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 to the Eye on the Cure podcast. I am your host, Ben Shaberman with the Foundation Fighting Blindness. And I'm excited about this episode because we're going to be talking about cell-based therapies, specifically state-of-the-art manufacturing of cell-based therapies, a very important topic. And my guest today is Marinna Madrid. She is co-founder at Cellino, which is an up and coming biotech company, building the next generation of cell-based tissues and therapies with a proprietary platform technology. So welcome to the podcast, Marinna.

Marinna Madrid:

Thank you so much. I appreciate it. Thanks for the opportunity.

Ben Shaberman:

We appreciate it as well. And listeners, Marinna's first name is spelled with two Ns, M A R I N N A, so if you want to Google her after you're done listening, which I'm sure you will, that's how you spell her first name, Marinna Madrid. So a little bit about Marinna before we get started in the conversation. She has an impressive background. She received her PhD and Master of Arts in applied physics from Harvard where she co-invented laser based intracellular delivery techniques. Those sound very cool. She received her Bachelor of science and biophysics from the University of California Los Angeles after transferring from Riverside Community College. She's the recipient of the Harvard Graduate Prize Fellowship, the Catalyst Accelerator grant from Harvard Medical School and is on the Forbes 30 under 30, 2019 list for healthcare. And Marinna has several patents, peer review publications, and wrote the first review paper on autologous IPSC based therapies.

And listeners, we're going to talk about some of those terms, concepts in a moment. I know I just threw some technical stuff at you. I want to add that Marinna is also passionate about access to education and the role the community college system plays in providing upward mobility for historically disadvantaged groups. And we're going to talk about that toward the end of our discussion. So to start off, Marinna, you received your PhD in physics and in the process, again, you co-invented a laser to, "poke holes in cells". So tell us about that. What are the applications for such a technology?

Marinna Madrid:

There are a ton of applications for lasers in biology and medicine. There's some that are very familiar to everyone, LASIK eye surgery. The reason why lasers are so useful in so many health applications is because one, they're very precise. You can make changes at the single cell level. It's much more precise than, say, using a knife or a scalpel during surgery. That's why lasers are used during LASIK eye surgery, but also it's a very sterile mechanism. So when you're doing anything that involves a surgical process or generating cells for a therapy, you want all of your procedures to be as sterile as possible. When you're performing manual operations with your hands or your instruments, it's more difficult to keep those sterile than it is when you're using light, essentially. When we first co-invented the laser technique in our PhDs, it was myself and my co-founder, Nabiha Sakalyen, she's a CEO at Cellino.

Originally we were focused on intracellular delivery, so we were using the lasers to poke holes in cells to deliver cargos into cells. And so you can imagine a lot of folks have heard about gene editing or gene

therapies. In order to perform gene editing, you need to be able to deliver a gene editing tool into a cell, but it's hard to get things into cells. The cells have a membrane and it's designed to be very selective about what it lets inside. And so what we were doing with the laser is essentially poking holes in that membrane, but the holes were temporary, so cargo could be delivered into the cells before the holes healed up on their own. And this is what we were using the laser for initially. When we co-founded Cellino, we started exploring other applications of the laser. And so this is something that I've always found as kind of interesting about building a company based off of a technology that you've built in your PhD.

It sometimes feels like doing things backwards, like the forward correct way to build a company would be to identify a problem, figure out the best solution for that problem. But when you're coming out of a PhD, you have a solution or a technology that you've developed and you think you know what the right problem is. But as a grad student, really you know the problem to the level of being able to write an introductory section in a paper, you haven't really done proper market research. And so it was interesting because when we built the startup company, we spent a good period of time just engaging with all of the potential cell therapy developers that we could.

And what we learned is that they were really interested in just killing bad cells. So we would talk to them about using the laser to deliver cargos into cells, and they would ask us, can you use the laser to just kill off the cells I don't like? And we were like, yeah, that's actually a much easier problem from a laser perspective. Intracellular delivery is pretty complex. Killing cells with a laser is not, it's a much simpler laser physics problem. So these days we're mostly using the laser to kill off bad cells during a cell therapy manufacturing process.

Ben Shaberman:

That's really cool. So you developed this laser without really knowing exactly what you were going to use it for, what the applications were?

