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In this episode, Taren Grom, Editor-in-Chief of PharmaVOICE magazine meets with Dr. Linda Marban, CEO, Capricor.

Taren: Welcome to the PharmaVOICE WoW podcast program, Linda.

Dr. Marban: Thank you very much for having me. I'm looking forward to talking to you.

Taren: Likewise. I did a little research into your background and I understand you came to the industry via academia. What led you to make that leap?

Dr. Marban: I had always planned on pursuing a career in industry, but I wanted to have all of the credentials of academia so that I could continue stellar development of products using the scientific pathway that we learn as academics. So I had always planned on it and when I had the opportunity to go from Johns Hopkins as a young faculty members to a spin-off company from Hopkins, I took the chance and have been in the industry for about 20 years now.

Taren: Excellent. What was that spin-off company?

Dr. Marban: The name of the company was called Excigen and it stood for excitable gene, and it was a company that was in the early stages of gene therapy. We were looking at treating cardiac arrhythmias like needing to put a pacemaker in your heart for atrial fibrillation with gene therapies. And it was really early days, so it was a lot to learn and the company did some nice partnerships with Genzyme and with Medtronic, but ultimately was too early in the process for those biotech companies and the technology was shelved and done. And then I moved on to Capricor from there.

Taren: I was going to say Capricor is your second startup that you've been with, early stage biotech companies, what draws you to that kind of – is it the excitement, because you really are forging some new ground here?

Dr. Marban: Yeah. I love the startup environment. I love the energy of it. I love the concept of taking something that's new and molding it into a product. I like the team spirit of it and I like the entrepreneurial aspect of it.

Taren: Because you really are. As I said, you're breaking new ground and all those things that you just noted are so important for a startup because it's just you all against the science, right?

Dr. Marban: That's right. That's right.

Taren: So tell me about your company's first in class therapy. Your pipeline, is that how you're going to go forward?

Dr. Marban: Capricor has been an incredible journey. We've had several lives already and it's still a pretty young company. So we started off as a stem cell therapy for heart disease. We thought that we had discovered a cell that was a stem cell that we would put in injured hearts and they would make the hearts better, would cure things like the scars from a myocardial infarction or reduce the amount of scarring from a heart that had congestive heart failure. But what we learned along the journey is that our cells are not stem cells. They don't actually go in and stick around, but what they are are cells that go in and act as sort of a local drug delivery system by releasing these very active bioparticles called exosomes, and exosomes then contain information inside that help cells repair themselves and reduce inflammation.

So we went from stem cells to a cell therapy that has these exosomes that we know are targeted to reduce inflammation and repair tissues that are damaged by driving the cells that are already there back into the cell cycle, for instance in Duchenne muscular dystrophy to make new muscle. But then because we became so intrigued by these little packets of cellular information, the exosomes, we then decided to start exploring those as a product candidate and now have emerged in yet a new opportunity to develop these exosomes as delivery vehicles for all kinds of products that we want to get inside a cell, particularly inside the nucleus where we can change things like genetic diseases, change inflammatory processes and other ways of influencing cellular behavior.

Three really iterations of this company – stem cell for heart disease, cell therapy for a variety of diseases of inflammation, most notably heart diseases, and now exosomes as delivery vehicles where we're engineering them to be the products that we want them to be.

Taren: That's terribly exciting. Wow. And I know that's a lot to unpack there, but that is – the exosome piece of that is really so exciting. What was the feeling in the company when you went to that next level for looking at the exosomes?

Dr. Marban: The exosomes have been an exciting journey. We discovered exosomes as a mechanism of action of our cells probably – and I'm not very good with timelines because they all sort of morph together when you go over 50 years of age, but what I can say is that somewhere in the last five years we discovered that our cells made exosomes and that was the mechanism of action. Because all the science that we need to do to prove that was lost in production of the exosomes and we've lost the action of the cells. We isolated out the exosomes and can drive the benefit of the cells.

And so now we have these exosomes made by our cells, and we start using them to treat all kinds of diseases in animals to try and figure out the power of these exosomes. And then we had a eureka moment in the company where we thought wait a minute, why should we be

passive bystanders to biology. Why should we just look at these exosomes and take what they're giving us? Why don't we tell them what we want them to do? And so that's when we decided to work on the engineered platform where we put different things inside. In fact, right now we're working on two versions of a COVID-19 vaccine using the exosomes as a platform, which I can talk a little bit about soon.

