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In this episode, Taren Grom, Editor-in-Chief of PharmaVOICE magazine meets with Holly Kordasiewicz, Ph.D., VP of Neurology Research, Ionis Pharmaceuticals.

Taren: Dr. Kordasiewicz, welcome to the PharmaVOICE WoW podcast program.

Holly: Hello and thank you for having me.

Taren: It's our pleasure. Holly, you have spent your whole career in the pursuit of understanding neurodegenerative diseases. What drew you to this area of care?

Holly: Ultimately, it was my family. One of my grandfathers had Parkinson's disease and the other had Alzheimer's, and one of my grandmothers had dementia. So we have a lot of neurodegenerative disease in my family, and I saw firsthand what that does. It's so hard to watch someone you love lose parts of who they are gradually and relentlessly and not all neurodegenerative diseases, but many, can take away what makes someone who they are and it feels particularly tragic.

And then as I learned more about neurodegenerative diseases, I learned about the inherited neurodegenerative diseases, so these are diseases attack whole families. For the dominantly inherited forms if you carry the mutation you get sick and each year your kids have a 50-50 chance of getting sick. So as a parent succumbs to the disease, the children take care of them, they watch them deteriorate sometimes knowing, sometimes wondering if this is going to be their fate and they have to deal with that. And it feels particularly unfair. If we can take that unfairness – for lack of a better word – that comes with inheriting a gene and turn it in a way to help somebody, I just think that's incredible. You inherit this gene and since we know what the gene is we can fix it, it feels really powerful. And we're in a time in science where we can make that happen. There's just so much potential and I get to be a part of it. I mean how could I not.

Taren: Well thank you so much for sharing that personal connection to your obvious passion in pursuing therapies, and if we could only hope cures for some of these really serious diseases that's impacting, as you said, whole families but society in the world at large. We just look at the numbers and they're staggering just for Alzheimer's alone.

You joined Ionis from the academic setting of working in the laboratory of Dr. Don Cleveland at the University of California in San Diego. Talk to me a little bit about your experience there and then what led you to make the leap from lab to the industry.

Holly: It was actually the Huntington program. I couldn't leave it. Huntington's is a dominantly inherited disease caused by a mutation in the Huntington's gene. Patients with Huntington's they lose motor function. They have behavioral and mood changes and cognitive dysfunction. By the time they ultimately succumb to their disease, they've lost 30% of their brain mass. It's just absolutely devastating.

At Ionis we use antisense oligonucleotides (or ASOs) to alter RNAs and we can basically turn down the Huntington gene. So at UCSD I was using the Ionis ASOs to lower the Huntington RNAs in mouse models of Huntington's disease and it worked. Like it worked shockingly well and that it kept working. There'd be an issue, we'd solve it, move on to the next question and I just I couldn't leave the program. It felt like we were on to something and I wanted to see it through, and I had been working with the team at Ionis throughout this time and they were all just really wonderful, very science and data driven where everyone's goal was to help someone and not just to help them a little, but to really try to change people's lives – so a whole group of people with that as their focus, I wanted to be a part of it.

Actually to be totally frank, when I made the change I thought I was giving something up. I thought I was going to lose some of my freedom that I had in academics to be my own boss, to follow my own path, all that stuff you hear in graduate school, but that's not the case at all. My only regret was that I didn't do it sooner.

Taren: That's great if that's the only regret. I think that it's an unusual path. So when we talk to women who are coming from the academic arena and they have to leave their labs, they really do consider it a big leap. So I'm glad you found it not to be so much a leap, but as an augmentation to your pursuits.

Holly: Yeah, and I really think it's because I had the opportunity to work so closely with Ionis as a post doc. So I was embedded in the academic lab, but I was literally driving up the coast to come and do some of the experiments with the scientists at Ionis. So I was really kind of living in both worlds while I was still safely in academics doing my training, and so I think it made it a lot easier than it might have been for other people.

Taren: What a great bridge to get into the industry side. That's fantastic. You talked a second ago about ASO and RNA, so talk to me about where you see the greatest opportunities for RNA therapeutics.

Holly: Well, obviously I'm pretty biased here, impartial to neurology and neurological indications. There are many inherited neurologic diseases and those with known genetic drivers and with the success it's been rather it's our drug for the treatment of SMA, we know that it can really work. We see children walking because of an RNA therapeutic.

If you're not familiar with the story of Spinraza, it's truly amazing. This is a drug that's taken children who were fated to die from an inherited neurodegenerative disease, to

meeting normal developmental motor milestones. It highlights the power of an RNA therapeutic and what can happen if you target the underlying disease. It's a game changer.

