

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 the Eye on the Cure podcast. I'm your host, Ben Shaberman with the Foundation Fighting Blindness. And I am excited for this episode to have as my guest Jami Kern, who is the chief development officer at Nacuity Pharmaceuticals, and they're a company which has a promising drug called NACA, and that's in a phase II clinical trial for people with Usher syndrome. And NACA holds promise for preserving vision in people with RP and Usher syndrome, and potentially other retinal conditions. And I'm really looking forward to taking somewhat of a deep dive into NACA and learning from Jami.

So Jami, welcome to the podcast.

Jami Kern:

Hi Ben. Thank you for having me.

Ben Shaberman:

It's our pleasure to have you. And just a little background on Jami. Prior to joining the Nacuity team, she spent 15 years leading clinical development and medical affairs at Alcon. She earned a BA in chemistry from Austin College, a PhD in biomedical science, biochemistry, and molecular biology from the UNT, or the University of Northern Texas Health Science Center, and an MBA from TCU's Neely School. So that's a great, impressive background.

So Jami, you spent 15 years in clinical development at Alcon. And you decided to take the leap to this startup company, really. So what inspired you to join Nacuity and tell us a little bit about your role there.

Jami Kern:

As you said, I've been a researcher in the ophthalmology space for over 20 years. And about five years ago I started to do some work with Nacuity as a consultant. And during that time I saw a few things that encouraged me to join their team full time.

So firstly, the Nacuity team is doing really interesting research and they're using it to address rare diseases that many larger companies are not willing to spend time and money on. And that was really interesting to me. So you may know that the CEO of Nacuity is the son of one of the founders of Alcon. So I share history with many of the members of the team at Nacuity, and importantly we share common work ethics and communication styles. We just want to get the job done and it's a really great fit from that perspective as well. And I think we work very well together.

Probably the most important to me though is the team's focus on the patients that they aim to serve. So I saw that immediately in the relationships that they have with other researchers, with patients themselves, with advocacy groups, and also with how they prioritize their time and their resources. So those things really encouraged me to take the leap, as you say, to a small biotech which is very different from a large company that I was very comfortable in for a long time. And I'm currently Nacuity's chief clinical officer, but of course, we're a very small team. There are only six of us, not all of those six are even full-time. And so we all wear multiple hats. We roll up our sleeves when something needs to be done, and that's something else I love about being part of the Nacuity team. So I'm really pleased to be in this space right now doing the work that we're doing.

Ben Shaberman:

That's great. And I think it's important that you mentioned all the folks that came over from Alcon because that's a really strong clinical development and ocular pedigree, if I can call it that. So yeah, Nacuity is a small startup company, but you're bringing a lot of experience, expertise, knowledge in the ocular disease space, in the clinical development space into this environment. I think that's really important and valuable.

Jami Kern:

Absolutely.

Ben Shaberman:

So to quickly summarize what NACA, this new molecule does is it mitigates oxidative stress. And we're going to talk more about that. Oxidative stress plays a big role in vision loss in the retina for people with retinal diseases. But we hear a lot about oxidative stress through media, through a lot of health communications, the health media. What exactly is oxidative stress? Tell us a little more about what happens in oxidative stress.

Jami Kern:

So we have free radicals in our bodies. They're chemicals like reactive oxygen species, and they're highly volatile. They interact with things in your body and they can damage cells because they can harm your proteins or your lipids, even your DNA. Under normal circumstances, your body keeps these molecules at an appropriate level and they play an important physiological role. So for example, free radicals and reactive oxygen species are important in cell signaling. So how the cell talks to each other, how they play an important role in our immune system to protect us. And they also are generated when the body uses oxygen. As long as they're under the right balance, they're exactly doing what they're supposed to be doing.

But oxidative stress appears when there's an imbalance, and free radicals form faster than the body is able to use and clear them. So the increase in free radicals allows these little molecules to roll around and wreak havoc in your tissue, then ultimately it causes tissue damage. There's a large body of evidence linking oxidative stress with different degrees of importance to the onset or the progression of several diseases. Things like cancer, diabetes, metabolic disorders, neurological diseases, even cardiovascular disease. Oxidative stress plays a role in all of these.

