Macular Chats

Understanding Stargardt Disease
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Transcript of Teleconference with Dr. Christine Kay, Vitreo Retinal Associates

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Please note: This Chat has been edited for clarity and brevity.

DR. PREETI SUBRAMANIAN: Hello, and welcome. My name is Dr. Preeti Subramanian, Director of Vision Science Programs at BrightFocus Foundation. I'm pleased to be your host for today's Macular Chat, "Understanding Stargardt Disease." Our Macular Chats are a monthly program designed to provide people living with macular degeneration and the family and friends who support them with information straight from the experts. BrightFocus Foundation funds exceptional scientific research worldwide to defeat Alzheimer's Disease, macular degeneration, and glaucoma. And we provide expert information on these heartbreaking diseases. You can find much more information on our website, www.BrightFocus.org. I'm pleased to introduce today's guest speaker, Dr. Christine Kay, who's an MD. Dr. Kay is a vitreoretinal surgeon with Vitreoretinal Associates in Gainesville, Florida. She attended medical school at the University of Florida, completed her ophthalmology residency at the University of South Florida and her vitreoretinal fellowship

training at The University of Iowa. She is now Director of Retinal Research and is actively involved in multiple subretinal gene therapy trials and is interested in optimizing surgical techniques for subretinal delivery. She is also principal investigator for several intravitreal gene therapy trials, including those for treatment of wet AMD and geographic atrophy. Dr. Kay, thanks for joining me today.

DR. CHRISTINE KAY: Thank you for having me.

DR. PREETI SUBRAMANIAN: Great, so to begin our Chat today, if you could start us by telling what is Stargardt disease and explain to our audience how it differs from age-related macular degeneration, or AMD, which we talk a lot about in our program.

DR. CHRISTINE KAY: Sure. There are some similarities, and this can be confusing, but there is a good answer to this. Stargardt disease is a genetically inherited retinal condition, whereas age-related macular degeneration is a multifactorial disease, where genetics does play some component; however, it's a multifactorial disease, so age is still the number one risk factor and environmental factors, and then there are a multitude of genetic factors that can predispose or protect. So, age-related macular degeneration is not what we call a monogenetic—meaning one gene causes the condition—type of condition. And it typically affects individuals 60 or above. There's a bit of wiggle room on that diagnosis, 55 and above, but typically, I would say average 60 and above would be a typical diagnosis of age-related macular degeneration. So, when I have a 35- or 40-year-old walk into my office that's been diagnosed as age-related macular degeneration, I'm already a bit doubtful of that diagnosis, and that is where we start to think about other diagnoses.

Stargardt disease is a genetically inherited disease that is typically inherited in an autosomal recessive fashion. And what that means is that one mutation is inherited from Mom, and one mutation is inherited from Dad. Typically, the parents are carriers of the condition but do not manifest the actual disease. Whereas the patient with Stargardt disease, who has these two mutations and, therefore, cannot make the correct protein, which I'll talk about in a minute, this ABCA4 gene encodes for a

protein that allows the visual cycle to function normally. These patients with Stargardt disease develop a macular dystrophy, which actually looks very much like age-related macular degeneration; it just happens at a much younger age. It has a different progression and a little bit of a different appearance on clinical features, and again, we understand the mechanism and the pathophysiology for what's happening much better in Stargardt disease than we do for age-related macular degeneration. I'll stop there and let you redirect.

DR. PREETI SUBRAMANIAN: So, the typical onset for this condition, would you say, is in the mid-30s, or could it be earlier? How early can one see any symptoms, and what are some of the symptoms that one would notice early on?

DR. CHRISTINE KAY: Okay. For Stargardt disease, which is predominantly what we'll focus on today, and I think that we'll talk a little bit about AMD at the end, but predominantly, today, we're going to focus on this genetically inherited Stargardt macular dystrophy. Stargardt macular dystrophy typically is a juvenile-onset disease—so, actually much earlier than 30, so actually a very common age is late childhood/early adolescence for first visual symptoms for the typical juvenile-onset Stargardt macular dystrophy, STGD1, which is what we call this disease. There's always confusing things, and there's always things that are caveats to everything in life. And for Stargardt, there is a late-onset version of Stargardt disease, just to confuse names, and that's the example of that 40-year-old that walked into my clinic with this diagnosis of age-related macular degeneration that I was a little bit doubtful of. There is a late-onset Stargardt disease that can be caused by two mutations in that ABCA4 gene that is genetically inherited and is indeed Stargardt disease; however, one of the mutations tends to be what we call a risk-factor allele, and it's a less-severe mutation in the gene, and we even know what this gene is, it's 1868Ile, and it is Asn1868Ile, and it, actually when I see this on genetic reports, I say, "Oh, I bet this is the late-onset Stargardt gene," and indeed, that patient often has much later onset. They often have foveal sparing, which means that the center of the macula—the macula being the most central part of the retina, the fovea being if you put a bullseye and you got the target right on the

bullseye, the fovea's the most central spot of the macula that's able to see 20/20. Patients with late-onset Stargardt often preserve their fovea. We don't fully understand why. If we did understand why, I think it'd be very helpful to research, but late-onset Stargardt patients often have very slow progression, and often they don't affect the fovea. We don't lose vision in the fovea, but that's a little bit of an outlier.