Marinna Madrid:

We had an idea for an application which was intracellular delivery, and it just turned out that that application didn't have as much need or demand in the market as this other application. And we were in the physics department, but we were collaborating with many of the biologists at Harvard. There were a lot of opportunities to collaborate. We collaborated with George Church, who is a well known geneticist and Derrick Rossi who is well known for co-founding Moderna. And so with them, we were doing these intracellular delivery experiments. That's what was interesting at the time. But then once we explored, we realized that there's a lot of opportunity to improve processes and cell therapy manufacturing, and one of the processes that needs to be improved is just removing the unwanted cells.

Ben Shaberman:

Got it. Got it. It's so impressive you were doing this while you were still working on your PhD. That's very impressive. So you mentioned Cellino, the company that you and your colleague created and Cellino manufactures cell-based therapies. And I know you're really focused on induced pluripotent stem cells. Can you tell our listeners what these are, these IPSC?

Marinna Madrid:

Right. So first I'll talk about stem cells. Stem cells are special because they have the code within them to become any cell type in the human body. So let's say, you have retinal cells in your eye, your retinal cells

can't easily become a different cell. It would be difficult for your retinal cell to become a dopaminergic neuron or a cell that you find in the layer of your skin. But stem cells, they're almost starting at an earlier stage. They still have the potential to become any cell type. From a stem cell, you could create retinal cells or you could create dopaminergic neurons or you could create cells that are found in skin. What induced pluripotent stem cells means is it's a special type of stem cell where you can actually create it from your own cells. So back in the days, stem cells used to be derived from embryonic sources, so that's the term embryonic stem cells.

And there was a lot of controversy around that warranted or not. And so one of the answers to that controversy was to figure out, okay, well how do we make stem cells using cells found in our own body? So with induced pluripotent stem cells, it's a really powerful tool because what you can do is you can take cells from your body. So I could take a sample of your blood, you could take cells from your skin, from a little skin biopsy. You could even use cells that you find in hair follicles, just taking out a follicle of hair. You can use cells found in urine. But what you can do is you can almost rewind the state of these cells back to a point where they are stem cell-like, and that's called induced pluripotent stem cells. And so what you could do with those induced pluripotent stem cells that now came from your body is you can use them to create therapeutic cell types.

There are a lot of diseases that happen because the cells in your body die off and they don't regenerate. So age-related macular degeneration is a really good example of this. It's retinal pigment epithelial cells in the back of your eye die off, your body can't replace them. So the idea with these induced pluripotent stem cells is to be able to take, let's say a sample of your blood or a small skin biopsy, use the cells in those samples to create induced pluripotent stem cells. Then in the second step, use those induced pluripotent stem cells to create, let's say, therapeutic retinal pigment epithelial cells, and essentially use that as a therapy to replenish the cells that your body have lost.

Ben Shaberman:

Right. And you are actually, if I understand correctly, involved in manufacturing for a trial of RPE cells. Isn't that correct?

Marinna Madrid:

We have a collaboration ongoing with Kapil Bharti at the NIH. And so what he's done, he's developed this IPSC derived retinal pig epithelial cell product for age related macular degeneration. Their IND has already been approved. They've already transplanted for their first patient, which was a huge, huge milestone in the field. This is the first IND approved for a personalized IPSC cell therapy in the US. He's manufacturing those cells manually right now. And the challenge with that is that manufacturing them manually, it's almost an artisanal process. It depends on a highly, highly skilled individual to make these cells. And it's a very long process. And so that process is difficult to scale.

So the reason that we're collaborating is because long term we would like to be able to do that clinical grade manufacturing, but using the Cellino platform. And so where we're at right now, we've built an automated R&D grade platform, so a research and development grade. So we're able to develop processes. They're not yet at the stage where they can be used in a clinical trial. So in parallel to having that automated R&D process development ongoing, we are building a clinical grade system to be able to do clinical grade manufacturing.

Ben Shaberman:

Got it. So you want to be a manufacturing source for people like Kapil Bharti and other investigators that are running clinical trials of therapies or actually developing therapies?

