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*In this episode, Taren Grom, Editor-in-Chief of PharmaVOICE magazine, meets with Casey Lynch, co-founder and CEO of Cortexyme.*

**Taren:** Casey, welcome to the PharmaVOICE WoW Podcast Program.

**Casey:** Thank you, Taren. Pleasure to be here.

**Taren:** I am so intrigued by your background. I know that you have founded a number of biotech companies, so my natural first question is, why are you a serial entrepreneur?

**Casey:** Yes, thank you. I came about it initially as a scientist. My scientific training was at UCSF and Stanford and I was working on Alzheimer’s disease. So I’ve always had love for science, but also had an interest in bringing that science further than an academic lab generally allows you to. So when I was at Stanford, a post-doc in my lab had an idea for a company and we worked together on both the science and the business plan and that was my first venture.

I think the fact that I’ve done it multiple times really comes from a drive around any particular idea. When there’s something that’s so compelling that it really just have to be brought forward and you realize you’re the only one who is going to do it.

**Taren:** What was that first company’s name?

**Casey:** The first company was called Aspira Biosystems, and we were working on a platform for understanding disease. It was the genomics, proteomics heyday and it was a platform for understanding 100,000 proteins at a time instead of looking at biomarkers one by one.

**Taren:** So that is such relevant research for today. How is that research being used currently? Do you know?

**Casey:** The company was acquired in a private transaction and it’s still ongoing. It’s a very difficult technology to control but a very high-risk, high-reward venture.

**Taren:** Excellent. What was your next company?

**Casey:** My next company was an investment advisory firm called NeuroInsights. We created this firm seeing the emergence of many companies focused around neuroscience that we felt

were underappreciated by investors. We wanted a way to write up the information about these companies, analyze the assets, bring the community together in conferences, for example. So I worked for many investors and pharmaceuticals over that time to look at a lot of different assets in the neuroscience space and do some matchmaking to bring, kind of create a tie that lists all those.

**Taren:** That's excellent. Does that investment background help you as you continued on your entrepreneurial journey, knowing what the ins and outs of what it is to raise money in a startup kind of environment?

**Casey:** Exactly. I worked with a lot of different – it started over that period and in addition to the in and out licensing analysis and so I just really loved doing that, helping scientist entrepreneurs, thinking through the strategy and raise funding. That's really what led me to Cortexyme actually. I've always been very interested in Alzheimer's disease, and this is really the first facet in Alzheimer's disease that I felt like could address the disease.

**Taren:** We're going to get into the Alzheimer's aspect in just a second, but I just want to go back to your entrepreneurial journey. Being a serial entrepreneur yourself and having worked with entrepreneurs through the venture fund, do you see where there are some commonalities in terms of that entrepreneurial makeup or mindset, and what might those be?

**Casey:** Well, I think there's a – there has to, number one, be a passion and a drive around the science. So again, just this feeling that this must be pursued and you're the right one to do it.

And then the second half of the equation is risk tolerance. That's something that I'm not sure where it comes from, it can't be taught, but I grew up in Silicon Valley so I think some of it was being around a lot of entrepreneurial people as I was growing up.

**Taren:** Something in the water there, right? You just become accustom seeing these people taking those risks and sometimes bigger risks and some big rewards, and sometimes bigger risks and not big rewards. But at the same time, it seems everybody sort of comes out on the top, and it's that passion that drives you all.

**Casey:** That's right. That's right. And realizing that you can't always control the outcome, but you can make your best effort and take all the necessary steps and that's really defined as success.

**Taren:** Fantastic. So let's talk about the work that your company is doing. There's been a lot of press lately about so many failures in that Alzheimer's space. So why do you think that you are on to a winning program?

**Casey:** Right. So we know that there's a lot more going on in the brain of patients than just beta amyloid, and the last 30 years of research around Alzheimer's disease has really been

focused only on that target, removing beta amyloid from the brain, blocking production of beta amyloid, but we know now that there's neuroinflammation in the brain. There's microglial activation which are the immune cells of the brain. There's inflammasome activation.

So there's about ton of different pathways, they're actually immune system pathways that are activated in the brain of patients, and when people started asking I think a very good question which is why is the beta amyloid being produced, this is the component of plaques, they discover that it behaves like an antimicrobial peptide, which are induced in response to infection.

**Taren:** That's fascinating. So you're saying that Alzheimer's might be approached in terms of treatment because of an immunological issue or factor?

**Casey:** Right. So I became very convinced that there was something upstream, an infection upstream of all of this pathology that was driving not just the beta amyloid, but all this other detrimental pathology and the ongoing toxicity itself, we've had a lot of trials, as you said, testing it for removing beta amyloid can help patients, and it just wasn't working. So it seemed clear, we need to get upstream of that. We need to figure out what's triggering all of this pathology.