So, just to summarize what most people are probably interested in hearing about today, and certainly, the most prevalent type of Stargardt disease is the juvenile-onset Stargardt disease. Let's just kind of overview that, because I think that's probably the most important thing to focus on. These patients present maybe between age 8 and 12. They might have failed a vision screening at school. They might have gone into their optometrist, and the optometrist told the parents, "Hm, this child is not being corrected to more than 20/40 vision, and we don't really know why," and so that patient might get referred to an ophthalmologist or eventually a retina specialist or an inherited retinal disease specialist, and we end up doing some testing, which I'll talk about what kind of exams and images we do. We end up doing genetic testing, and we confirm a diagnosis of juvenile-onset Stargardt disease. Usually, the progression pattern for the typical childhood or early adolescent Stargardt disease is that over a 10- to 12-year period, the visual acuity can slowly decline to a 20/200 central blind spot. That is, with the pathophysiology of this disease, is to start to affect the central retina—that central macula—and to cause an atrophic—which means degenerative—lesion in the center of the macula that does cause a blind spot. So, the patient is slowly losing visual acuity to the level of a small central blind spot that's about 20/200 visual acuity—that's corrected with glasses—and that happens, again, over a 10- to 12-year period, generally speaking.

Again, there are always outliers and patients that manifest earlier. For most genetic eye diseases and Stargardt is one of them, the earlier onset the disease, typically the more severe the mutation. So, if I have a 5- or 6-year-old who's coming in with vision problems and I see a bullseye, which is one of the early-onset things I sometimes see in very early–onset childhood Stargardt, they may progress more rapidly, and they may end up having more peripheral retinal involvement in life and progressing to

something we would end up calling a cone rod dystrophy, which is where more of the peripheral retina is also involved. And again, that's an outlier, and we already talked about the outlier of the late-onset patients, who present later and have a very mild course.

DR. PREETI SUBRAMANIAN: Right. So, you covered about the disease being a genetic condition. It is inherited. So, is there a pattern for inheritance? You mentioned the parents are carriers for the disease, so what are the chances that the child would have inherited this condition? And are there genetic tests that are currently recommended or available for this?

DR. CHRISTINE KAY: Yes. By definition, Stargardt disease is genetically inherited, and we're looking for, with genetic testing, we're looking to find two mutations in the ABCA4 gene, which is a gene that encodes a protein in a photoreceptor outer segment, which you don't really need to know what that means, other than the photoreceptor is the vision-sensing, light-sensitive cell in the outer retina that perceives the light. It's the first step in the pathway to perceive that light and kick out a visual cycle signal to the rest of the inner retina that transmits the signal through the optic nerve, eventually to the brain, so that's step one. If you don't have a photoreceptor that's receiving the signals—that's the receptor that receives the light signals—then the rest of the pathway is not going to matter. You need to have that photoreceptor working to get that visual signal through to the brain. So, yes, I think one of the really important things, and this is something that's often misunderstood or not really clearly understood, even by ophthalmologists and retina specialists—the idea that you have to see a big family history for a condition to be genetic. That is actually not the case, and the reason that's not the case is because the most common inheritance pattern for a genetic eye disease is autosomal recessive. And that means that mom and dad are both carriers, but they're unaffected. And likely their parents were carriers but unaffected, and their siblings are unaffected, but one out of four times—so, a 25 percent chance—that mom and that dad have siblings, so they could have four kids. Only one of those four kids will happen to have inherited both of the affected alleles. We tend not to use the word "mutation"; we tend to use the word "variants" now in genetic

eye disease. So, the variant alleles, which are affected with an abnormal mutation—the other word you could use—would go to one out of four offspring of those parents. So, in families in the U.S., your average number of children is less than four per family, so often, that patient will have no affected siblings. They might have two or three siblings; they might be unaffected. And, importantly, when that child grows up and has children themselves, they're likelihood to pass this on is less than 1 out of 100 and has to do with, of course, if they married someone who has Stargardt disease, that is a different calculation, but if they married someone who is unaffected with Stargardt disease, that person could be a carrier. Maybe the prevalence is roughly 1 out of 100 of carrier prevalence, but the likelihood for them to pass on is very low. So, what I'm saying here is, yes, it's a genetic condition, but given the way that it manifests, you don't see it. If you draw up this family tree, there's going to be one person that's affected, but it is indeed still genetic.

DR. PREETI SUBRAMANIAN: Right.