So yes, we were gobsmacked and excited, and I love my work anyway, but this new adventure I feel like I'm sort of reliving what happened in a monoclonal antibody space but 30 years later.

Taren: Wow, that is – well, that's quite the comparison. That's exciting. We'll talk about COVID. I do want to touch on your work though with Duchenne's because it is such a horrific disease and I know that there has been just – they're trying so hard to find a treatment which is so devastating. Talk to me a little bit about that program if you don't mind.

Dr. Marban: The Duchenne muscular dystrophy program is one that's very close to my heart. It's become intricately woven within the advocacy community. We know the families. We know their sons. And as I often try and tell people when I talk about Duchenne, imagine looking at your child everyday and knowing that they're alive one less day because their muscle function is down and will continue to go down and is a downward trend until death. I can't even imagine the pain. So it's a labor of love as well as of science.

We got to Duchenne muscular dystrophy as an indication because we knew we had a cell that worked in treating heart disease. It reduced scar and it reduced damage to heart tissue and it also reduced inflammation. And we realized that Duchenne muscular dystrophy, one of the main causes of loss of life is the cardiomyopathy or the heart disease and it's the cardiomyopathy, the heart disease of Duchenne is caused by the aggregation of scar, fibrosis from constant inflammation and breakdown of muscle.

And so we decided to do some pilot experiments in the mdx mouse, which is a sort of naturally occurring mouse model of Duchenne muscular dystrophy and what we found was profound. We found not only did we see an improvement in cardiac function which actually we expected, but we also saw improvement of skeletal muscle function. And that was all during this timeframe of sort of eureka moments where we knew the exosomes were immediate in the mechanism of action, and so it became obvious that they were targeting muscle cells driving them to repair themselves and also reduce the inflammation.

So the profound data that we saw in the mdx mouse led us into the clinic and now we're at a point where we believe that we have beautiful data with implications for improved muscle function in patients with later stage Duchenne muscular dystrophy, those boys and young men that are non-ambulant that have really no other options in front of them. We're really excited about this opportunity to make them potentially better by improving quantity as well as quality of life.

Taren: That's fabulous news for all those families as you say, because it is just heartbreaking. So congratulations and best wishes for continued success along that pathway for sure. Let's talk about now COVID and the work you're doing there because it's so immediate and there's such a need. So talk to me about that program a little bit.

Dr. Marban: We're attacking COVID in a multidimensional way. We are treating patients with severe COVID with our cells. We're initiating a randomized controlled trial very soon where we will be looking at those patients hopefully sitting on the edge of the very severe implications of ARDS, but not quite at the point where they need ventilation or the ventilation is required to sustain their lives and that's one opportunity. That actually is hand and glove with our Duchenne program. It's the same product, CAP-1002, and you might scratch your head and say, 'wait a minute, you're treating Duchenne muscular dystrophy and COVID-19 with the same therapeutic and you think that's going to work?' Yes, because the main mode of action of CAP-1002 is its ability to immunomodulate – and that word modulate is very important. It's a word that becomes much more in the scientific arena in the last couple of years because what we realize is pure, simple anti-inflammation doesn't typically cut it when you're looking to modulate or to improve outcomes in diseases of inflammation.

You have to have bad inflammation shut down and good inflammation which happens to stimulate repair that would be driven and that's what CAP-1002 does. For example, for instance, a layperson, any of us who go to the gym end up hobbling around the next day because our muscles are sore, that's good inflammation. It's repairing our muscles and making us healthier and stronger. So we want to encourage that but also of course, reduce the implications of the bad inflammation. And so that's what we do in Duchenne muscular dystrophy and COVID-19. We've used the cells in other diseases of inflammation and fibrosis like pulmonary artery hypertension and heart failure with preserved ejection fraction, other diseases of inflammation where the cells are implicated.

Now, the other approach we're taking – and as I told you, the most exciting thing I've done in a long time is this engineered exosome program and as I mentioned, we're using the exosomes as platform to build two vaccine candidates, and the data is looking very exciting. We're not ready to present it yet, but we are using the exosomes as a twist on two vaccine candidates that are already out there and being tested in people. The Moderna vaccine and some of the other vaccines are using lipid nanoparticles on which to load the mRNA. Lipid nanoparticles are like exosomes without an address. So they have no real way of getting them to the cells that we need them to go to, where the exosomes are an addressed envelope.

