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In this episode, Taren Grom, editor-in-chief of PharmaVOICE Magazine meets with Sharon Shacham, PhD, Founder, President and Chief Scientific Officer at Karyopharm Therapeutics, Inc.

Taren: Sharon, welcome to the PharmaVOICE WoW podcast program.

Sharon: Thank you for having me. I'm excited to be part of it.

Taren: Well, we're excited to have you. I did obviously a little bit of research before we were to speak this morning. Your story is amazing. Can you please tell our listeners how you founded Karyopharm?

Sharon: Let's go back a little bit. My background is in computational biophysics and in my PhD and then in my first company that I was the technology founder I was focusing on using algorithms developed on the computer to create three-dimensional models to complicated proteins, and then use those models to facilitate drug discovery.

Before Karyopharm I wanted to use this approach to identify proteins that are very important for the survival of cancer cells, and then develop drugs that will inhibit them. I was spending about six months looking for some of these pillars of cancer, if you may. I don't know if you know but Dr. Michael Kauffman, my husband, is the CEO of the company. Back then he developed already two cancer drugs and I would ask him what do you think about that. Every time he would say that's a bad idea. That went on for six months. Every dinner he would kill another idea of mine.

Then when I came up with the idea of inhibiting nuclear export he couldn't kill it, so I was kind of now I have to do something with it. That's how we started to work on the nuclear export.

Taren: That had to make for some interesting dinner conversations, I can imagine.

Sharon: We need to ask the kids about that.

Taren: Literally, you started the company by yourself at your let's say for lack of a better word at your dining room table, and you discovered this compound.

Sharon: Just to be accurate, it was the kitchen. Yes, I thought about the idea and then I used these algorithms to do some incidental screening. We bought the original compounds and we found the original hits. We did store the compounds in the refrigerator for a while until we tested them, but the kids looked fine so I guess it was okay.

Taren: Nothing like moving the milk aside to find the compound. This was about 12 years ago, correct?

Sharon: This was in 2009.

Taren: From a one person operation to now a 300-plus global company, has your mission for the company changed along the way?

Sharon: No, we always looked and still this is our mission, is to develop new therapies for patients with advanced cancers. Selinexor was the first one and we got the approval in the first indication but we hope to expand the use of selinexor in many other cancers. And then to advance our other compounds through clinical trials to approval in some of these indications.

Taren: Awesome, so as president and chief scientific officer you work alongside your husband still in the company. How is that dynamic? How does that work for you all?

Sharon: That we'll need more time to discuss. We share the same passion for medicine, for patients, for science. So this is a big plus for this. We are both entrepreneurs in our nature, we are both impatient so that makes it more interesting. I think we should ask the employees how they are doing with this. It took us some years and we finally managed to put this is yours, this is mine, this is what we do together. So far I think it's an amazing journey. I wouldn't want to do it with anyone else.

Taren: I was going to say, sometimes that shared journey because you are working long hours and there's so many ups and downs in terms of that drug development process, that it must feel very good to have somebody who's in your corner and that you can share that experience with.

Sharon: Yeah, and understands the ups and downs and understands when a patient doesn't respond or when an animal model doesn't work or when the chemistry fails someone that understands and is okay when you bring work home from time to time.

Taren: Sure. So let's talk about one of those highs, and that is the XPOVIO. Did I say it correctly?

Sharon: Yeah.

Taren: That you brought that drug from inception to FDA approval. Talk to me about what that process was like for you all.

Sharon: Think of the biggest roller coaster you've ever been on, and now multiply that by 100. Getting drug approval, it must be a mission and a vision. It's consuming, and it should be. Every success or every milestone that is being achieved until you get the drug approved is so big and it's such a high. Then when things don't work it's really, really tough. We got the approval for selinexor in last line myeloma on July third and then we went out and there were fireworks and we felt that the fireworks were for us that day.

Taren: I love that. And why shouldn't that be? That's great. So the New York Intellectual Property Law Association recognized your scientific research and achievements for XPOVIO with the 2019 Inventor of the Year award. That's pretty significant. What does that recognition mean to you?

Sharon: A lot. And I would say as a female leader, as an immigrant in this country, it is so important. I think I was the first woman that got it in maybe ten years, I'm not sure. But it's so important that this work is recognized, that we can speak about it and I hope that it encourages other women to pursue their dream and try to become leaders in an industry that still today is heavily, at least at the top, includes mostly men.

Taren: Absolutely it does still include mostly men. What are some things that you think that can help to change that dynamic so that more women can achieve their dreams? What are some of those barriers that need to be broken down?

Sharon: I would say that there are barriers that are objective and there are some self-imposed barriers for women. In Karyopharm there are more women than men in general. It's a very diverse company. We speak I think about 20 languages within our over 300 employees. Even in the executive team I think it's almost equal men and women.