DR. CHRISTINE KAY: You asked about genetic testing. So, we would do genetic testing, and I often do that at my first visit. So, I'm, of course, going to take color images and OCT, which are pictures of the thickness of the macula that we do on a fancy machine. We take autofluorescence images, which show us the health of the RPE cells, which underlie those important photoreceptor cells. Sometimes we do multifocal ERGs and microperimetry and all kinds of fancy tests. But at the end of the day, once I've had a good clinical exam and see the OCT picture and I'm pretty sure this is Stargardt disease, I'm going to send genetic testing. We we can either send a blood sample or a saliva sample. Most of my patients vote for the saliva sample; it's easier. And then we send it through—I tend to use the My Retina Tracker registry, Foundation Fighting Blindness. And it gets sent off to a genetics lab. It's a big panel that's run—so, 300 genes that are testing for inherited retinal dystrophies; they are tested all at once. You could use Invitae, which is another free, funded genetic testing option. You could try to bill through insurance. There's all kinds of ways. There's all kinds of genetic labs that do these inherited retinal disease panels. So, we tend to send a panel, just to make sure that we're going to get a result and not just test for one gene at a time, because that will be

silly. And then, a few weeks later, up to 10 weeks later, depending on the lab that I use, I get back the report. And the report's going to tell me what mutations were found in what gene, and then we also, importantly, do genetic counseling to explain to the patient their results.

DR. PREETI SUBRAMANIAN: Okay. That seems what you explained about the process of diagnosis. Once somebody has the diagnosis, has all these results, the genetic testing, what is the next step? Are there any approved treatments that are currently available for Stargardt disease?

DR. CHRISTINE KAY: So currently, we do not have an FDA-approved treatment yet for Stargardt disease. There are some important things that we tell patients to avoid, but there are some important things we tell patients to consider that are potentially things that slow progression like vitamins, and then importantly, I know everybody's interested in hearing about clinical trials, and there's a lot to talk about in clinical trials—we talk very much about what clinical trials a patient might be a candidate for because there are a multitude of clinical trials that are quite relevant, some of them fairly far along in the clinical development pathway, and moving towards a potential FDA approval. But again, nothing is FDA approved as of today for Stargardt disease. But one thing to avoid—there are a couple things to avoid.

Number one, avoid smoking. We know that smoking is very, very toxic to the retina for any macular disease, including macular degeneration; I tell my AMD patients this, as well. Same thing for Stargardt. So, if you already have a defect that's hurting your retina, you don't want to be smoking and causing more retinal cell loss. So, no smoking, no secondhand smoke. Number two. Vitamin A is the enemy, in a way, and I want to clarify that statement. But vitamin A is something that we should avoid. And that doesn't mean that you can't eat carrots; there are a lot of patients that get really worried and nervous about this, and they really want to try to limit everything in their diet, and that's not the case. So, a patient can basically eat whatever they want. We do tell patients to avoid liver, because that's very high in vitamin A, and we tell patients to avoid any pills that have vitamin A. So, we don't want you taking a pill. Even the original AREDS1 vitamins for AMD had high-dose vitamin A, so we don't want that. We

don't want the 10,000 units of vitamin A. Luckily, that's fallen by the wayside for RPE. That's been debunked; that doesn't help RPE. But I have some Stargardt patients that, unfortunately, are coming in taking vitamin A! So, it's very important, no vitamin A. Don't take extra vitamin A. And the reason it's a problem is because of this ABCA4 mutation, the retina is not able to process vitamin A byproducts correctly. And that's why I wanted to clarify my statement. Vitamin A is not really the enemy; it's the fact that we don't have an ABCA4 enzyme to get rid of the vitamin A byproduct. We need vitamin A; you can't deprive the eye of vitamin A, or you'll go night blind. And we know that people on a ship out to sea for 3 months ended up with ERG changes and night blind because they were depriving vitamin A. So, we can't just deprive vitamin A, that's not the answer. But we want to try to help the eye get rid of the vitamin A byproducts that are created because the ABCA4 enzyme is not working correctly.

DR. PREETI SUBRAMANIAN: Yeah, that's great. So, it's okay to have normal amount of vitamin A in the diet but just not to have any fortified supplements or liver that might have excess amount because the eye has lost its ability with this variant of the protein, and the retina has lost the ability to metabolize vitamin A.

DR. CHRISTINE KAY: Correct.

DR. PREETI SUBRAMANIAN: Right. So, before we jump on, I know you mentioned we'll talk a little more about clinical trials. I just want to ask about the genetic testing. I know I get asked a lot of there are any genetic testing for AMD. Can you talk a little bit about what's out there and if there are any? I know there aren't any recommendations for the genetic testing for AMD, but if you could talk a little bit about that?