It also can cause tissue damage in the retina, and that's really where we are focused at the moment, just as it does in these other tissues. In fact, in rod-cone dystrophy is like RP, retinitis pigmentosa, oxidative damage that results from oxygen free radicals is considered to be a major contributor to the death of the cones in that disease.

Ben Shaberman:

Got it. So what actually causes this imbalance where you have too many free radicals? Is it because cells are less able to process oxygen properly? Am I saying that correctly?

Jami Kern:

Well, when you're talking about RP, retinitis pigmentosa, it's caused by different genetic mutations. So those result in the death of the rod photoreceptor cells, and then we see a gradual death of cone cells after that. With the death of the rod photoreceptors, the oxygen consumption in that tissue, the

amount of oxygen that's used by the cells is really reduced because all those rod cells that have died aren't using the oxygen that's normally there.

And so you have super high levels of oxygen in the outer retina, and that produces reactive oxygen species that are really high level. So as the rods continue to die because of these genetic anomalies, you get more and more cumulation of these reactive oxygen species and those go on then to have an effect on the cone cells, which we know over time we lose as well.

Ben Shaberman:

Got it. Thanks for that explanation.

Jami Kern:

Sure.

Ben Shaberman:

About what actually happens in the retina, why oxidative stress occurs. So Nacuity was actually formed specifically to develop this drug called NACA or the longer name is N-Acetylcysteine amide. What inspired Nacuity to develop this drug?

Jami Kern:

So NAC, N-acetylcysteine is a really well-known antioxidant. It's been around forever. It's been approved in most countries for over 50 years. And it's used as an antidote for things like acetaminophen overdose. It's used as an anti mucolytic in patients that have respiratory conditions where they have thick excessive mucus, to thin that out. Used for a lot of different things.

But Peter Campochiaro and his lab were researching NAC in the retina. And they showed that NAC protects against retinal cell death induced by oxidative stress in both their cell and their animal models of retinitis pigmentosa. That's really interesting.

NACA which is the molecule that Nacuity has, with that, it's just a simple change to the chemical structure. So instead of N-acetylcysteine, you have N-acetylcysteine amide or the amide form of NAC. And the amide is used to make the molecule more lipophilic and more bioavailable. And I can speak to that in a minute.

But we worked with Dr. Campochiaro and his team to test NACA in their retinitis pigmentosa models. And what we found was that NACA was about three times more effective than NAC in protecting the structure and the function of those retinal cells in RP models. And so from those results, we were very excited to continue NACA development and have moved through toxicology studies and into the clinic as we're going to talk about.

Ben Shaberman:

Right, thanks for that great explanation of the difference between NAC and NACA. And I'll add for our listeners that the Foundation did fund Peter Campochiaro for that lab research for the original molecule, NAC. And then we are now funding the company Nacuity through our RD fund, our venture philanthropy fund for the phase II clinical trial that's underway.

And who do you think, Jami, NAC should benefit? You already have a clinical trial underway for people with Usher syndrome. Who else do you think may benefit from this treatment?

Jami Kern:

Yeah, so one of the really neat things about NACA is that it's a gene agnostic approach. Most of the other approaches that are in clinical trials right now are gene specific, which are also really great approaches, but that limits their applicability to the number of people that it can help. So that means that anyone diagnosed with RP might benefit from NACA regardless of the genetic anomaly that's causing the disease.

Ben Shaberman:

Got it. And so you launched the phase II trial for people with Usher syndrome in Australia. So a couple of questions about that. Why did you target people with Usher syndrome specifically, and what are you hoping to see from the trial? When do you think you might get some results from that study?

