

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 am your host Ben Shaberman with the Foundation Fighting Blindness. And I am pleased for this episode to have as my guest, Dr. Kenji Fujita. He's the Chief Medical Officer at Atsena Therapeutics and Atsena is a company excitingly developing gene therapies for retinal diseases including LCA1 or Leber Congenital Amaurosis type one, which is caused by mutations in the gene GUCY2D. And that's doing well. We'll talk more about that.

And they're also developing gene therapies for X-linked Retinoschisis and Usher Syndrome type 1B. And it's important for our listeners to know that the foundation has invested in Atsena through our RD Fund, our Venture Philanthropy Fund. So excited about Atsena's work. And Kenji we're excited to have you on the podcast. Welcome.

Kenji Fujita:

Thanks for having me Ben.

Ben Shaberman:

And you are relatively new to Atsena. How long have you been with the company now?

Kenji Fujita:

Well, we're a new company, so I've been with the company for about a year and a half now.

Ben Shaberman:

Oh, okay. So longer than I knew. That's great. And a little background on Kenji. He is an MD. He's an internist and cardiologist with more than 20 years of experience in academic medicine and industry. And his experience spans preclinical to post-marketing research across a wide range of disease areas in therapeutic platforms. And throughout his career, Dr. Fujita has led five successful regulatory filings. So you've helped get five products across the finish line. That's pretty cool.

Academically, Kenji has completed a residency in internal medicine and a fellowship at cardiology at Columbia and is board certified in both specialties and Kenji holds an MD from Harvard Medical School, a bachelor's degree, summa cum laude in biochemical sciences from Harvard College as well. That's impressive. So to start off, Kenji, you have a really strong background in cardiology and internal medicine. What brought you into ophthalmology and the retina?

Kenji Fujita:

So I was in a medical program called HST, which was designed to combine traditional medical education with research. So I did a lot of research during my medical school years and residency years. I spent a year during medical school doing research in ophthalmology molecular biology lab where I did research on the cellular and molecular impact of diabetes on the retina. And that research really left a deep impression on me.

Ben Shaberman:

That's cool. So you've been with Atsena for a year and a half. Have you had different roles at Atsena? I know now you're Chief Medical Officer, did you come in at that role?

Kenji Fujita:

Yes I did. So I've been the chief medical officer from the beginning and in my role as Chief Medical Officer, I oversee all activities that support human trials. So the bulk of that is clinical development, but also includes operations, regulatory affairs, safety, biostatistics, and medical writing. So a lot of pieces going into getting a drug approved.

Ben Shaberman:

Right. And it's exciting obviously with the LCA1 clinical trial and a couple other emerging therapies, gene therapies moving toward the clinic. I'm sure that's keeping you very busy.

Kenji Fujita:

Yeah, yeah. I mean I've been interested in gene therapy for a long time. Just looking at the trajectory of my career. I started off in small molecules, then moved to large biologics, then move to RNA interference, which is getting closer to gene therapy. And finally here I am in a company that delivers healthy genes to patients. And I think the reason why I've been so interested in this, is that current note traditional therapies really treat the downstream effects of defective genes, whereas gene therapy goes right to the source and offers potential cure.

So I think it really is the wave of the future and we've learned a lot of lessons over the past couple of decades and I think we're at the dawn of a golden era where all those lessons are coming to fruition and we're going to start to see a lot of new therapies come over the finish line.

Ben Shaberman:

Right. I think that's a really good point about gene therapy, getting at the root of the issue in our retinal diseases, they're virtually all caused by mutations in a single gene. And if you can address that gene, replace it, augment it, then you have a good opportunity to save and in some cases restore vision. And we often think of gene therapy, I know I'm explaining it to our patients and families. We just say, "Hey, we're replacing or augmenting the defective gene with a good gene. But gene therapy has a lot of complexity to it."

And I'd like to just talk about some of the elements of a gene therapy. What are the different components and what goes into developing a gene therapy? And I know the one component we talk a lot about is the capsid, like the container. Can you talk about what a capsid is?

Kenji Fujita:

Let's start at the basics. So a gene is a sequence of DNA which encodes proteins-

Ben Shaberman:

Right.