DR. CHRISTINE KAY: Yeah, it's an interesting topic, and I've liked watching this. Emily Chew at the NEI has been a big speaker on this, and the idea of looking through our AREDS study data and trying to decide if any of the genotypes were more of a risk for progression and what vitamins might be more helpful in different genotypes versus others, so there's certainly clinical research that needs to continue to be done. But all I can say in summary, and then there've been a lot of small companies that are proponents of doing genetic testing panels because they're sponsoring

genetic testing panels with the companies and trying to look at, you know, is zinc more useful if you happen to have a complement factor H mutation, or should we avoid zinc, so it's gotten very, very complicated, but, I can just tell you, at this point, the Academy of Ophthalmology, at least most recent guidelines, does still not recommend genetic testing—standard genetic testing—for age-related macular degeneration for the average person in a clinical setting. Some clinical trials are gathering that information, and it's still something that needs to be explored, but as of right now, for the general patient and the general ophthalmology retina clinic, the Academy of Ophthalmology is not recommending genetic testing in order to impact any choices that we would make in how we manage them or what vitamins we give them at this point. That certainly could change.

DR. PREETI SUBRAMANIAN: Okay.

DR. CHRISTINE KAY: And the moment it changes, the moment that the AAO comes out and changes their tune, I'll change my tune, but that's the current guideline.

DR. PREETI SUBRAMANIAN: Great. And also you mentioned at the beginning how it's more relevant in Stargardt disease, given that it's monogenic, where the genetic variant has a direct impact on the outcome of the disease, and AMD is a much more complex condition, multifactorial.

DR. CHRISTINE KAY: Right. Several genes we're looking at, correct.

DR. PREETI SUBRAMANIAN: Right. Okay. Great. So, we can switch here to talk a little bit more about the active research that's ongoing for Stargardt disease and what clinical trials are out there that's in the pipeline.

DR. CHRISTINE KAY: Active clinical trials, I'll try to give you a little bit of an overview of the recent and the current landscape for Stargardt disease, and then I can give you some of my predictions for where we'll be in the next few years because there are several things in the preclinical pipeline for Stargardt disease, and I'll explain why we've had some difficulties. And everybody wants to hear about gene therapy. That's the buzzword—you know, why has every other condition had a gene therapy trial, and why

has that been problematic? And I'll explain that a little bit today and why that makes sense and why that's been challenging for this disease. And I'm an investigator for a number of these trials, and so I'll mention that, and I'll tell you what trials I've been involved in and my experience as an investigator at my site. I'm a retinal surgeon, and I'm an IRD specialist. I'm in Gainesville, Florida, at a practice called Vitreoretinal Associates, so we've been a really active site for a number of trials, so I've had the honor of being involved as a PI in a number of these trials that I'm going to mention to you.

Maybe the first one that I'll mention is a company—a pharmaceutical company called Alkeus, and the product gildeuretinol, which is an oral drug—so, we're going to try and segment this; I'll do the best I can to keep this sort of organized. Let's do some oral drugs first, then we'll move into gene therapy and surgical trials at the end. So, oral drug called gildeuretinol, ALK-001 is what it was called in our earlier protocols. This is a modified form of vitamin A. So, imagine vitamin A, like we talked about a little bit, is not exactly the enemy. It's the fact you know, we need it, we have to dark it up, we have to see, we need vitamin A. But we don't want vitamin A to build up as a byproduct. So, what ALK-001, or gildeuretinol, has the capacity to do, and I was very, very impressed with the preclinical data in this particular drug. It allows the visual cycle to occur normally, so the eye thinks it's vitamin A, and it looks just like vitamin A. It's a molecularly modified form of vitamin A, where one of the hydrogen atoms has been switched to a deuterium nonradioactive isotope of hydrogen, so it just looks different, but it still functions the same way as vitamin A—allows the photoreceptor to do what it does, and the visual cycle to do what it needs to do. But it does importantly, it significantly decreases the ability for vitamin A byproduct to dimerize, and what that means is for the byproduct to bind to itself and form a toxic byproduct.

And that toxic byproduct, if anyone on who's listening to this has heard the word lipofuscin, or you have yellow flecks in your retina, or there are yellow spots in your retina, and had your retina doctor show you these autofluorescent photos where you see yellow spots—yellow stuff is the debris that I've been talking and alluding to today that happens with the vitamin A byproduct, and that product is toxic. So, that yellow stuff in the

retina, over time, will cause photoreceptor and RPE cells, which is the cell that neighbors the photoreceptors and lives underneath it, it causes those cells to eventually die or become significantly hurt. So, that is the general pathophysiology of Stargardt disease. And what this drug does is it decreases the byproduct of lipofuscin from building up in the retina and it allows decreased byproduct accumulation in the photoreceptor cells and RPE cells. So, that oral drug trial has been going on for many years. We've been an active site in Gainesville, Florida, here at Vitreoretinal Associates and have had many patients involved in this trial. So, actually, several publications—several presentations—at Academy of Ophthalmology and Subspecialty Day over the last several years, and this Alkeus company is moving us toward the regulatory pathway toward what we would call an NDA submission, where they're trying to move toward FDA approval.