So we now have our tau program on Alzheimer's disease, a synuclein program in Parkinson's disease both, which I am very excited about based on my family, but also because these target the underlying pathology of the disease and have the potential to be those game changers. There's another one that I'm really excited about. We have some positive results coming out of our SOD1 ALS program and we have another C9ORF program for ALS, which ALS if you remember the ice bucket challenge that was real big a few years back that's Lou Gehrig's disease, just horrible and those programs again are hitting the underlying cause.

We also have programs in ataxia 3, Spinocerebellar ataxia type 3 and Spinocerebellar ataxia type 2 and type 1. These are more dominantly inherited neurodegenerative diseases where our preclinical data show that we can have really large benefits by going after these toxic dominantly inherited proteins.

I'm really biased about some of the neuro stuff, but outside the neuro space there's also some really exciting opportunities in the pulmonary indications where they're gaining targets in places we have the potential for some of those more game changing benefits.

Taren: I love that you're calling them game changers because we really do need some optimism in a lot of these therapeutic categories that you just identified – Alzheimer's, ALS, Parkinson's. So at what stage are some of your programs in? Let's talk about the tau program for Alzheimer's.

Holly: That's in a phase 1-2 study, so there it's the early study where you're looking for safety in Alzheimer's patients and making sure that the drug is doing what you think that it's doing. It's lowering its target RNA and in this case that's tau and that it's doing it safely. So we're moving right through that phase.

Taren: And you addressed tau and in the past it's been about amyloids. So what features is about the tau?

Holly: There's two. There's actually Alzheimer's amyloid beta and tau. It's both. There's been a lot of focus on amyloid beta because it's an extracellular protein that can be targeted with antibodies, and so that's where a lot of the therapies have been.

Tau is another pathology that actually correlates better than amyloid beta to the cognitive dysfunction that happens in Alzheimer's patients but it's been a lot more challenging to target with traditional pharmacological agents. With oligos, that's not issue because we target the RNA. We stop the protein before it's ever being made so we're not trying to

come up with ways to target this intracellular protein. We're actually just stopping it from being produced. So that's why it's really exciting because it's different and can potentially be very additive to some of the things that are going on out there with a-beta.

Taren: That is exciting to stop it even before it's being produced rather than trying to control it once it has been established. What about your ALS program, where are you in the clinic with that?

Holly: For ALS, our SOD1 ALS, so that's targeting an inherited form of ALS, that is in a pivotal trial right now. It's being led by our partners at Biogen. So they've completed the early trial looking at safety and now it's in the pivotal trial. And then we also have our C9ORF program which again is just getting started in that phase 1-2B studies.

Taren: Fantastic. So you're in that phase 1/phase 2B arena right now. Do you think you'll continue to partner or is this research that Ionis can continue on its own?

Holly: It's both. That's a fantastic question. The way our business model is set up – and I'm not one of the business people, so I might not articulate this the best, but the way I think about it is it's set up so that we can find the best home for each one of our drugs. For our neurologic indications, we partnered with Biogen where they get a first shot at each one of our neurological drugs that come through that we come up with, so they can say yes or no, they want to develop it. And the targets they've taken on are Alzheimer's targets like tau, our SOD1 program, the ataxia program that I've mentioned, so we have all those wonderful things that we're working with them.

But there's also going to be things that they're not interested in that we can still drive forward ourselves. One of those examples that we're taking forward independently is our Prion program.
I don't know if you know about Prion disease, it's a really fascinating disease. It's a really rare, progressive, fatal neurodegenerative disease and it's caused by mutations in the Prion gene, but also there's acquired cases and sporadic cases, and it's usually less than a year from diagnosis to death. So it can be really – it's just really devastating. But we have some preclinical data that, again, is really compelling that if you prevent that production of that protein that you can really just dramatically halt disease, even in really late stages of the disease. And so that's a program that we're going to be able to and it's wholly Ionis owned that we can take forward ourselves. That's really exciting and going to be coming up soon.

Taren: Exciting is not the word. I can't imagine. That's got to get you buzzing everyday when you go into the office.

Holly: It's amazing. And the people that we're working with on this, the collaborators that we're working with, they're actually – they're a couple that were on a totally

different path in life and then she found out she was a carrier for the gene, so they stopped everything that they were doing, decided to go back to graduate school and study this disease and are now trying to find a cure with us. They work with us on it, and they're just two of the most just brilliant people and we get to work with them and help them try to find a cure for their disease.

Taren: That's amazing. I've got chills. What a connection and to be purpose-driven and to be potentially being able to impact the world with what you're doing has really got to feel great. It's the sense of purpose.

Holly: Yeah. Yup.

Taren: Let's talk a little bit about your career path. You touched on it a little bit earlier. Leading to your current role as VP, you took a little bit of a non-traditional path there bridging from academia into the industry side. What advice do you have for other women scientists who might be looking to make that move and who look to you as a role model?

