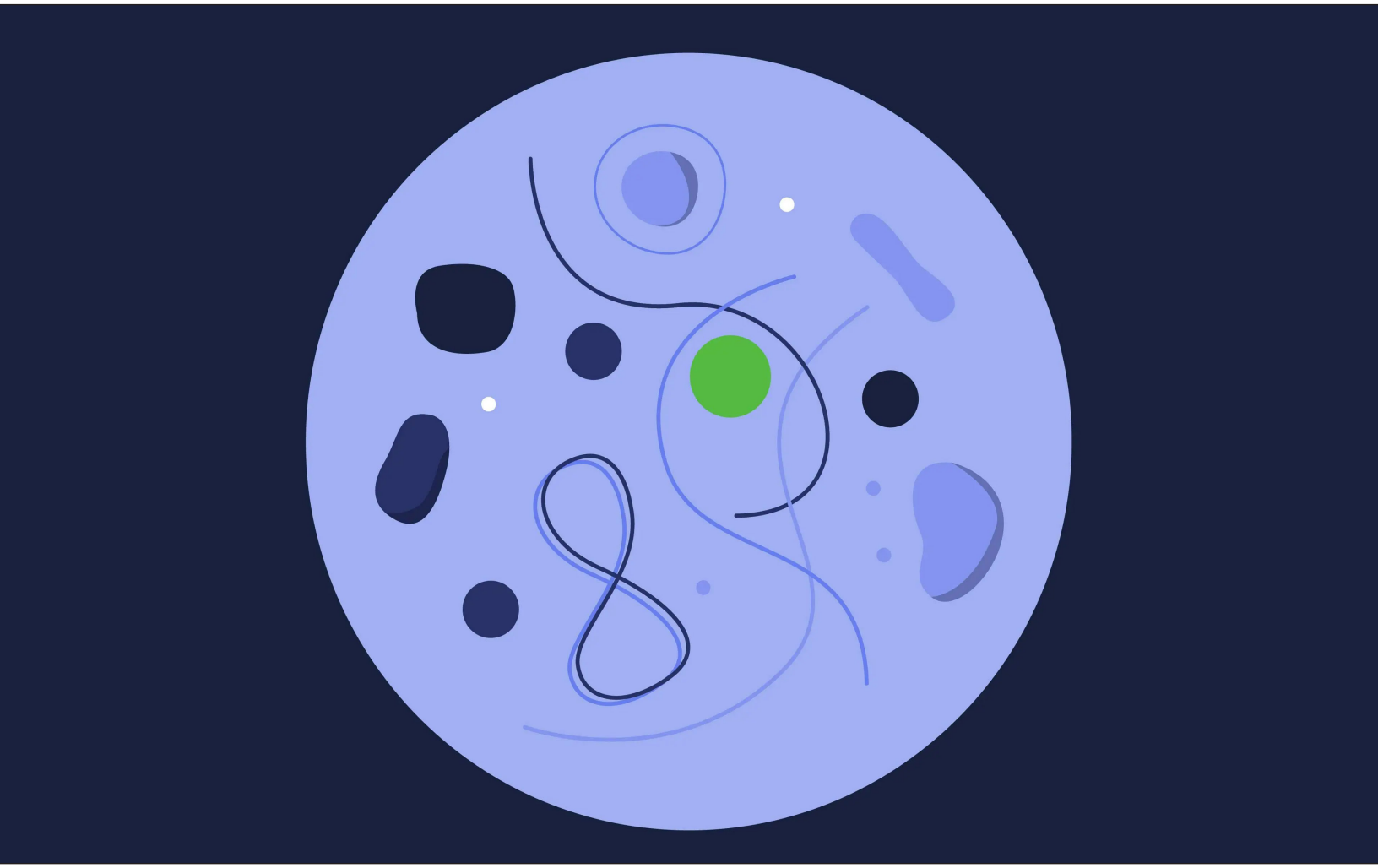
Revolutionizing RNA Therapeutics at Avidity Biosciences

"We could not just change the lives of people living with myotonic dystrophy, but we could actually change the whole RNA field. That's pretty ambitious," says Sarah Boyce, President and CEO of Avidity.