So if you think about it, we have to use a lot of lipid nanoparticles because they have to get in the body and go somewhere. They don't know where they're going, they're just swimming around. And they also have some toxicities related to them because you're putting basically foreign balls of fat inside your body. But we are using a human-derived exosome that the human body sees as familiar and then we can load them with the mRNAs to hopefully have a much more sustained and also less toxic effect.

Now in addition to that, we're not just stopping there, we're using four of the major viral proteins not just spike or the S protein because thinking of our scientists is that why would you stop with one protein where you want to mount an immune response to prevent a disease, you want it to recognize a lot of the bad guys. So we'll see. We're in early stage experiments, they're looking promising, but that's an exciting one.

And then the other vaccine candidate – go ahead.

Taren: No. I was going to say that is exciting science. Keep going. I'm fascinated.

Dr. Marban: The other vaccine candidate is even more exciting. So this one is based on like premise of turning the exosomes into virus-like particles. So exosomes are kind of like viruses, right; they're packed with nucleic acid. They've got membranes to protect them from degradation and they can get inside cells. The difference is is they don't cause disease. They don't cause bad things to happen unless you load them with something bad. So we are using cells to make large amounts of these exosomes which are now able to be called virus-like particles because of what was put on the outside, decorating the outside with these same four viral proteins that can become the antigen that the body recognizes and we use that as a vaccine candidate.

VLPs are a chosen source of vaccination, and if you read about vaccine it's one of the favorites of those that study vaccines or infectious disease for life. The issue has always been we don't really have a good vector. Some of the virus-like particles that are being used now for instance for COVID, use a system of exosomes or little particles made by flies, by insects, and we can sort of take out those little particles and put antigens on the outside, but the problem is that people really generally don't like in their bodies to get insect proteins, so some people have a bad response. There can be hypersensitivity. There's manufacturing issues that's really hard to get these fly-type particles to be quality controlled. So we're using technology to drive new advances on things that are already out there, and so that's what makes it really exciting and also possible for a small biotech to participate in.

Taren: Wow, that's incredible. Well, again, we will keep a close eye as you progress down this path and hopefully, fingers crossed, good science, it comes out on the other end in a really great place because what you're really doing is revolutionizing vaccine technology and that's…

Dr. Marban: Yeah, that is exactly what we're trying to do and it's an incredibly…

Taren: Way long overdue for an overhaul, right. That's awesome. As the CEO of the company you obviously set the tone and the tenor for the organization, and as exciting as all this is and the eureka moments that happen, there's also disappointments along the way. How do you keep your teams inspired? I know you're working on really tough diseases and you're breaking new ground, at the same time how do you temper all that excitement with the reality that you bump into everyday?

Dr. Marban: Well, running a small biotechnology company is very challenging and very rewarding. So I would say we have high highs and low lows. We have a small team. We're almost always undercapitalized, although right now our balance sheet is very strong for the first time in a long time and it feels fantastic. You have a lot more issues in terms of keeping all the trains running on time because you have very few people. People typically have to work very hard and very long hours. They have to be able to operate outside their comfort zones. Sometimes you need people to do things that they either have not been trained to do or were not hired to do, but all hands on deck kind of thing.

We have a lot of situations where we have sort of the self-declared Manhattan project. We've got to figure this out now. We've got to get it done. And I see our cash as sand through an hourglass, right; it's always running and I'm always competing against that. So it's got its challenges for sure, but at the end of most days I feel that I'm doing the work that I want to do with the team I want to work with.

Taren: That's awesome. You've obviously created a fantastic and a successful career path for yourself and reaching the C-suite isn't always easy for women as we look across the – just the numbers aren't proving it out. So as a woman sitting in the C-suite, what advice do you have for other women who look to aspire to reach those top rungs?

Dr. Marban: So what I can say is equal to my passion for my career is to help women. I've mentored many women across the years, and I'm proud to say that a lot of them have gone on to very successful careers mostly in science and medicine.

To give you a perspective, I went through graduate school as a single mother with four kids. So I sort of was in the trenches working incredibly hard and juggling a family responsibility so I know how hard it is. And I'm respectful of all of the pulls and tugs against us as women, we want to be there for our family, we want to take care of our children and yet we also want to achieve and we absolutely should achieve.