What's interesting is that it's the network that helped us. Once we added the second woman and the third woman then when we are looking for another person because it's such a small community then you use each other's networks. Once we expanded above my network we had the head of regulatory that joined, Ms. Tanya Lewis, and we used her network and the general manager of Israel. Once we started to use all these networks we found out that we see many more CVs for high-level women at the high-level roles. It's very important that you actively do that.

The second one I think is we, and I think some of it is our nature – well, I don't know the reason but what I know about women is we don't use our feathers as much as men. I know when I meet with my female leaders they'll always talk to me, I'll come to the meeting and they will ignore all their success which is huge and just talk to me about what are the obstacles they are facing now in order to achieve their goals. Obviously it's not everybody's like that, but in general. Then when you meet men many times they'll say did you see how this worked and did

you see how amazing that was. We will focus time celebrating their success and then move to discuss what are the issues.

In middle level management that's fine. When we move into executive level, board seats and etcetera it's really important to come with a story and to discuss your success and to highlight your success. I think we overcome it at Karyopharm by providing a lot of mentorship to the female leaders.

Taren: That's fantastic. I was going to ask you do you consider yourself to be a role model? And how are you modeling that role?

Sharon: Since I'm like all the other – I don't like to use my feathers. But I hope I can be a role model. Many women entrepreneurs contact me and I will always try to help. Often it's when they are trying to start a company. Not only in biotech actually. They talk to me, I will use my network to help them. Also, sometimes we just meet in small groups of women and just talk about the issues and provide mentorship that way.

Taren: That's wonderful. You noted earlier that as a woman and as an immigrant to the United States what are some of the unique challenges that you have found, that you have faced, in trying to start up the company? Perhaps it's in trying to find funding, etcetera. What are some of those lessons that you've learned along the way?

Sharon: Let me tell you a good story. I started the company by myself. I very quickly realized – I had a group of people that helped me. Interestingly most of them were from ex-US. But also some – or Israelis that live in the United States. But I realized that I don't have the kosher stamp that you need from Harvard or MIT, which is how most of biotech companies start.

In a very Israeli way I sat at a Panera and wrote 10 or 15 emails, cold emails, to professors at Harvard, MIT in the area that are participating in the scientific advisory board and asked to talk to them, tell them about my idea. At that point I had some data to share with them my results and see if they can join.

I have to say, many of them actually responded. I think most of them. And quickly. But the first one that responded, Dr. Ron DePinho, that later became the president of MD Anderson, he actually said, "Come, I want to meet with you immediately." By the time I was home I already had the first email. He became one of the founders of the company and a mentor for me and a great friend and a great help for us to push the company forward.

Taren: Wow, so he really saw something not only in your science but in you to take a leap, I guess.

Sharon: I think so, I think so. And he added other people. His network was amazing so we were able to expand, do more work and collaboration, understand the files better, get more results

and all of that was critical. But to your original question, I think some of it is being out of the club. That's the when you come from outside there is a club here of where you graduated from and when you worked and which companies you worked for. I was outside of all of this so I had to find my way through the club.

Taren: Which isn't always easy because there's no roadmap. There's nobody that has a guide that says this is how you navigate through this kind of closed environment. So you just had to figure it out.

Sharon: Yeah, and I have to say for a female and for a female immigrant it's tough. I agree with that. But on the other hand there were really many people like Ron DePinho and others that said we like this idea, we want to help you and they helped me. Even before we got our first funding.

Taren: That's fantastic. Earlier you said you didn't really consider yourself to be a role model, but you are a role model. Talk to me about how you define yourself as a leader. You are sitting at the top of this company, you are having to marshal your troops, you have to keep them buoyed and motivated. How do you do that?

Sharon: I was an officer in the Israeli army and I think the most important lesson you learn from there, and a lot of my leadership is built from interestingly when I was a young officer in the army. For me one of the most important values as a leader is to lead by example. And to sit with your team. When we have a tough time, when we have a complicated problem to solve we work together. When we need to stay late we stay together late. And some of our best nights here was when we have to work late for a request by the agency and we all stay overnight and we make it into a party.

But it's really never ask anyone to do something that I wouldn't do myself. It's to be more of a teacher I would say than a boss. And to show compassion. So this place is a little bit – even though we are over 300 we are still running it a little bit like a company. We know the kids of many of the employees, we know their stories and we share our family issues, our family celebrations. This bond is very important.

Taren: It's important to keep that kind of collegial atmosphere. It's easy to do when you're a smaller company, even though 300 people isn't small. But how will you manage that as the company continues to grow? You talked about having additional products in the pipeline. It's hard to keep that personal one-on-one connection, I would think.

Sharon: It's very hard. It was harder when we moved from five to 20 to 50 to 100 to now 300. The whole reason is to make sure that this kind of approach is also taken by the people that report to me and to Michael. Some of it is really just knowing that part of my time should be devoted to work with the younger employees and to spend time with them.