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Piratip Pratumsuwan: Welcome to the RTW Podcast. I'm your guest host, Piratip Pratumsuwan, Managing Director and Research Analyst on the RTW Asset Selection Team. Today I have the privilege of speaking to Sarah Boyce, president and CEO of Avidity Biosciences, a company that is revolutionizing delivery of RNA therapeutics for patients living with debilitating rare genetic conditions.

Over five years, Sarah transformed Avidity into a publicly traded leading genetic medicines company with three neuromuscular programs in late-stage clinical development. Before that, Sarah was the president of Akcea Therapeutics, where she led the commercialization of oligonucleotide therapies. Sarah, it's great to have you here in New York at RTW's headquarters. Thank you very much for crossing the country to join us today.

Sarah Boyce: Thank you. And it's a pleasure to be here.

Sarah Boyce
President and CEO of Avidity Biosciences

Avidity Biosciences: Pioneering RNA Therapeutics

Piratip Pratumsuwan: Our audience knows a lot about what you do, and what Avidity does. But can you tell us a little bit more about Avidity's value proposition?

Sarah Boyce: Yeah. At Avidity we're trying to do two things. One is to revolutionize the RNA space, and two is to make a profound impact in people's lives. We have cracked and solved the challenge and delivery of cells and tissue types outside of the liver.

Our first franchise is skeletal muscle where we now have three programs in the clinic. Two of those programs are for large, rare diseases, with population sizes of 30-40,000 people living with those diseases in the U.S.

We did it for myotonic dystrophy. We've done the same thing for FSHD, where you really show when you understand biology, you can engage a target with an siRNA and all the dots connect together from delivery to being able to engage your genetic target, to then being able to see functional changes.

We have a franchise in precision cardiology, and essentially, we are leading the field.

Joining Avidity: A Bold Decision

Piratip Pratumsuwan: We think that you are an optimistic person, and you're incredibly savvy. So, what convinced you to join the team and lead Avidity?

Sarah Boyce: There was part of me going, "Well, if they can deliver RNA to muscle cells; no one can do that." So, I was intrigued. At that point Avidity was private. We were 20-something people. Pre-clinical.

I met with Troy Wilson, and he was like, "Well, spend time with Art and see the data." Art and I had this very clandestine meeting, 'cause San Diego is a very small community. We were inside this golf club to make sure no one saw us, and he took me through the data.

And I was like, "So you're using an antibody. Like, why has no one thought of that? We all know antibodies are great at targeting certain cells."

I've worked at platform technology companies previously and know that one of the great things is when you understand your safety really well you know how to translate that from one program to another.

Piratip Pratumsuwan: What were some of the biggest concerns at the time?

Sarah Boyce: Most of my experience is in late-stage development, commercialization, and building global companies. Art tells the story of how he sat in his office, and he showed me the phase-one design and I'm like, "Yeah, but that's great. But what indication are we going for, and what's our target label, and what's gonna be our phase-three design, and what does that look like?"

I actually went home to my husband that afternoon and went, "I don't know how it's happened, but the perfect CEO role for me just presented itself in front of my feet." I'm incredibly grateful for Troy and Art for their faith and trust in me.

Navigating Challenges and Embracing Opportunities

Piratip Pratumsuwan: One of the things that stood out to me and others working to finance the company at the time, was the overhang of the Ionis data with their first-generation DM1 Oligo. That didn't quite pan out. Was that ever a consideration when taking this role?

Sarah Boyce: Certainly, the early data helped connect the dots. But the fundamental challenge was not being able to get enough RNA into the cell. And I remember feeling that what we had at Avidity was the answer. I also knew from that experience how incredible the myotonic dystrophy community is, how engaged they are, and the key opinion leaders around it.

I know how big the medical need is, and understanding what was the fundamental problem. The challenge was getting siRNAs into muscle cells which, on the non-human primate data, I mean, it was so clear.

It's perfect for an siRNA approach. And it didn't matter what muscle was looked at. It was just obvious, the potential here that we could open up the whole space.

Piratip Pratumsuwan: That said, drug development is never a straight line.

Sarah Boyce: Absolutely.