Jami Kern:

Great question. So we've been conducting this study at four clinics in Australia since 2000. As everyone knows, clinical research during a global pandemic was really difficult. But we were really lucky to be in Australia where they were relatively isolated and we experienced less disruption due to COVID than other research centers around the world. We chose Usher syndrome patients because it helps us focus our original data. It creates less variability in the data. So the Usher syndrome community really had not a lot going on, and we were hoping that this might help preserve vision for those patients.

Even though it's gene agnostic, you might expect that NACA could behave differently in different patient populations. And for sure, different diseases progress at different rate. So by keeping it to a very specific group of patients, we're hoping that we have a better chance to show that our drug is working in a smaller group of patients. So that's really why Usher.

Our study is following participants for two years, Usher syndrome patients. They can have Usher of any type, and as long as they meet the other inclusion criteria. And we're really aiming to demonstrate the safety of NACA tablets taken orally. So these are tablets that are taken by mouth at doses of about 500 milligrams a day. We had some shorter term clinical study data, but this is the first time that we're looking at long-term chronic use of the drugs. So we wanted to ensure that it's safe.

And then of course we want to show that it can delay progression of vision loss in patients with RP associated with the Usher syndrome. We're looking at both retinal structure and function in the hopes of seeing it slow down or maybe even stop disease progression if the patient's taking NACA. So that's the hope.

Ben Shaberman:

And of course that would be wonderful if you could significantly slow disease progression. And so one thing I want to better understand, I know with N-acetylcysteine, the original molecule NAC, it's taken for lack of a better example, like Alka-Seltzer, right? You put the tablets in liquid and they fizz up. I think we call that an effervescent therapy, and then you drink it. Is NACA taken the same way?

Jami Kern:

No. So we actually have two forms that we've tested in the clinic for NACA. One is a liquid that we used early in our studies, but in this clinical study we have tablets. And so they're just pills that you take, regular sized tablets. At this point in this study, most participants are taking one tablet in the morning and one tablet in the evening. And one of the nice things about the NACA versus NAC is that because the amide increases the lipophilicity of NACA, which means that it can get into cells easier. It gives it better bioavailability, that means that more of the drug goes where we want it to go, or at least that's the hope.

And so with better bioavailability, the amount that the patient has to take in order to get a therapeutic effect should be less. So with better bioavailability, the amount a patient might need should be less. And practically that means that patients have to take fewer tablets and that they experience fewer side effects. So that's the hope with NACA.

Ben Shaberman:

I love that term you used. I learned a new word, lipophilicity.

Jami Kern:

Yes. Means it can go through the lipid barrier of a cell.

Ben Shaberman:

Right, right. You explain that well. And if I understand correctly because I was looking at clinicaltrials.gov, I think the amount of NAC that somebody would take is more than three milligrams. Oh, I'm sorry, three grams. It's a lot compared to what is it, the 500 milligrams that you would take with NACA?

Jami Kern:

That's right. And to be fair, this is our first clinical study and we're hoping that we're at the right therapeutic dose at 500 milligrams a day. We may not be at the optimal dose, but we think we're probably close based on the preclinical data that we have, especially comparing to NAC. But yeah, it's a significant decrease which should make it easier for patients both just easier to take over the course of the day and also hopefully have less side effects. Because the more drug you pump into your body often, the more side effects it goes other places and it creates other issues. So that's the idea.

Ben Shaberman:

Certainly. And so the goal of the phase II trial is to monitor people for about two years. And if I understand correctly, you hope to have a readout in the not too distant future. Is that correct?

Jami Kern:

Yep, we're very excited. So the first goal as I mentioned, was just showing the safety. So I want to talk a little bit about that because we already have some of that data. We did an interim analysis last year, amended our IND in the US with that data. So we see that the patients are having no real issues taking the tablets every day for over two years now. And the side effects reported have been minimal. So that's really great news. It gives us confidence that the dosing is safe. In fact as the first participants who started in September of 2020, we're starting to get close to their final study visit, so that was last September, they were going to be coming off the study after their two years on the study. They were asking if they could continue treatment.