Holly: It's very humbling to think that I might be somebody's role model, so that's an interesting place for me, but the best advice that I can give is just to focus on doing the best job that you can, know your stuff. At least at Ionis – and I have to believe this is true in most places – is if you can advance the science, you'll advance too. Ask the right questions. Follow the data. Dream big. Push the envelope. That's just good advice for anyone.

But also one that may be more personal is just to be sure to find your voice. Have a vision and an opinion and know when to share it. I've learned to always walk into a discussion with the recommendation and a position. I know that does not may mean dogmatic and not participate in a discussion or to not change your opinion based on a data. You always have to follow the data, but think about the question and the data, have an opinion and don't be afraid to share it. So if you believe in something, share your ideas while the decisions are being made. Now make sure you can back up those ideas with sound rationale, but speak up.

For my younger scientists when they ask what I think about something, I'll encourage them to tell me what they think first. I ask them to give their opinion, what the rationale is. I push them on their logic a bit to help them refine their rationale and it's a good exercise. It helps them find their voice and it's also a fantastic way for me personally to think about things from a different perspective.

Drug discovery is really hard and it's based on so many judgments with imperfect and incomplete data, and so there's often no right answer and that's like so important to speak

up, particularly if you're the one closest to the data which the younger scientists who are doing the real work often are and know it best. So don't be afraid to speak up.

Taren: I think that's exactly right, speaking up. And you just touched on another point is working with these very tough diseases and working in that early stage it can be de-motivating sometimes when there's a setback. So how do you keep your teams motivated?

Holly: It's a really interesting question. It can definitely be a tough area to work in. You think you're close to solving an issue and then new data comes through and you realize you've just scratched the surface. However, we're really fortunate that we have so many projects going on that if one isn't moving as fast as we'd like and another is at a stage where it's giving exciting data, so I try to make the point to share the wins and celebrate the wins when they happen to remind us all that they're out there.

But I have to say I don't have to do much motivating. The patients really keep us motivated. We follow things by targets that we're going after and we can definitely get lost in the science, no question about that, but behind each one of those genes is a person. And more often than not, just like I had mentioned previously, we know some of those patients and their families. They're our collaborators. They're literally waiting for us.

With these neurodegenerative diseases they're going to get worse, and they're going to get to a point of no return and their diseases aren't going to wait for anyone. So you just do it and you just keep going. I think a lot of people just they know that that's our mission and they know that that's our vision, so the people who are here and working those hours are working for those patients. So they don't require a ton of motivation for me.

Taren: Well, you sound like you're very motivating. I can see where your teams would embrace that sense of passion that you bring to the table. You talked a little bit ago about a couple of the tips you have in meeting some of your teams, especially those younger scientists. Holly, when you look to lead your teams going forward, are you particularly invested in mentoring and/or sponsorship of some of those women scientists?

Holly: I wouldn't say women scientists in particular. Just everybody on my team is incredibly valuable and they're also very talented that I work with all of them. I think working with the younger people and helping development of them is incredibly important. I also start with the foundation that people are going to work best if they love what they do, and I really believe that people do best when they're internally motivated and excited about their jobs. Fortunately, I'm in a position where we have so many things going on that there's so many different opportunities to find that right fit for each person. Some people love technical problems. Some love detailed pathways and mechanistic work. Some really need to be close to the clinic to feel fulfilled. So I see

my job is to help people on my team find that fit where they can enjoy what they're doing to succeed.

Now of course, there's going to be times when there's work that just needs to get done that isn't particularly stimulating, but if you balance that with projects people are passionate about that's going to help, that's going to help them be successful and help them grow and help them find their voice in what they want to do. And so I see that as one of my big jobs in terms of mentoring people is helping them find that perfect fit for them.

The other thing that is important in my job I think is given our technology we can move really fast. There are so many opportunities for people to help and we get regular emails and calls from physicians and families looking for help. We have a vice to say yes, but as you can imagine that can lead to a really intense work environment with lots to do in a good way, but it's still a lot. So my other job is to make sure that my team is supported, knows that I'm here to help them, fight for them. We're all in this together. When one project gets in the weeds, we have other people to help them out so that everybody knows that they're part of this team and that we're all moving these drugs together and we're really doing this for the patients and that they're going to succeed and they're going to grow as these things all go.

So it's really listening to people, finding their fit and then helping them know that they have the support that they need to be successful. It's really setting everybody up for success.

Taren: Fabulous.

Holly: Does that make sense?

Taren: Absolutely. That sounds wonderful. I'm motivated. I'm coming to work for you. Holly, you received a big award in 2019 the OTS.

Holly: Oligonucleotide Therapeutic Society.

Taren: Thank you very much. You won the Young Investigator Award. What did that award mean for you?

