3 and targeting complement factor 5, in this whole cascade, and if I tell you the numbers three and five, you're probably guessing there's a one through something, there's a one through nine actually, when you get to five through nine, those are the actual cells that cause cell death. It's called the membrane attack complex. If you can target somewhere in the cascade and stop the cascade, then you might be able to stop cell death. This is relatively recent knowledge and it's being tested in clinical trials. The clinical trials look promising.

Ben Shaberman:

Yes, thank you for sharing that perspective on the dry AMD space. When I'm thinking about the complement system, I know that the first treatments, or really the first treatment, for wet AMD was FDA approved in 2006, but it wasn't until 2005 that researchers really identified that the complement system was a factor in the development of AMD. That's a benchmark of the fact that the dry AMD research is a little further behind the wet AMD.

To round out our discussion, I wanted to get your perspectives on the inherited retinal disease space, for conditions like RP or Stargardt disease or the myriad other conditions. What's going on in that space that you think is interesting and exciting right now?

Dr. Nancy Holekamp:

Oh, there's so much interesting research being done in the inherited retinal degeneration space. We are so lucky that there are so many smart, creative scientists who are problem solving in so many different ways. The field of retina is the first field that has an FDA-approved gene therapy. Now, that's Spark, that's Luxturna, Spark is the company, Luxturna is the product. It treats and prevents blindness from an inherited RPE65 gene mutation. It was FDA approved, I believe, in 2019.

What's so exciting to me is that if you can do it once, you can do it again, and so I think the floodgates are going to open up. I think we will have more gene therapies that target other inherited retinal degenerations and really make a difference in people's lives. It's so exciting for me, because I've been a retina specialist for 27 years. When I started, there was no hope for people with inherited retinal degenerations. We would pat them on the back and say, "I'm sorry, there's no treatment that we know of," and we would refer them to low vision services or adaptive services. Now when I see people with inherited retinal degenerations, there is hope. I tell them that in my lifetime we will have treatments, maybe not all inherited retinal degenerations, but we will slowly be ticking them off as we make progress in these diseases.

So happy that Spark opened the floodgates for gene therapy in the inherited retinal degeneration space, but there are other smart people working too. Last fall, I was at the Retina Society meeting and I heard about a Phase 2 clinical trial from a study named Alkeus, it's an oral pill. Here, it was smart chemists who decided that they could substitute a heavy isotope of hydrogen for the hydrogen atoms that normally exist on the molecule, and they could interfere with the progression of geographic atrophy that

Stargardt patients have. It's humbling to think of how many smart people worldwide are working actively in this area. Again, I am very, very hopeful and it's an incredibly exciting area right now.

Ben Shaberman:

Yeah, I definitely agree with you, especially given just all the clinical research that's going on. We're somewhere in the neighborhood of 40 to 45 clinical trials. A lot of these gene therapies are moving forward, For X-linked RP as an example, we have one treatment in Phase 3, another one moving into Phase 3. Hopefully, again, we'll get something across the finish line for XLRP pretty soon, and then there are many others following in those footsteps.

Nancy, this has been great. In the short half hour that we've been talking, or however we've been chatting, you've given us such great information about AMD and inherited retinal diseases. We really appreciate the great work you're doing for not only your patients and your clinic, but also in clinical trials. Thank you for taking time out of your busy day to be on the podcast and help educate our community about the great work that's going on out there. Thank you for, again, joining us. Finally, I want to again thank obviously our listeners for joining us, and again, our sponsor of this episode, Apellis Pharmaceuticals.

Nancy, I'll let you get back to your day. Thanks again, and maybe we can have you back in the not too distant future to give us an update.

Dr. Nancy Holekamp:

Well, thanks, Ben. I enjoyed it tremendously. Thank you for having me.

Ben Shaberman:

Thank you.

Speaker 1:

This has been Eye on the Cure. To help us win the fight, please donate at [foundationfightingblindness.org](http://foundationfightingblindness.org).