So we amended the study protocol to expand it. We created basically a secondary protocol that they could join if they chose to do so. Perfectly voluntary. They could just finish the study and move on with life, or they could choose to stay on their assigned treatment for some more time while we finish the study. The response to the study expansion protocol has been incredible. I've been blown away. Every single participant who's completed their two-year limit to date, has decided to continue on the assigned treatment and continue with the study. It's really amazing.

And what that tells me is that the tablets are easy enough to take daily, that they're not having issues with that and that the participants are not experiencing major side effects that make the tablets hard to tolerate over time. Two really great signs and feedback already that gives us good confidence in the ability of this treatment to work for these patients.

But then as you say, beyond the safety data, we have an interim look at the efficacy data planned for later this year. We're probably going to have a look at it in September, is my guess. We're just doing the final counts on patient numbers in order to determine that. But in that assessment, we'll get the first look at how the drug is actually working for these patients, and if the study is appropriately powered with the right sample size in order to show what we want to show.

Ben Shaberman:

That's great. And safety, tolerability are paramount. I know everyone is always excited about efficacy, which is the end game, but you do need safety along the way and it's really [inaudible 00:18:55].

Jami Kern:

Absolutely.

Ben Shaberman:

That people are excited to keep taking it and are tolerating it so well. So you have this initial phase II readout for later in the year. And how many people will have been monitored at that point?

Jami Kern:

We just actually met our full enrollment at 48 subjects. There will be 48 subjects, maybe 49. We still have one in screening. And I committed to the sites that if they had anyone in screening, they could continue to enroll them. So we'll see. We may be at 49, but regardless, 48, 49, 50, somewhere around there, patients at different stages of the study. When we get to September, we should have over 20 patients who've already been on the treatment for at least two years. And we'll even have some at that point who've been on it an additional full year, so three years even. So we'll have great data to look at to give us a good idea of how things are moving.

Ben Shaberman:

Excellent. And then from there if the phase II results are encouraging, what do you think the next steps could be?

Jami Kern:

Good question. So of course it depends on what we see when we look at the data in September. But there are a couple of different things that could happen. If the data show that we're on the right track but that we need some more patients in this study to get to the statistical levels that we need, we already have an approved protocol in the US under our IND here to expand this current study into the US. So that's an option. And in fact, we already have an investigator. He's really keen to get started. We're just waiting to see if it makes sense to do that before we pull the trigger on that.

Alternatively, we could do a separate study, a separate confirmatory study. But either way as long as we see promise, we plan to expand the clinical development of the program in order to hopefully come to fruition with this treatment for these patients as quickly as possible.

Ben Shaberman:

Well, you have a lot of people out there hoping for the best, so our fingers are crossed. And one thing I'll emphasize that you mentioned at the beginning is that this is gene agnostic. And when you look at diseases like RP where there are more than 80 genes each of which when mutated can cause the disease or Usher syndrome, where I think there are at least 12 genes associated with the disease, to have something gene agnostic really provides a great opportunity to potentially benefit a lot of people. So we are all about the gene agnostic therapies at the Foundation, and we're excited about the progress you've made thus far.

Jami Kern:

Yeah, we're very optimistic and we're hoping along with all of our patients and everyone else that this work for them. We really hope that it does.

Ben Shaberman:

Well, we're very pleased at the great work you've done thus far.

Jami, thank you so much for taking time out of your day to tell us a bit about Nacuity, and NACA, and oxidative stress. It's been interesting. It's been fun. I learned a few things. I'm sure our listeners have learned a few things. So thank you for, again, joining us.

Jami Kern:

Ben, thanks so much for the opportunity to talk. It was great to talk with you today and I look forward to hopefully sharing positive news in the future.

Ben Shaberman:

And thank you, Jami. And thank you to our listeners for tuning in to another episode of Eye on the Cure. Stay tuned for our next episode.

Speaker 1:

This has been Eye on the Cure. To help us win the fight, please donate at foundationfightingblindness.org.