Holly: It was really lovely because it's voted upon by a panel of really talented scientists in the field, and I'm not an RNA biologist by training. I'm a neuroscientist by training. I've learned RNA biology based on my job and working in this field. So to be recognized by an organization that's really focused on the chemistry and the technology, it was just really special because I don't necessarily see myself as an RNA scientist; I see

myself more as a neuroscientist. And so to realize that I'm doing that enough to be recognized for it, it was really wonderful.

Taren: Congratulations.

Holly: Thank you.

Taren: I also found out that some of your work was recently featured in a PBS documentary by Ken Burns – *The Gene.*

Holly: Yeah.

Taren: What was that experience like?

Holly: Oh my goodness. Well, other than sitting on my couch crying as they were playing it because we were seeing all of our patients and our collaborators and friends up on the television and we talked to people on the phone, but to actually – and they send us pictures of the kids with these different diseases, but to actually see them playing and hugging their family and that was just incredibly motivating to be able to see that and to be able to have that visual connection with a lot of the stuff we do by phone and email and everything was really special.

And then also I just thought they did a lovely job explaining the science and teaching people about the what the genomic revolution has meant and what things like RNA therapeutics can really be doing in a tangible real live way for helping people. So it was really wonderful to see it all captured in a place all in one spot and just told in such a compelling way. They did a great job with it.

Taren: That's fantastic. So can we find it somewhere? Is it on YouTube or how can the audience here find you?

Holly: That's a great question. I actually don't know. They posted it internally on our internal website for everybody at Ionis to watch. We got a little preview a couple of days before they came out, so that's where I've watched it. I hope it could be found online.

Taren: I actually did find it as we were talking. There are some episodes that are available on YouTube. I encourage everybody to go and find that show. So that's awesome. As we switch a little bit tacks here, as you think back about your career and you've taken some bold steps and you've made some bold moves and you've accomplished so much already, is there anything you know now that you wish you had known when you were moving up the ranks?

Holly: That's a really good question. There isn't anything that jumps out in terms of specific insights I wish I would have known, other than some of the stuff we've talked about before, but there are definitely skill sets that I wish I would have made more of an effort to develop earlier. I did not appreciate how important it would be as you move up the ranks to learn how to delegate. My training in academics and my nature that if something needs to be done, you just do and it did not help me to develop the skill at all. And it is a skill. The work we are doing now is so big with so many parts, it's just not possible to be intimately involved in every aspect always. So I needed to learn what I need to know and when I need to know it and when to let somebody else take the reign. It's still one that I'm working on, but it's definitely one that I wish I would have started developing earlier.

Taren: I think that's a good one. I think we can all have some lessons in learning how to delegate. And so finally – and I know this is going to probably be a tough question for you, but I'd like to know if there's one accomplishment or a wow moment that has shaped your career.

Holly: Oh, I can't pick just one. Can I do two?

Taren: Yes, we'll let you do two.

Holly: Okay, thank you. The two biggest wow moments for me have been the human patient data that's come in from the clinical trials. So the first was when we saw the reductions in mutant Huntington in the CSF of Huntington patients. So we were using the Huntington and CSF as the pharmacodynamic biomarker to tell us that our drug was doing what it was supposed to be doing. And our drug did exactly what it was designed to do. Not only that, but the predictions that the team had made which we worked so hard on, they were spot on and that never happens. And when you see that and you see the reductions in Huntington, you really get that sense that we have a real shot at helping people, that this might actually work and we're such nerds that we actually took to the graph and put it on a T-shirt.

Taren: I love it.

Holly: And then the second one was when I first saw the data from the SOD1 ALS trial. Superoxide dismutase (SOD1) it's the first gene that was identified that caused inherited form of ALS. We were having a team meeting with our partners at Biogen and they shared the data, and the patients who received the drug and based on the mutation that these patients carried, they were predicted to have the worst disease, really, really progressive disease. They had flatlines. They didn't progress. This is a relentless disease, and in a few months of that study they should have gotten worse and they didn't. And those were real people who got better because of what we do, and I just can't even begin to describe that feeling that we might actually be helping someone. And when they

showed the data, the room was silent and the whole group of us who normally just don't stop talking were quiet. And then of course everyone started talking, but that moment of silence where everybody just took it in really… I'll never forget that.

Taren: I have chills sitting here and you just recalling that because I can't imagine what a profound moment that had to be for all of you.

Holly: Yeah. It was just incredible.

Taren: I want to thank you so much for spending a few minutes with us for our WoW podcast. I am really looking forward to hearing future data readouts from the important work you're doing. I love your passion. I love how invested you are in trying to find some treatments and cures for these devastating diseases. So thank you for what you do and thank you for spending some time with us.

Holly: Thank you so much for having me. This was lovely.

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