I guess what I can say to every woman out there is it's absolutely possible to have it all. We as women have to look at it as a 24-hour day in which we get it all done as opposed to our male colleagues over many years who could go to work at 7:00 a.m. and come home at 7:00 p.m. to dinner and kids in PJs. But we're not able to do that. But I have over the many years found ways to come home to dinner with the kids, get them settled and then hit my computer again.

Taren: Yeah, it is a 24-hour day. There's no doubt and especially as we're hearing now coming into COVID with the additional demands of homeschooling and being on 24/7, that's even harder for some women to balance it all.

Dr. Marban: I can't even imagine. I really can't. It's so hard.

Taren: Touching back just a little bit to your – when we were talking about your role as the CEO and how you put your teams together and asking people to stretch outside of their comfort

zones, what are some of those qualities you look for when you bring in new team members to build out your executive level teams or even just your working teams? What do you look for in folks?

Dr. Marban: It has to be a can do spirit, people who work very hard. I literally have buzzwords that I listen for when I chat with somebody that we're contemplating bringing on and those would be 'I like to get my hands dirty,' 'I work really hard,' 'I'm willing to have an all hands on deck mentality,' or they tell me about projects that they've done in other jobs that are outside their comfort zone or bandwidth. I like people that have come from small companies because they're a little bit more used to bootstrap mentality that we have to have a lot of times. So mostly I guess dogged ingenuity and motivation and ambition.

Taren: Fantastic. Again, some of those pressures as you look at being a woman at the top of her game and having to go out and raise money and talk to investors and I would imagine often you're the only woman in the room. What are some of those unique pressures and challenges? How do you manage those?

Dr. Marban: Yeah, so I am often the only woman in the room. And what I can say is every hill or mountain that we women have to climb, I have climbed. There have been the times that people have made lewd remarks. There have been times where I literally once had an investor look at me and say, "Okay honey, you're real nice, but who's really running the show there."

Taren: God!

Dr. Marban: And that really happened and that kind of thing. And then there's also the other side of it which is even more unfortunate, which is sometimes women are the worst to each other. I've worked with women in hedge funds who very clearly like being the only woman in the room. So we have a lot of mountains to climb.

What I can say is that you have to recognize that you're operating outside your comfort zone in certain ways, and the best way, for me anyway, to embrace it is to not try and be apologetic for being a woman and not try and be a man in the room. I am a woman and I'm proud of it, and I'm a woman CEO. Thank you.

Taren: Awesome. You know one question I ask all of our WoW podcast interviewees is is there anything you know now that you wish you had known as you were moving up the ranks?

Dr. Marban: Oh yes.

Taren: She says 'oh yes.'

Dr. Marban: I think probably the last statement I made, which I'll say again for reference is that be unapologetic about the fact that you want to have a family and you also want to be an executive. We're only going to triumph if we stop trying to put on a man's pair of loafers and

stand up in our high heels which hurt, but stand up and be proud for who we are and how we do it. It's okay to be unapologetically female.

Taren: Love it. And finally because this is our WoW podcast program, tell me about an accomplishment or a wow moment in your career that either has lasted with you or helped shaped or change the trajectory of your career.

Dr. Marban: There are so many, but I guess when I'm on the spot I think I'm going into running a public company. So the months leading up to the announcement of our company reverse merging and becoming public, the board of directors and other members of the management teams sat there and fed me all kinds of stories about how hard it was going to be the CEO of a public company and how there's never enough investors and how I was going to have to take on finance and the science is my background, so I was nervous about how to manage all that. And I jumped into the deep end and what I can say is it's become one of my favorite parts of my job, which is interacting with Wall Street, interacting with investors, doing investor presentations and embracing that part that was so difficult. So that was probably the biggest challenge and accomplishment over the last many years.

Taren: Linda, that's awesome and you do it, you have a great story to tell. So I can see that it's the – you mentioned before that the financing you have a positive balance sheet right now that that storytelling and the story you have to tell is so powerful and you do it so well. So congratulations.

Dr. Marban: Thank you.

Taren: And again, we will keep an eye on the progress that you're making because you really are breaking new ground, and it's exciting to talk to somebody who's right there in the midst of it all and looking to significantly change the science. So congratulations.

Dr. Marban: It's a lot of fun. Thank you so much and thank you for your time, and I look forward to keeping up with what you're putting out there as well.

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