Piratip Pratumsuwan: You know (LAUGHTER) that super well. Following the first DM1 readout, you had the second readout. The FDA also surprised you with a partial clinical hold.

And a lot of people, said, "Look, the second data cut was less than convincing." It must've been an incredibly tough time for you and the team. Help us understand what was going through your mind at the time. And how did you navigate these challenges?

Sarah Boyce: There was no question in our mind at any point. We have a drug that can really help people. I've seen all sorts of things happen over my career. I've seen drugs get withdrawn. I've had CRLs.

Piratip Pratumsuwan: We know how to work through this. That, as a CEO, is probably where you get really tested and you show what you're made of.

Sarah Boyce: You've gotta lead a group of people. We also knew this is gonna take time. The data's gonna mature. Everyone's continuing to receive drug. We know what we're hearing from the sites.

And then it's engaging with the FDA to communicate, to advocate for patients, and to work that through. We saw the open-label extension data. We've negotiated a really efficient phase-three design. That study's now open and enrolling.

But in biotech, if you expect it to all be sunshine and roses, you're in the wrong business. Up until that point, the wind was in our sails. And it was almost a year we needed to have. It actually made us a stronger organization.

Piratip Pratumsuwan: A lot of people, perhaps investors included, were giving you unsolicited advice. Maybe give us a behind-the-scenes look at which ones you found the most useful.

Sarah Boyce: I'm a great believer in the importance of listening. And when someone gives you advice, and they're generous enough to do that, some of it you choose to take, some of it you choose not to. There was some advice around, "Oh, you know, you need to focus on other programs." And that we very much kept to our plan.

One person who was pretty important was one of our board members, Tamar Thompson, who is the head of market access and global policy at Alexion. She brought a different perspective around, "You need to start networking with some of the rare disease advocates within the FDA, within the biotech community." And that was great advice. In something like a partial clinical hold where a data readout isn't seen as well as you think it is, you have to also maintain your reputation. You can't be seen as not being clear or trying to hide things.

Piratip Pratumsuwan: I remember when the news broke, we went to work. We did all the research we could, and we felt pretty comfortable talking to you as well.

Sarah Boyce: We went so deep. I mean--

Piratip Pratumsuwan: I think we went pretty deep together.

Sarah Boyce: We did. (LAUGH) We dove in. We had every advisor you could possibly think of from different areas of expertise to make sure that we did. And you see it in the way we do our science. We always go really, really deep.

Piratip Pratumsuwan: You mentioned the advice from your board member about working with the advocacy group, understanding the disease in a deep way. And that led you to get vHOT as a primary end point for your phase-three trial. That was a huge and value inflection point for Avidity as well. So, congratulations.

Sarah Boyce: Thank you.

Piratip Pratumsuwan: How would you describe the direction of the FDA on the efficient registration path now for not just your disease, but many?

Sarah Boyce: There's some really positive progress that we've seen recently. The proposal around platform technologies, and then also just looking at rare diseases. And one of the challenges at the moment is that there's different approaches between two centers.

We submit our BLA to CDER. So we're reviewed under CDER. But there are multiple examples of where you see CBER leaning into accelerated approaches, and CDER being more traditional.

There's an example, at the moment, in a space that we're not in where there's two drugs. One's in CBER, one's in CDER. The time to market is gonna be a year different, and it shouldn't be. And for a patient living with a rare disease, that's simply not right.

We've seen the FDA recognize this. We've also seen this get attention on the Hill. There's appropriations language that's through Congress and Senate around the importance of having a consistent approach.

We still have a long way to go, but I think the recognition of some of the challenges is there. The desire to get drugs to people living with rare diseases quicker is there.

Us and others are partnering with the FDA as the Rare Disease center becomes established, to help make that successful. The other area that I think is also really interesting and exciting for us as a platform company is the potential for platform technologies where you can leverage one program to another.

I feel a lot more optimistic for the rare disease community in general than I did a year ago. For Avidity, we have the drugs that we're working on, but I want to see the whole community do better.

Piratip Pratumsuwan: Right. You paved the way for other companies developing DM1 products, too. Being a genetic medicines investor, I'm really grateful for the work that you did, especially on vHOT, because now other rare diseases are benefiting from it too. And I say this all the time, that this is the year of genetic medicines. Like, I'm serious. So, let's knock on wood for that.