And I don't know, I'm an investigator in a trial, and I'm not in the company myself, so I don't know timing and exact logistics of that, but I'm certainly hopeful as an investigator that this will continue to move forward in a positive direction. I can tell you that I've had the honor to be able to present some of the general data, and the general data on that is that in one of the studies called TEASE-1, which was the earliest rendition of this trial, where we treated late-stage patients who had a relatively large atrophic lesion, and we watched the autofluorescent signal over time. We saw, it was an 18-month endpoint, we saw a significant difference between patients who were on placebo, meaning they were not getting any drugs, versus the patients who were getting drugs. And that was, I believe, a 21-percent difference in the growth of the atrophic lesion. So, basically, taking the ALK drugs, ALK-001 or gildeuretinol drug, was slowing down the atrophic lesion growth in patients who are treated versus placebo patients. Of course, that atrophic lesion just grows and grows. That was exciting data, and we got that exciting data from the TEASE-1 study, and again, companies continue to move that forward into the regulatory part of the pathway now, which is with the company at this point, and I'm the investigator.

DR. PREETI SUBRAMANIAN: So, basically, the drug is at a point right now where the data has to be submitted to the FDA for review and to see whether it meets their criteria for approval and be available as a drug in

the market. And you mentioned that this was an oral pill that was being investigated in this trial. So, yeah, that's fantastic. Tell us about some of the other trials that you've been working on.

DR. CHRISTINE KAY: Yeah, and that is an oral, take-a-daily pill, and the safety profile is also very good. That's one of the nice things about being able to put patients into this trial is I don't have really high concerns about the safety profile. It's an excellent safety profile, so the other things that we're following and looking at bloodwork and all the things that you'd follow in any kind of FDA-sponsored trial, but things have looked very safe.

DR. PREETI SUBRAMANIAN: That's great.

DR. CHRISTINE KAY: We also enrolled for Belite Bio, which is a different company. That's also an oral drug. It's a different mechanism, so it's an RBP4 inhibitor, and without going into extensive detail about that, just imagine that you have a little truck that's carrying your vitamin A through your bloodstream to your eye, and then you slow that truck down. So, that's the idea of an RBP4 inhibitor is that we're decreasing systemically the ability for vitamin A to be delivered to the eye. And I set myself up for this earlier of why that could have some side effects and dark adaptation and delay and things. But if you get it exactly right, you know, if you happen to have the exact right dose, that maybe that you could figure out the perfect point where you slow down vitamin A just enough to slow down atrophy and slow down lipofuscin and not have issues with the things that I mentioned could be issues if you slow down vitamin A to the eye, which are dark adaptation and delay and night blindness. So, that is a company called Belite Bio that is working on a study that I was at site for in the U.S., and they had an earlier ex-U.S. site that had some promising data and open label—that means that all the patients were treated—and they are focusing on a younger population. I believe it was 20 and below—20 years old and below—so more of a pediatric population of patients and hoping to be able to intervene early to prevent disease acceleration. Another similar oral drug.

There were other trials I won't even really go into because I wasn't at site and some of them did have some positive efficacy signals that had some

safety issues and side effects. Emixustat, studied both in Stargardt and in AMD, and let's move away from oral drugs to gene therapy, and I will even talk at the very end about optogenetics, because I do want to mention, "What about the late-stage patients?" because, I think that group of patients often gets forgotten, and I have a lot of those patients in my clinic that want to know, "What about me? I already have a 20/200 blind spot, what about me?" So, we'll get to that. But the next category's gene therapy. And when I say, "gene therapy," I typically mean replacement gene therapy with an adeno-associated viral vector, or in the days of the original Sanofi trial, it was a lentivirus vector, and the reason that the vector's important, not to bore everyone, but the vector is what we use to carry the gene into the photoreceptor. So, imagining the truck scenario again. We have to have the right size truck to carry the passenger. And the ABCA4 gene, it's a very big gene. It happens to be a very large gene. So, the reason you don't see Stargardt disease in every gene therapy trial that's going on right now, and all the big companies working on X-linked RP and working on achromatopsia and working on X-linked retinoschisis, those happen to just luckily be smaller genes, and they happen to, luckily, just fit nicely into the AAV cassette, which is the virus that we like to use because it works the best. The lentivirus is twice as big. It fits 8 to 10 kilobases, and so Sanofi, a company, a few years ago used a lentiviral vector to deliver the entire ABCA4 gene. And that trial was Paris, Isabelle Audo, a good colleague and friend of mine, a very great site, was involved in this, and OHSU, a wonderful site in Oregon—the Portland, Oregon OHSU site—and so, they have solid data. That trial has been terminated, and there wasn't an efficacy signal. There were a few safety and inflammation signals that were released, but in any event, that study did terminate.