Marinna Madrid:

Exactly. Our goal is to enable the field. There are a lot of cell therapy developers working on very important therapeutic products that could alleviate just so much patient suffering. But if we're not able to manufacture them in a scalable way, those therapies won't get to the patients who need them. So that's where Cellino comes in.

Ben Shaberman:

Exactly. And you can do that much more quickly and I presume cost efficiently.

Marinna Madrid:

Exactly. So let's say in a manual process, you have one highly skilled operator generating or manufacturing clinical grade cell products. One highly skilled operator might be able to handle a couple of patient doses at the same time, and the process might take six to nine months. So to only be able to get out one to two patient doses in six to nine months, that's just not enough, especially for some patient populations. Some patient populations are massive, but with an automated approach to clinical grade manufacturing, you could in theory manufacture thousands of patient doses at the same time.

Ben Shaberman:

Right. Now, earlier I used the word autologous to describe the induced pluripotent stem cells that you're developing. Explain why autologous cells are so attractive. What does that mean, autologous?

Marinna Madrid:

So autologous is, when folks talk about autologous, you also kind of have to talk about allogeneic. In general, there are two approaches to developing these cell therapies. There's autologous and allogeneic. The allogeneic approach is much like donor transplants. Most folks are familiar with heart transplants or lung transplants. The way an allogeneic IPSC derived cell therapy works is that the IPSCs were derived from blood or from a skin sample of a healthy donor, not from the patient themselves. So the cell product that you're generating is similar to a donor transplant in the sense that the patient has to be matched to the donor. With an autologous approach, what you're doing is you're manufacturing the cells from the patient themselves. So from the patient you get, let's say blood cells or skin cells, you make IPSCs. Then let's say you make retinal pigment, epithelial cells, and then you transplant those cells back into the same patient.

And what's so attractive about the autologous approach is that because it's not essentially a transplant, because it's generated using your own cells, you don't have to undergo immune suppression. And immune suppression can be very, very challenging, particularly for certain populations of patients. But the other advantage is that we're able to treat a wider range of patients. If you have an allogeneic cell therapy or let's say a donor transplant, you can treat the patients who happen to be a match for that donor. But with the autologous approach, in theory, you could treat anyone who needs a therapy, not just the ones who happen to be a strong donor match.

I'm half Mexican, half Filipino. I would probably have a really hard time finding a donor match if I needed something like a lung transplant. So that's what's attractive about the autologous approach. The challenge with the autologous approach has always been the manufacturing. Because as you can

imagine with allogeneic, you can make one massive batch of therapeutic products at once, but with an autologous approach, you need to do the manufacturing over again for each and every single patient. So that's the problem that we're trying to solve.

Ben Shaberman:

That's very cool. Very cool. And we're excited because you are in the retina field, you're working with IPSC to make some retinal cells. What are some of the other applications that are on your radar screen?

Marinna Madrid:

So there are a ton of really exciting applications right now. We work through partnerships. So we're interested in engaging with anyone who's developing an autologous IPSC derived cell therapy, whose program we could enable. Retinal pigment epithelial cells are the ones that are furthest along in the clinic right now. There's another program that recently had an approved IND, and that was for heart failure or for congenital heart disease, excuse me. So cardiac cells. There's a lot of work going on in the Parkinson's space, developing dopaminergic neurons for Parkinson's. There's some really exciting work going on in the skin space. So developing skin grafts for patients suffering from epidermolysis bullosa, which is a rare disease. There's some exciting work happening in the muscular dystrophy space. So there's a company called Vita Therapeutics that's developing satellite cells or myogenic progenitors for a range of muscular dystrophies. So it's really any chronic degenerative disease that you could imagine could potentially be addressed by an autologous IPSC derived cell therapy approach.

Ben Shaberman:

That's great. So many important applications, and you can potentially manufacture cells for all of those. So what are the next steps for you and the company? What are some of your short-term goals? What are your long-term goals?

Marinna Madrid:

For the company, we are aiming to get to clinical grade manufacturing as quickly as we possibly can. That's our goal. We are right now at a stage where we have automated research grade process development work cells up and running. We've developed an automated reprogramming process to generate IPSCs at the R&D stage. And we are in the, I would say the design and early prototyping phase for two clinical grade systems that we're building. And so our goal is really to get to clinical grade manufacturing as quickly as possible.