Kenji Fujita:

... and these proteins in turn affect the structure and function of cells, tissues, and organs. And many diseases stem from defects in these genes which can result in a loss of expression of a functional protein

or the production of proteins that are actually toxic. So the first challenge in gene therapy is to deliver a copy of a good gene into the cell to replace or silence the gene that's causing the disease.

So one of the number of different technologies that's been developed to do this, the leading one is to use a modified virus as the vehicle to get the genetic material into the cell so that's what the capsid is. It's basically the shell of a virus that's been modified, so in itself can't cause disease and can't replicate.

Ben Shaberman:

Right. So again, the capsid is the container?

Kenji Fujita:

Right.

Ben Shaberman:

Sometimes I like to use the analogy of the virus is really this vast container system, container system like ship with all these containers carrying cargo, so-

Kenji Fujita:

Right. And all capsid aren't created equal. So it's really one of the big challenges is to choose the right capsid. The ideal capsid is one that is not going to trigger an immune response. Because remember these were originally viruses and the body recognizes viruses as foreign and can mount an immune response, which can dampen the effect of the therapy as well as creating safety risks. So you need capsid that are not going to trigger a response. And the other thing is you need a capsid that's going to target the right cells and that's going to deliver sufficient copies of the gene to the tissue of interest.

Ben Shaberman:

Right, right. Good points. So another component of a gene therapy that's really important is the promoter. And I sometimes think of it as the gas pedal for the gene therapy and I'm sure that's oversimplifying what a promoter is. Can you talk more about what a promoter does?

Kenji Fujita:

Yeah, so a promoter is a sequence of DNA which is next to the part of the DNA that actually gives the instructions for making the protein. And as you put it, I think a gas pedal is a good way to describe it. There are a different mechanism within the cell that can either activate or silence expression of the gene acting through the promoter.

And one key aspect of promoters is that different promoters are active in different types of cells. So in retinal gene therapy, we use a promoter that's specific to the retinal cells so that even if the capsid were to escape or to infect other cells in the body, the gene would not be expressed there, only expressed in the cells of the retina.

Ben Shaberman:

Right. So promoters can be cells specific, which-

Kenji Fujita:

Correct.

Ben Shaberman:

... is important. So another aspect to gene therapy that I think is really important to discuss is how it's injected into the retina. And there are basically three ways that gene therapies are injected these days. There's the subretinal injection, which of course goes underneath the retina, intravitreal into the vitreous. And an emerging approach, at least it's being studied a little more than it was previously, is suprachoroidal. Can we talk about these different approaches first starting with subretinal, what that involves?

Kenji Fujita:

Sure. I think the good order to go is the most direct, at least direct. So subretinal is the most direct. That's where you take a catheter, you use it to introduce a small hole into the retina and inject the material containing the capsids underneath the surface of the retina. And so you get direct contact of the capsid with the cells that you're trying to transduce. And that's the approach that we use, less direct but easier, technically easier is intravitreal.

So subretinal injection requires a high degree of skill and expertise, which is not available everywhere. Intravitreal injections are technically much simpler. What this involves is, introducing the catheter into the globe of the eye, just into the corner posterior at the back part of the eye and injecting the capsid into that fluid, hoping that it will come in contact with and transduce the retinal cells, the couple of problems.

So the advantage of intravitreal is that it's easier and it's technically less demanding. The issues are a couple of issues. One is that the vitreous part of the eye, that back part of the eye is more immunogenic than the retina. So foreign materials injected there are more likely to trigger an immune response than when it's more surgically delivered underneath the retina. The other issue is that there are multiple layers of cells in the retina and usually the target cells are the photoreceptors. These are the cells that actually convert light into chemical process. Those are buried under a couple of other layers.

So by injecting the capsid into the vitreous, you're not directly touching the photoreceptors. And what we found in some recent clinical studies, is that we're probably not actually getting the vector where you need to get it. And then finally the suprachoroidal, that's the most recent and least invasive, that involves actually going outside of the eye into a blood vessel rich layer called the choroid, which nourishes the retina. So that's been used for a number of small molecules that can just be carried in the bloodstream to the retina, but there hasn't really been any success to date in using that approach to deliver capsid which are really large molecules.