So, other preclinical work is being done, and trying to get around the problem of the ABCA4 gene not fitting into a typical AAV virus, and some of the companies are working on something called dual-vector therapy, where you cut the gene in half and try to have it recombine, something where you take a smaller part of the gene, all kinds of interesting preclinical work. And we absolutely will see in the next 5 years some other companies probably developing programs for Stargardt disease with gene therapy. But the one that's in the clinic right now, and my site was

the first to have a patient recruited and treated, and I sent my patient for surgery—and some of these things might be confidential of timings and where sites were, so I won't go into exact details—but the first patient has been treated in the Ascidian trial, which is an RNA-editing trial. What does that mean? Now I'm getting really complicated. So, we were talking before about gene therapy, where you replace the DNA. RNA, for those biochemists who are on the call, is a middle part of the equation—you have DNA, and then you have RNA, and then you have proteins. So, this particular company is getting around the fact that they can't fit the AAV—the DNA into the AAV—and they're editing the RNA. It does address exons 1 through 22, so about half of the genome, mutations have to be on that side of the gene for it to work. But it is in clinical trial right now. We don't have any data to share, obviously, it's way too early, but it is exciting that we have a gene in RNA editing, first-in-human trial that's just begun with a company called Ascidian Therapeutics.

DR. PREETI SUBRAMANIAN: That's great. And also, I know you mentioned gene therapy and using viral vectors. I want our audience to know that these viral vectors are safe for use, and they are typically used as carriers of the genes that are being replaced in studies and in treatment options that are available out there. That's really exciting because it looks like we are trying to target the disease by not only at the protein level but at the gene level and also at the RNA level with this new trial that you just mentioned about. We have a question from one of the listeners. The question is: My grandson is 17 years old. Is there a point in time where he will not be eligible for these new treatments? And I know you mentioned about one of the Belite Bio trials that is under the age of 20, but if you could share some insight into that about the eligibility for these new treatments?

DR. CHRISTINE KAY: Yeah. There are always age requirements for these trials. There's an inclusion criteria of what age patients are being recruited, and it always depends on what phase the trial is in. So, we have these early-phase, 1/2 subretinal surgical gene therapy trials. They're not going to have a kid be their first patient in the trial. The FDA's not going to endorse that, and the company's not going to suggest that, so typically, a surgical trial starts in adults, so it would be common for 18 and up to

be the first adult cohorts to go through. Often these trials will have an expansion phase where pediatrics are being treated. So, I know a common age would be 6 and up. We don't have 1-year-olds who have a diagnosis of Stargardt's disease; it doesn't manifest that young, but it depends on the gene. It depends on the disease and the onset of when we would typically see a patient recruited. So, was the question a "17-year-old was my grandson?" Is that the question?

DR. PREETI SUBRAMANIAN: Right. So, is there a point in time for eligibility, and I think you alluded to that by saying that it's typically 18 years and above for being eligible for most of these trials?

DR. CHRISTINE KAY: And that really depends on the trial and the mechanism of therapy. So, for some of the oral drug trials, we were very early on the Alkeus trial recruiting pediatric patients—again, risk–benefit here—once safety has been established, we're often treating pediatric at the earliest manifestation of Stargardt disease in the oral drug trials. Again, the Belite Bio company was only treating pediatrics—20 and below were the inclusion criteria. They weren't treating you if you were 22 in the current trial. So, again, it does depend on the risk of the therapy itself. So, for an oral drug, generally speaking, the risks are going to be lower than for having to go to the operating room and having a vitrectomy, retinal surgery, and have a surgeon inject the vector under the macula.

DR. PREETI SUBRAMANIAN: Right. You mentioned about the Alkeus trial. So, the Macular Degeneration Research Program at BrightFocus Foundation, in 2010, funded the first study that led to the development of this novel treatment with gildeuretinol, ALK-001, and the drug is also now being tested for geographic atrophy in clinical trials. So, can you tell us a little bit about that study and how this treatment can benefit individuals with AMD?

DR. CHRISTINE KAY: Sure. The trial is called SAGA, and we were a site. Of course, it's a placebo-controlled trial, at that point, and it was several years ago that we were beginning recruitment for that, when there were no approved GA drugs, which is now a different story because now we do have a couple FDA-approved drugs for geographic atrophy that involve injecting an eye, Syfovre® and Izervay™. But anyways, at the time of the

enrollment of SAGA, there were no other FDA-approved drugs, so there was a placebo-controlled arm randomized trial, and that data have been recently unmasked, meaning that they were able to calculate and look at the data. And that is going to be released at some point in the relatively new future, so stay tuned. At one of these academies, these data will be released, and I certainly would not want to burst that bubble, and that is for the company's timing to release that data to the public. So, stay tuned.

DR. PREETI SUBRAMANIAN: Okay, great.

DR. CHRISTINE KAY: Yeah.

DR. PREETI SUBRAMANIAN: I know you mentioned about optogenetics for the advanced form of Stargardt, and I know that there's a lot of interest in that, even for advanced vision loss with AMD, too. So, tell us a little bit about the optogenetics study.

DR. CHRISTINE KAY: Sure. And I have not been an investigator for the company Nanoscope, but I've actually been an advisor and a consultant for the company, and part of even some of the meetings they've had with the FDA recently. So, they have a program—their optogenetics program, which I need to explain—for both Stargardt disease and for retinitis pigmentosa. Those are the two programs that the Nanoscope Therapeutics company is evaluating their optogenetics therapy in. Optogenetics—now you've got to think a different way here—is a totally different mechanism than anything we've talked about today. So, optogenetics, remember how earlier today I was saying, "If you don't have any photoreceptors, you're kind of in trouble. We can't fix that." Well, that's true; we can't replace easily photoreceptors yet. And there are a few stem cell trials, which I won't even really get into today, but nothing prime time is working perfectly yet, with stem cell therapy yet, in human clinical trials for sure. But we can bypass it. At least, we theoretically can bypass a photoreceptor cell. And that is called optogenetics.