For example, in the summer we had over 20 interns from high school to graduate students. So about 10% of the workforce in that time was interns in the summer. We not only do it for them to do some jobs that no one else wants to do, but we spend time teaching them drug development. So each of the head of function spent lunch with them and talked to them almost at least twice a week about what he does and how it is impacting drug development.

Taren: That's a nice way to keep that personal touch and still mentor that next generation, so it serves a dual purpose.

Sharon: Yes, and we have to get used to our millennials.

Taren: What is the difference in managing millennials versus the more seasoned professionals?

Sharon: That was a tough one. Hierarchy is less important to them so they feel it's okay to talk to anybody and get advice. I actually love that. They are very, very focused on their career path. They would want to know from the interview what are they going to learn here. And how fast. Being aware that to what this place provides them as a career advancement and learning about this from the very beginning and make sure you deliver on that is critical in order to keep employees engaged.

Taren: It's interesting. It's certainly not the way I grew up through the business, to go in and be able to just walk into the CEO or the founder's office, that was not the case back 20 or 30 years ago. I do appreciate, like you say, that hierarchy isn't as important to them. They're looking for a purpose, in some ways.

Sharon: Yes, yes. And the mission of the organization is very important for them. How you deliver this mission. They want to make sure that this organization we are involved in the community. This all I think is actually pushing us, the older guys, in the right direction, in important directions.

Taren: Understood. As you sit and reflect back on your career, is there something you wish you knew then that you know now?

Sharon: Yes. We definitely did mistakes in pushing selinexor forward. One thing that we did that I think was just two years of development was to push to the highest dose possible based on the very short dosing interval of one month and not understand the chronic complexity. We dosed selinexor in many indications to many patients in doses that are about 50% higher, in some cases almost double than what was recently approved. We even are now studying in other indications lower doses.

As I move now with the new drugs, the quality of life of a patient that takes the drug every day is so important. So as a drug developer you have the responsibility to really understand the toxicity profile. If you want your patient to take your drug until disease progression then you

have to understand how this will look like, not in a month but in three months or four months on a large number of patients before you select your dose.

As I mentioned, that really cost us a lot of time and I think it also cost the reputation of the drug because it is considered – there are concerns about the side effects. And it cost us time for the approval. Now we understand the side effects profile and actually on the other side we are very up front about it and we are very concerned about educating prescribers and physicians in the clinical trials to make sure that the patients side effects and symptoms are being treated well.

Taren: Excellent. Talk to me about what’s next down the pike for you all in terms of your pipeline. What’s the next one that you are really focusing on?

Sharon: We submitted the NDA for the approval of selinexor in patient with relapsed refractory DLBCL that are not eligible for transplant or CAR-T. I don’t know if you saw, but in today’s press release the FDA accepted the filing.

Taren: That’s exciting.

Sharon: Yeah. That was from the press release today. Then we have the BOSTON study, which is the phase 3 study of selinexor in combination with bortezomib and dexamethasone –against bortezomib and dexamethasone. That study completed enrollment and, as we’ve publicly said, we are expecting results in early this year. Then we have several studies, including a study of patients with liposarcoma and a study for patients with endometrial cancer. These are phase 3 studies that are ongoing.

Then we have two compounds in the early stage. One is another nuclear export inhibitor – eltanexor – and another one is a different mechanism of action.

Taren: Excellent, so we should be looking for more fireworks later this year hopefully.

Sharon: I hope so, yeah. I’m all for fireworks.

Taren: Finally, you’ve had a really successful and varied career. Can you identify one wow moment of your career that either changed the trajectory of what you were pursuing or that stands out to you as really a pivotal moment?

Sharon: Of course, and it’s a moment – I always say that to entrepreneurs, you have to imagine the things. Because it’s so hard. When you’re down and things are not working you have to imagine a picture and that picture helps you move through this low place and get there. For me it was always to meet a patient that receives selinexor.

So we were fortunate enough to meet several of them, but when I met the first woman that got selinexor I remember she arrived with her husband. I remember I was shaking when I shook her

hand. It was so humbling for me and I was so grateful that she had the courage to try selinexor in the clinical trial. She responded well. She did have a lot of side effects, and I think then she gave a talk to the company and one of the employees asked her why do you take the drug if you have side effects. She just looked at him and said, "I wouldn't be here alive talking to you if I didn't take the drug." For me and for the other employees, when you meet that it gives you all the energy and the resilience and the courage to move forward with what we do.

Taren: That is a wow moment. That's amazing. It is that power of the patients that fuels so many folks in the life sciences industry. It's those personal moments that provide meaning to the work you do.

Sharon: Absolutely. It's the most important thing.

Taren: Wonderful. Well, I want to wish you continued success and thank you for sharing your story with us for our WoW podcast program.

Sharon: Thank you very much for the time and for having me on the program.

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