Ben Shaberman:

Right, right. Thanks for that great overview. There are pros and cons to each approach, but I think the subretinal approach which you're using, the key advantage there is, you're getting the therapy so close to the cells that need it, so you have the best chance of efficacy there. With that said, you're actually causing a detachment of the retina because you're lifting the retina up with the tiny drop of fluid that's injected, so that can be a little tenuous with a fragile retina. But in terms of potential efficacy, definitely subretinal has its advantages.

Kenji Fujita:

Yeah. So one of the technologies that we're developing is what we call a spreading vector. So most current conventional vectors are injected into under the retina, and as you pointed out, you have to create a separation or a little bubble. And that bubble only occupies a fraction of the retina. So with

conventional capsid, they only deliver the gene to the cells that are right adjacent to that bubble. We're developing a capsid that can actually spread laterally throughout the retina, so you can inject it pretty much anywhere in the retina.

And you can do multiple small injections and then count on the spreading characteristic of that capsid to blanket the entire surface of the retina. So we're very excited about this technology. We've shown some really promising results in animals and we will have our first and human experience with that technology with our XLR5 Program, which is coming up early next year.

Ben Shaberman:

Right, right. Yeah, we're very excited about the spreading capsid technology. And of course you have an opportunity with that to reach more cells-

Kenji Fujita:

Right.

Ben Shaberman:

... in the retina. Would you say it's safer too?

Kenji Fujita:

It's definitely safer because the most valuable cells in the retina are the ones in the center of the retina. And so in order to deliver gene to those cells, you need to physically manipulate that part of the retina with, and as you pointed out, the surgical risk associated with that, the spreading vector allows us to inject into less critical parts of the retina, on the outskirts if you will, of the retina while counting on the spreading characteristic of the capsid to so seep towards the center of the retina.

And deliver gene to those cells without disturbing the structure or the anatomy in that area. So we've shown an animal studies that we're able to get really robust expression throughout the entire retina with this spreading vector and actually even higher expression in the area that's injected than we have seen with more conventional vectors.

Ben Shaberman:

Very exciting technology. And a nod to your colleague Shannon Boye, who is a real pioneer and innovator in gene therapy design, who her lab came up with that. So a question that I often get from patients and families about gene therapy is what can they expect? Now, obviously in a clinical trial we're still learning about what a treatment, whether it's a gene therapy or something else, what the potential for that therapy is? But can you talk about what people might expect in terms of whether something might save vision or restore vision if a gene therapy might do one or both?

Kenji Fujita:

It really depends on the nature of the disease. Every inherited retinal disease has a different clinical course. We think the ideal case or the diseases where while there's loss of function of the cells, the structure and the viability of the cells is maintained. And in that type of a patient, we think that we can actually restore vision. And that's the case with LCA1, there are other diseases that tend to be more rapidly degenerative and in those diseases the focus might be more on preservation. In other words, by restoring the gene, halting the process of cell destruction. So-

Ben Shaberman:

Right.

Kenji Fujita:

... yeah. Overall, really, I can't give a general answer to that. It really depends on the disease.

Ben Shaberman:

Right. But I think the important takeaway is in some cases the gene therapy might be more about just preserving vision. And in other cases, restoration.

Kenji Fujita:

Right. So there is one gene therapy that's been approved for inherited retinal disease that's looks turnout, that was developed by Spark and they actually showed improvements in vision. And the way they measured vision was through a patient's ability to navigate a maze under different light conditions. They demonstrated that after treatment, patients were able to navigate the maze safely and accurately under lower light conditions than they were able to do before. So that correlates with better ability to navigate around one's home, around one's neighborhood under a wider variety of conditions.

Ben Shaberman:

Right, right. And that's a great segue into your LCA1 trial, the GUCY2D trial. That trial has been underway for I think, at least a year. Can you tell us about the results you recently reported?

Kenji Fujita:

Yeah, so we're now coming in on actually three years on our initial patients.