For myself, I'm a co-founder and a chief product officer at Cellino. The co-founders all wear a lot of hats, so there's a lot that each of us are doing. What falls into my area of responsibility on the product management side is essentially engaging with experts in the space. And so this is why events like the Foundation for Fighting Blindness investing in Cure Summit is so important to me and so valuable for me to be able to attend is because a big part of my job is engaging with the cell therapy developers and making sure that we are building the right platform to solve the right problems that they're facing.

Ben Shaberman:

And it was great to have you at that event. And manufacturing isn't something that we at the foundation highlight very often. We're usually talking about the trials and moving the technology forward through lab studies, but manufacturing, especially a cell therapy is no small feat. And it's great to have a company like yours and the knowledge you bring to the table to really handle that important aspect of

getting therapies into trials and ultimately, hopefully through trials. So Marinna, at the beginning when I was going through your bio, I mentioned that you started out in a relatively humble way. You started out at Riverside Community College. Is that correct?

Marinna Madrid:

Yeah.

Ben Shaberman:

I would expect that's not the usual trajectory for people like yourself who are going on to get a PhD from Harvard and co-found a company. Can you talk about that journey and why that experience is so important to you?

Marinna Madrid:

I loved my time at community college. It was a really important time in my life. It's interesting, I actually started off in journalism in my undergrad career. This is so long ago. When I first graduated from high school and went to NYU to study journalism, and it was just a terrible, terrible fit for me. The school was a terrible fit, the city was a terrible fit. Journalism as a major was not a strong fit for me. I ended up dropping out in the middle of my first year and then moving back home and essentially starting over at community college.

And that's where I really discovered my love for science, my love for physics and math and biology. I had a couple of very, very supportive professors while I was there. And that's something that I really appreciated about the community college system is that the professors were very focused on teaching and engaging with students versus some of the four years, the really big four year universities are often more focused on research and then teaching is kind of something that you have to do on the side, but your main job is to lead a research group.

So I appreciated that about community college. The professors were very committed. I really found that I enjoyed and was good at physics and math and biology. And my professors there were the ones that encouraged me to transfer to UCLA to study what was technically biophysics. At the time, they didn't really have a biophysics department, so it was really a physics degree with a couple of biology and chemistry classes that were added to it.

Ben Shaberman:

That's such a great story and kudos to you for figuring out at such a young age what you like, what you didn't like, and taking action for that. Did you take a lot of science in high school?

Marinna Madrid:

I did well in my science classes, but it didn't really occur to me that that was a career path that I should consider. It's interesting, I was in AP physics and AP biology, and I remember my AP physics class because our teacher would do this interesting thing where he didn't tell anyone he was doing this at first, but he would seat folks according to their grade. So if you had the worst grade in the class, you would be in the front row and if you had the best grade in the class, you would be in the back row. And I was always in the back row. I was usually, I don't know, maybe second or third, not necessarily the best grade in the class, but always the second or third grade. And it took everyone a while to figure out how he was seating people.

So I did really well in my science classes, but I think at that point in my life, I was just exploring and just learning about what the different career opportunities could look like. And I would say even in grad school where you're pretty close to embarking on a more formal career path, I hadn't really thought about the startup path. So there's definitely been a pattern in my life of taking exciting opportunities as they came up, because I wouldn't have expected, to your point in high school, to necessarily go into science. But even in grad school, I wouldn't have expected to go down the entrepreneurial path.

Ben Shaberman:

Right. You've already had a fairly interesting journey and there's so much more that you can do. And on behalf of the foundation and our constituents, we're really excited that you're doing what you're doing and developing cell therapies because ultimately those provide a lot of hope for patients and families with these retinal conditions. And sounds like you might be able to help a lot of other areas of research and treatment development. So we look forward to hearing more from you in the near future. And thanks for taking time out of your, I'm sure very busy day to tell us about yourself and what you're doing.

Marinna Madrid:

Thank you so much. I appreciate it.

Ben Shaberman:

Thank you. And listeners, thanks as always for joining us at Eye on the Cure and we look forward to having you back for our next episode.

Speaker 1:

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