Optogenetics is genetically engineering—it's genetically re-engineering a cell to be different than it was originally designed to be. So, depending on the target and the promoter in the Nanoscope program, the bipolar cell, which is the inner retinal cell—so, not a photoreceptor, because we know

some of the photoreceptors are gone—the Nanoscope program targets the bipolar cell with an AAV vector—that adeno-associated viral vector—and it delivers into the bipolar cell, which is this neighboring inner-retina cell that's, kind of, just hanging out there doing other things in life. It tells this bipolar cell by delivering something called multicharacteristic opsin—an opsin is a photopigment—it tells that bipolar cell to wake up and start seeing light and sensing light. So, it basically redesigns a bipolar cell to think, sort of, that it's a photoreceptor. And I'm totally misconstruing that, but that's the general concept just to think about it very casually is that we're telling an inner retinal cell to start sensing light. And it's an algae-based gene, called multicharacteristic opsin, or MCO, and delivering that gene to a bipolar cell. And so it's turning on that bipolar cell's ability to sense light, and patients in their RP program and their Stargardt program did have some really interesting efficacy signals, where they had some improvement in their visual acuity and ability to navigate mazes and do these shape discrimination tests.

So, you know, exciting, interesting data, where we're actually improving and restoring visual function. And that's what my 20/400 patient wants to know about when they come in the door. My 60-year-old patient with Stargardt who's had this his whole life, who's not a candidate for, or wouldn't really totally help him to slow him down at that point; he's probably already progressed to about where he's going to be. It wouldn't hurt him to be on an oral drug that slows his progression, but it might not restore anything. So, the idea of restoration, the idea of improvement, that is a very important concept to not forget to talk about today. And that's one of the types of therapy to talk about is optogenetics. And one of the companies that may be farthest along in that is Nanoscope.

DR. PREETI SUBRAMANIAN: That's really exciting to really be able to bypass the regular pathway but awaken some of those cells that are just unaffected by the disease and just make them think that, "Okay, you can step in and help with this visual pathway now." It's really exciting. It's really very futuristic studies. And, hopefully, these are going to be available in a very disease agnostic way, which can be applied to other diseases of the eye, too. So, going back to Stargardt, what are some of the resources that are available for patients and families that are dealing with the disease?

And one of the listeners has asked about: How do I find local support groups in my area?

DR. CHRISTINE KAY: So, I think that networking is very important with these relatively rare diseases. I forgot to mention the prevalence of Stargardt disease today. It's actually not that low. Of the rare diseases, it's one of the most common—it's actually the most common inherited retinal disease I see in my clinic. Approximately one out of 8,000 prevalence. So, if you add that up, in my little town here of Gainesville, Florida, I have about 250 patients that are genotyped with two mutations in ABCA4 that have a diagnosis of Stargardt disease that live, kind of, near me in the North Florida area. Some are referred from Georgia, etc., and that's just the beginning. There's also Bascom Palmer down there in Miami that has a big IRD population with a lot of Stargardt patients. So, there are a lot of patients with Stargardt disease. And it's important, I think, especially with a new diagnosis, to consider ways to network into and find support groups. Foundation Fighting Blindness (FFB), to jot down some names, is probably my first go-to. And I love this group. This is a group that actually funded my career development award coming out of my fellowship at Iowa, where it began me on a clinical scientist track on intravitreal optimization of adeno-associated viral gene therapy. So, I started working at University of Florida with a career development award from FFB. FFB funds researchers. They really focus on funding young researchers and helping start researchers into clinical scientist tracks, and then they also really focus on patients. And they focus on patient education, patient seminars, patient outreach. They have a vision group that I go to pretty much every time they have it, which is an outreach, it's either once a year or once every other year, depending on how ... we went through the COVID pandemic there; they did it every other year, but it used to be every year, and it would often be in Baltimore, and it would be a national conference where we would have usually a 2-day conference and have rooms on Stargardt disease updates and gene therapy updates and the stem cell update room with David Gamm. We had multiple different talks going on for a 2-day patient networking conference, and they also have VisionWalk, where they have patients get together, and I often get invited to come give a talk, either in Tampa or in Jacksonville. So, lots of outreach, lots of teaching and support. Other groups, of course, do this, as well. Research

to Prevent Blindness, RPB, is another group that focuses on inherited retinal diseases. And then as far as other support groups outside of that type of an organization, where they're raising money for research, Division of Blind Services is actually a wonderful organization, as well as Lighthouse for the Blind. And you can look in your phone book/Google networks and look up what resources are near you and, hopefully, talk to your ophthalmologist or optometrist. If you haven't seen a low vision optometrist, that's worth a separate visit. They are super-specialized. We get very specialized in all of our fields, but optometrists often might just give you glasses and send you out the door, but a low vision optometrist is going to sit down and spend an hour with you working on something called a CCTV or something as far as what magnifications can we use, what type of software can we add to your iPad to help you change contrast from black to white to white to black, things that actually make a world of difference for patients with Stargardt disease, and you don't really know until you've tried.