Ben Shaberman:

Oh really?

Kenji Fujita:

Yeah. So we announced, we had our first announcement of interim results. This was a Phase one two multicenter trial. We announced our interim results at the American Academy Ophthalmology on October 1st. And so just if I can give a brief overview of the trial, we enrolled 15 patients between ages 12 and 76, which is a pretty wide age range. Patients received a subretinal injection of a capsid containing the GUCY2D gene, which is the gene that's defective in LCA1.

We tested three increasing doses in three groups of patients and took the most promising dose, which turns out to have been the high dose into an expansion phase where we tested it in six additional patients. So as I mentioned, we've now had almost three years of experience on our initial patient and close to six months of experience on our most recently dose patient. We've shown really excellent safety.

There have been no serious adverse events related to the therapy, very minimal inflammation in terms of the efficacy. So I mentioned the maze. We did test the maze in five of our later patients. And we were able to show improvements in those patients. So of those five, all of them after therapy at either a perfect score or an improvement to a level that the FDA would consider to be clinically meaningful.

Ben Shaberman:

That's great. Just awesome. And obviously this is a form of LCA, which is a pretty severe form of retinal disease.

Kenji Fujita:

Yeah.

Ben Shaberman:

So now you're working toward a phase three, the pivotal phase.

Kenji Fujita:

Yeah. That's right. So our plans are to... We will have one year of data on all of our patients, middle of next year. So the plan is to take the data from those patients, go have a meeting with the FDA to talk about what a phase three study would look like, and assuming that we continue to see the good safety and efficacy that we're seeing so far. We fully intend to go through with a phase three study, but we do first need to meet with the FDA just to come to some agreement on how that should be designed. And there a lot of logistical things that we need to set up in order to implement the trial.

Ben Shaberman:

Sure, sure. Well, congratulations on the phase one, two results and good luck in moving toward the phase three. I think you're-

Kenji Fujita:

Thank you. We're very excited about it.

Ben Shaberman:

... doing great things in that program. So another program, and you mentioned it briefly earlier, is your XLRS X-linked retinoschisis gene therapy plants. And you mentioned that will be the first gene therapy where you will use the spreading factor and XLRS is a pretty difficult retinal condition because the layers of the retina split. And can you just tell us where that program is at and when you hope to be in a clinical trial?

Kenji Fujita:

Yeah, so we've generated some really promising animal data there and we're now in the process of finishing up those studies, finishing up manufacturing of the vector and submitting what's called an IND in the United States or CTA in Europe to get clearance to proceed with the study. And we are planning to start dosing patients early next year.

Ben Shaberman:

That's awesome. I know we have a lot of XLRS families out there who are excited about the progress you're making there. And then your other program that you're moving toward the clinic is for Usher 1B and Usher 1B presents a bit of a challenge because the gene is big.

Kenji Fujita:

Right.

Ben Shaberman:

Can you talk about how you're addressing that?

Kenji Fujita:

Yeah, so all the capsid that we use have a limitation in the size of the gene that they can carry. And as you point out, Usher 1B is an example. It's caused by a gene called MYO7A, which is too large to fit into a single capsid. So the approach we've designed is to split the gene into two parts, package it into two separate capsids, and to deliver the capsids simultaneously to the cell.

And the two parts are designed in such a way that once they're delivered to the cell, they recombine to form the full length gene and then express the protein in the cell. We've seen some really promising results from animal studies showing that this approach is working. And so we're really excited about testing this new approach in our clinical study.

Ben Shaberman:

Excellent. I can see all these programs are very exciting and congratulations on the success in your LCA1 Program. It's-

Kenji Fujita:

Thank you.

Ben Shaberman:

... very exciting times. Kenji, thank you for taking time out of your busy day. Clearly, these projects are keeping you hopping. I am sure. It's been very informative, enjoyable, and good luck in moving these forward.

Kenji Fujita:

Thank you very much. It's been a pleasure speaking with you, and thank you for having me.

Ben Shaberman:

My pleasure. And thank you as always to our Eye on the Cure Podcast listeners, and stay tuned for our next episode. Bye-bye.

Speaker 1:

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