And meanwhile, my co-founder, Steve Dominy was at UCSF. He's an expert in HIV dementia. So he was researching infectious causes of neurological disease. I came across some very important literature showing that periodontal disease or gum disease is actually a risk factor for Alzheimer's later in life. So he went looking for the bacteria called Porphyromonas gingivalis, which causes this chronic degenerative disease in the mouth, and also very similar low-grade in other pathways that we see activated in the brain. He went looking for it in the brain of Alzheimer's patients and found it there.

**Taren:** That's fascinating. And so what are you – where are you right now in development or in progress with looking with all with your findings?

**Casey:** Yes. So the next step when I came onboard in order to prove causation, we infected some mice with the same bacteria in their mouth, and we found that it got into their brain and triggered beta amyloid, inflammation, detrimental effects on health, and most importantly the degeneration of hippocampal neurons, which are the memory center of the brain.

So we went on to develop our own small molecule therapeutics. We went through phase 1 studies including some Alzheimer's patients with some very promising data, and now we're conducting a pivotal phase 2-3 study called the GAIN trial in the US and Europe.

**Taren:** How many folks are involved in that trial?

**Casey:** This will be a 570-patient study. So it's very well-powered to show efficacy.

**Taren:** Its fascinating. You know, I have learned something about the tau protein a while back and there's been some research in that as a counter to the amyloid research. So you're following a somewhat similar pathway. Yes? No?

**Casey:** Yeah. We think tau is very important and we've shown that this bacteria is an intracellular asaccharolytic bacteria. So asaccharolytic bacteria actually use proteins for nutrition. So they actually fit inside cells and traps that protein and tau it's one of its favorite targets. So it'll create these fragments of tau that leads to the tangles are known to see these tangles that you see in the brain of Alzheimer's patients. So yes, we believe tau is an important part of the pathology that this gingipain hypothesis, as we call it, can explain. But we also can explain the downstream inflammation, the triggering of the complement cascade. So again, we think that the bacteria and it's secretion of these proteases is upstream of many parts of the pathology.

**Taren:** Casey, this is fascinating. You know, obviously, myself as well as millions of people are hoping that you have found successful formula for approaching Alzheimer's disease. What is the response then from the scientific community so far?

**Casey:** It's been really excellent and gratifying. We were in stealth mode for about five years. We published a paper and science advances in January with all of this – not all of the data but a huge amount of our data including both the human findings, which we worked on in collaboration with University of Auckland as well as the mouse findings as well as the therapeutic approach. When people see that data altogether, it's very compelling and very exciting for the scientific community and for the investigators who are working on our study.

**Taren:** Yeah. I would imagine. So have you had any knocks on the door from larger companies looking to partner up with you?

**Casey:** Most certainly all the larger companies are very interested in Alzheimer's disease. It is the single biggest unmet medical need, a biggest market out there especially with the disease-modifying therapy so certainly they're interested, and I think they're interested in this upstream data. Again, if you're looking at a company that's addressing one part of the inflammatory cascade or just the tau pathology, people are very interested in an approach that may be upstream of all of that.

**Taren:** Excellent. When do you expect to have your phase 1 trial completed?

**Casey:** So the phase 3 study that we're doing now?

**Taren:** I'm sorry, phase 3.

**Casey:** We are guiding for top line beta Q4 2021, and we are in discussions with the FDA now about the physical analysis qualms that we are potentially planning an interim analysis in 2020, Q4 2020.

**Taren:** That's awesome. I was going to ask you, how close are you working with the regulators at this point.

**Casey:** Yeah, it's important and we are working to have as many conversations as we can with the regulators to make sure they're familiar with the approach and agreement with our plans and that we can agree on the fastest path to market for patients.

**Taren:** So again, I wish you great success. We hope this is a winner going out there. So let's switch tacts just a little bit here. I'd love to talk to you about you being a role model, not only for women in this space, but for scientists in this space. How does that sit with you?

**Casey:** Well, I think it's great of course. One thing I think about in addition to being a role model, another way that I like to think about it is changing people's pattern matching and unconscious bias. They can think it's not only about motivating women to go into new careers, but it's about changing the way investors think about what is the person who is the CEO. Where is the person who has made the money in the past? They have certain biases, unconscious biases about what those people look like, and I think the more we can shift that, the better.

**Taren:** I love how you termed that, pattern matching. I hadn't heard that before. That's an interesting term to explain what you just described.

**Casey:** Right. So you want to create the bottom push but also the top-down pull for new opportunity for women.

**Taren:** Absolutely. And you're right. Not all CEOs are old white men sitting in corner offices anymore.

**Casey:** Right.

**Taren:** Or so we hope, right?

**Casey:** Exactly.

**Taren:** That's excellent. So not only you founded multiple companies, but you also founded the neurotechnology industry organization and you served as its board member from March 2005 I guess to September 2018. Tell me about the work that the association is doing. Why do you feel the need to start that organization?

**Casey:** Right. This is along a similar vein and why we started NeuroInsights. We felt that there was a need to bring the community together to talk about common issues, for example, around endpoints, around financing, around funding, and that industry organization really did create a great community of investors who are interested in CNS, of the companies who might have common problems or common celebrations and additionally, it allowed us to go up onto Capitol Hill and lobby for increased NIH funding to these areas of importance throughout America.