Sarah Boyce: I would say we're just getting started. Maybe it's the decade.

Piratip Pratumsuwan: Yeah, I like that.

Sarah Boyce: When we were building our clinical trial design and negotiating that design, we were actually very conscious around, "This is opening up a space." And if you look at the work that Sarepta pioneered in DMD, they opened up that space.

It was really important for del-desiran, but also for myotonic dystrophy, to be able to negotiate a clinical trial design that were--it's pretty straightforward. vHOT is the primary. The key secondary is a hand grip, quantitative muscle strength testing, and DM1-Activ, which is your quality-of-life endpoint, which together gives a really good package.

The other key was being able to achieve that we can submit at 30 weeks. It's a full-approval strategy with this real acceleration opportunity. And it's a pretty simple, straightforward phase three.

Design-wise, this is about the myotonic dystrophy community, and the foundation couldn't be more excited with the design that we were able to negotiate.

FSHD and Fortitude

Piratip Pratumsuwan: Well, maybe let's touch on FSHD. Last June, you delivered a highly anticipated data set, Fortitude, which is a phase-one/two trial for FSHD. Can you summarize for our audience what you saw?

Sarah Boyce: Yeah. We were doing something that no one had ever done before. We were the first drug to go into the clinic that directly targeted the underlying cause of the disease, which is the aberrant expression of DUX4.

Perfect for an siRNA approach. What we saw in that data was this beautiful connecting of the dots, from delivery to muscle cells, to then we looked at the downstream genes of the DUX4-regulated genes where we do bulk RNAseq. And then at types of genes that are involved in inflammation or cellular apoptosis. So, it's where you can start to see the whole cascade.

We identified a circulating biomarker. That was two years of work to be able to do that. And that is really important when it comes to our dose selection and dose interval. We saw changes in circulating CK that we know is a marker of muscle damage.

And then we saw signs of functional improvement, even at a four-month point as we thought it was gonna take 12 months to see signs of functional change. It was just a great example of when science does what you think it's gonna do.

It was just a really beautiful data set when you see everything line up.

Piratip Pratumsuwan: When you look at the reachable workspace data, what does that mean for patients?

Sarah Boyce: I think on reachable workspace we've got education work to do as a company, and then as the community around why it's important and what it means. And reachable workspace is actually a very well-developed mechanism of measuring how someone can move their arm.

One of the patient advocates, Amy Bekier, is the head of the local chapter in San Diego. When I first met Amy, she was painting. She had to give up painting 'cause she was unable to position the brush anymore.

If you can't lift your arm past your shoulder, there's a lot of things that you cannot do. Cleaning your teeth becomes something where you have to take a very specific position or wash your hair. To be able to lift something up or get something out of a cupboard.

Piratip Pratumsuwan: I'm sure you were very intentional with naming the FSHD trial Fortitude. When I thought about the FSHD readout and the way it was named, I felt like you picked an incredibly meaningful word to describe the plight of people living with FSHD. So, tell us, what was the genesis of that? What hope does it bring to the patients?

Sarah Boyce: The aspect around it was if you could use a word to describe the FSHD community, "fortitude" was almost like a signature of the community.

FSHD typically affects people in their 20s and 30s. So, in the time of your life when you believe you're invincible...and you know what? You should be. And then you sort of get impacted by something like FSHD, but there's incredible strength and courage.

And people could not be more excited. The FSHD society themselves are very intentional working on, "How do we get more people genetically diagnosed?"

As a community, they're now preparing four drugs to be available. Hope is a powerful thing, and I think we've brought tremendous hope to the community.

Piratip Pratumsuwan: And you also recently talked about the trial design moving forward. It is accelerated. Incredibly savvy for the team to come up with something like that. Maybe talk through the strategy to move the program forward.

Sarah Boyce: The data is so clear. And for us, it's like, "How can we do this as fast as possible?"

We have the circulating biomarkers. We have the plasma CK. It's like we can build a very compelling biomarker strategy here. The Fortitude study was always designed to be the umbrella and to add cohorts to that study.