DR. PREETI SUBRAMANIAN: Right. And it helps with the day-to-day navigation of once-everyday routine with these kinds of recommendations.

DR. CHRISTINE KAY: Right. Yep, so I think that the low vision optometry visit is very important. That's a specialized visit. It may just be a one-time thing to get you headed in the right direction. Division of Blind Services will also sit down with patients and talk about job optimization, work resources, and sometimes even vocational rehabilitation, which means maybe this job is not best for me right now; what else can I be best suited for right now and helping to adapt? So, it's all about adaptation and working with what we have and using technology to help us. And some of these organizations, that's what they're built to do. And the people who work at them are trained to do. Your ophthalmologist, we're really good at looking at eyes and taking pictures of eyes and maybe getting your genetic testing going, but we're not going to be able to spend the time or have the resources or even the knowledge of what exact CCTV or magnifier might be the best to actually help you function on a day-to-day basis.

DR. PREETI SUBRAMANIAN: Right, yeah. That's excellent. We talked a lot, and it's almost nearing the end of our session. So, Dr. Kay, is there any best advice for families, children, young adults suffering from Stargardt disease that you would like to say?

DR. CHRISTINE KAY: You're not alone. There are many patients out there and many families out there that are at all different dates of processing this information. Some are newly diagnosed; some have lived with it their whole lives. Being able to share that journey and that pathway with another individual, the humanity of this is so important. Being able to share that with another family, another individual is so helpful and so important. So, I would say, reaching out and networking. Step one is being on a call like we're all on today, and listening and educating yourself to what updates there are in the field. Number two, get genetic testing. If you haven't had genetic testing, this is the new standard of care, and inherited retinal disease is actually Academy of Ophthalmology's new guidelines. They actually updated it to say, "It is now the standard of care to do genetic testing on patients with monogenetic disease," which we talked about is Stargardt disease. So, if you have not had genetic testing offered to you, ask. And at this point, your ophthalmologists or optometrists should've at least heard of it. They might not be able to be set up in their clinic to get you genetically tested that day, but they can get you referred to a site that can get that squared away for you, so you do need to pursue it and ask. But genetic should be done to confirm disease and also evaluate potential clinical trials. And number three, stay up to date. And these things change every month! We're activating new trials literally every week. At my site, I'm looking through new site surveys to look at investigator brochures and evaluate preclinical data and see if I think it's a good therapy and whether it's a Stargardt or another inherited retinal disease. It's a booming time right now for the development of new novel therapies for inherited retinal disease, and certainly, Stargardt is probably the most highly focused on because it is so prevalent, and the disease mechanism is so well understood. And always maintain hope. And adaptation—the human spirit and body is so amazing and able to adapt, and the psychology of adaptation is so important. I have people who are athletes in Paralympics and Paralympians and patients with Stargardt who have written books and done amazing things. So, nothing is out of reach,

and all things are possible. So, I think I would want to leave everybody with a note of hope and optimism and that we're really in an exciting time right now for novel therapies and research for Stargardt disease.

DR. PREETI SUBRAMANIAN: Wonderful. Thank you so much, Dr. Kay, for sharing so much about Stargardt disease and sharing all the promising research in the field with us today. To our listeners, I sincerely hope you found today's Chat helpful. Our next Macular Chat will be on Wednesday, October 30, and it's titled, "Taking Charge of Your Geographic Atrophy." Thank you, again, to our listeners for joining us today. This concludes today's Macular Chat.

Useful Resources and Key Terms

To access the resources below, please contact BrightFocus Foundation: (800) 437-2423 or visit us at www.BrightFocus.org. Available resources include—

- Macular Chats Archive
- *Healthy Living and Macular Degeneration: Tips to Protect Your Sight*
- Research funded by BrightFocus Foundation
- What is Stargardt Disease?
- Juvenile Macular Degeneration
- Possible Stargardt Disease Treatment Shows Promise

Other resources mentioned during the Chat include—

- Eye health organizations
    - Academy of Ophthalmology guidelines
    - Foundation Fighting Blindness
    - Research to Prevent Blindness (RPB)
    - Lighthouse for the Blind
- Suggested care provider types
    - Ophthalmologist
    - Retina specialist
    - Inherited retinal disease specialist

    - Low vision ophthalmologist
    - Genetic counseling
- Genetic registry and testing
    - My Retina Tracker
    - Invitae
- Trials, sponsors, and treatments
    - gildeuretinol, ALK-001 - Alkeus (trial sponsor)
    - Belite Bio (trial sponsor)
    - Nanoscope (trial sponsor)

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