**Taren:** So what was some of that experience like on Capitol Hill? Trying to explain the science to the folks that you wanted to get the money from.

**Casey:** Well, people are very receptive. I mean, nearly everyone has a relative with Alzheimer's disease. Looking back five years, there was a lot of interest in PTSD and other CNS injuries related to the troops. And also these diseases, including Alzheimer's, are a big drain on the healthcare system. People are very worried about the aging population and the cost of that aging population if we don't change the course of diseases, like Alzheimer's.

So I think people are very receptive. There's been quite a bit of increased NIH funding, so that's again, kind of the bottom up approach to increase the R&D. I think it's important also to think about the top-up again, the top-up pull, so working with regulators as we talk about to create clear and efficient paths to market, thinking about price controls and how that impacts investment into innovation. These are all things that it's important for industry to have an ongoing dialogue with Capitol Hill about.

**Taren:** And so at the start of your journey, what led you to focus on neuroscience? Why is this a passion for you?

**Casey:** I was always very interested in how our brain controls us both just day-to-day and then in disease, how your whole personality can change, memory can change. But also I do have two grandparents with Alzheimer's disease, so I think that certainly must have had an impact on my interest.

**Taren:** Sure. It's a personal journey for you as well.

**Casey:** Right.

**Taren:** Excellent. So as a non-traditional CEO, what lessons have you learned along the way that might benefit other women to aspire to reach that executive level?

**Casey:** Yeah, I think it's really important to be a driver of the conversation, to speak your mind, for better or for worse, that is what people respond to and see as leadership. I think some women may shy away from this, may shy away from sharing their opinions strongly, and I think that's really important.

**Taren:** I agree. Describe your leadership style for me. How is it that you rally the troops because let's face it, what you're doing is hard work and it's fraught with a lot of areas that are right for failure and how do you keep your teams motivated.

**Casey:** My team is really motivated by the benefits of patients, by the science we see every day and the benefit that we're going to bring forward. So I don't find I need to rally them day-to-day. I feel like our team is so self-motivated to help connect the dots for other people outside the company, for the scientific community and for investors. So every day they're making new contributions to this hypothesis, so just being on the forefront of such an exciting discovery really seems to motivate everyone to work hard and contribute in every way they can.

**Taren:** Wonderful. You've been through a couple of companies, startups, and each one has turned into another opportunity. So how do you define success for yourself? Is it that completion of a milestone? Is it the small winds along the way? So how do you define success for yourself?

**Casey:** So for entrepreneurs, I think success has to be defined as making your best effort and the decisions with the information you have. You can't always control the outcomes, but you can really do your best to plan for both the best and the worst outcomes. So I think it's really important to plan both the fastest plan to market, as well as risk mitigation and multiple paths to be sure that there are no surprises.

**Taren:** When you are encountered with a surprise or an obstacle, how do you navigate around that? What are some tips that you can provide?

**Casey:** For example, in pharmaceutical development, manufacturing can always be a surprise obstacle. So on that, for example, being really ahead of the game, not cutting your supplies too close, having multiple manufacturers when it's appropriate is one of those types of things that I'm talking about.

**Taren:** Excellent. Is there a piece of advice you'd like to give you to your younger self?

**Casey:** I think trusting your gut on hiring decisions is really important. I like to hire people who are very passionate and engaged and hands-on and also the personality fit with the organization and the executive team is extremely important. So sometimes you may have a niggling feeling when you're making a hire and I found often that feeling should be listened to.

On the converse side, sometimes you just have a really good feeling about somebody, and in those cases, I've been very persistent about getting that person on board and that's always panned out really well.

**Taren:** Excellent. And finally because this program is called the WoW program, can you identify a wow moment in your career that either changed the trajectory of your career path or provided some form of inspiration or was a significant impact on you?

**Casey:** We took Cortexyme public in May and that was a really significant milestone, not just for the company but for me personally, and most importantly, it brought in financing that allows us to accelerate our development, speed up enrollment, do all the regulatory work that's required to keep moving the program forward the most rapidly for patients. So that was a really exciting milestone that I'm happy we were able to achieve.

**Taren:** Congratulations. That is a significant milestone and that is a wow. Tell me what you felt like that day. How was that?

**Casey:** Well, that day was really exciting. There was a moment where I was in the room – I was the only woman in the room with about 20 men. All of us were celebrating, and the whole team did just an incredible job, and then we got on the plane while the stock was trading and we just had an incredible first day of trading. It's been a very successful IPO, not only for early investors but for the later investors. So it was really gratifying. I felt great. It was a great day.

**Taren:** Congratulations again. And I hope the next time you go IPO that you're not the only woman in the room.

**Casey:** Right, me too.

**Taren:** Casey, thank you so much. This has been a fascinating conversation and we will track how Cortexyme does and look forward to the results from that phase 3 study.

**Casey:** Thanks so much, Taren.

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