That actually allows us to be incredibly efficient in enrolling patients in the study. There's Cohort C and Cohort D. Cohort C, as you say is the biomarker cohort. That is being designed as an accelerated approval strategy. It's also where you see us really leaning in as a company 'cause we have a really strong balance sheet.

That study, in all likelihood, will be started before we've actually got the regulatory agreement. We expect it will enroll pretty quickly. And then there's a job of negotiating that along the way.

But also at the same time, we've added a fourth cohort, which is cohort D.

That is a functional study. There will be no muscle biopsies in that study. There, we'll use the circulating biomarker. And that will be designed for full approval, and we're looking to initiate that in the first half of next year.

If we're in a situation where the FDA says "no," or they say "maybe," we're gonna go back again when we have data, of course. And if there's a situation where the FDA still says "no," we didn't waste any time starting the functional study and we can also be able to use the patients from cohort C to add to the functional study. It's an overall acceleration strategy, but it has this turbocharge which is the biomarker cohort.

Piratip Pratumsuwan: Now, with both DM1 and FSHD in very promising positions, you've also raised a strong balance sheet. Why do you think having the amount of cash you do now is important to you?

Sarah Boyce: Bottom line, we have a lot of work to do, and that balance sheet enabled us to do what we did for FSHD. We have data coming up this quarter for DMD as well. But it's also part of building our global organization and building our commercial team. We're pretty deep into that now. That gives us a lot of strength in our overall position as a company.

Looking Ahead: The Future of RNA Therapeutics

Piratip Pratumsuwan: So, what's next for Avidity?

Sarah Boyce: As a team, we're most excited about the potential of how many people's lives we can change. In terms of five years from now, we're looking at a global commercial organization that has launched and is continuing to launch drugs that

are opening up new spaces. And we're in some large, rare disease indications.

As a company, we're looking to open up more and more new spaces. If you look at precision cardiology, that is what we found: underlying genetic diseases that are ideal for an RNA approach.

No one's been able to deliver to the heart simple, gain-of-function mutations. I'm really excited about what we can do there, and working with our partner at BMS on genetic targets that we have with them, to actually be starting that work of fundamentally changing what happens in a cardiologist's office.

That's, like, changing the practice of medicine. And in terms of our research organization, it's incredibly efficient. We also, as you know, are very purposeful and intentional about the words we use.

When we did our vision, it's simply, "We're revolutionizing the RNA space." We never said we were a muscle company. We never said we were a heart company. We never limited ourselves like that. Nor did we ever say we were an AOC company. We've said we are an RNA company.

Sometimes you find that companies fall in love with what they have and they kind of stand still and others come around them. And for several years now, we've been working to make sure that does not happen.

At its core, if you can make a profound impact on people's lives the way we can, you know that's building an incredibly important company in our industry.

Championing Women in Biotechnology

Piratip Pratumsuwan: A little bit more about you as a CEO. You represent other women in this position. What does it mean to you when other people look up to you and want to do what you do?

Sarah Boyce: I'm one of not many women who are CEOs of companies with market caps of $5 billion-plus. I think it's less than ten. And I know that part of what is my responsibility is to be a cheerleader and a champion, both internally within Avidity, but also within the industry.

I'm involved in a group called the Biotech Sisterhood. It was started by Sheila Gujrathi, Angie You, and Julia Owens. It's one of the most powerful networks I've ever been involved in. There are 278 female biotech CEOs in that network.

The only entry criteria is you're a female CEO and you are motivated to lift up and support other women. It's one of my greatest joys, being part of that community and really supporting, cheering people on when good things happen, and when, "This is biotech, (LAUGH) it's not a straight line," also being there when that doesn't happen for someone as well. If I can offer some advice that may be helpful for someone, then I make sure I do that.

Piratip Pratumsuwan: Well, Sarah, thank you so much for speaking with us today.

Sarah Boyce: You're welcome. It's been a pleasure and thank you for inviting me.

This interview and testimonial was given by **Sarah Boyce**, CEO of Avidity Biosciences, a company in which RTW has made an equity investment on behalf of its managed funds. No compensation was provided to Ms. Boyce.

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