Dr. Anderson's Fellowship Research

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[00:00:00] **Dr. GG deFiebre:** Hello and welcome to the SRNA "Ask the Expert" podcast series, "Research Edition." My name is GG deFiebre and I moderated this podcast with Dr. Monique Anderson. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org.

[00:00:22] Our 2023 "Ask the Expert" podcast series is sponsored in part by Horizon Therapeutics, Alexion, AstraZeneca Rare Disease, and UCB. Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:00:52] Alexion, AstraZeneca Rare Disease is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development, and commercialization of life transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they are committed to ensuring that patient perspective and community engagement is always at the forefront of their work. UCB innovates and delivers solutions that make real improvements for people living with severe diseases. They partner with and listen to patients, caregivers, and stakeholders across the health care system to identify promising innovations that create valuable health solutions. For this podcast, I was joined by Dr. Monique Anderson.

[00:01:35] Dr. Monique Anderson is a native of Brooklyn, New York. She received her bachelor’s degree in human biology from Stanford University. She attended the University of Virginia School of Medicine, where she earned her PhD and her Medical Degree, and she completed her residency training in Neurology at Emory University School in 2022. Prior to beginning her residency, Dr. Anderson completed the research in support of her PhD in the lab of Dr. Steven Jacobson at the NIH, where she studied the role of regulatory T cells in HTLV-1 associated myelopathy/tropical spastic paraparesis. She was interested in both neurology and infectious diseases, which led to her pursuit of a fellowship in neuroimmunology with Dr. Michael Levy at Mass General. During residency, she worked with and treated patients with MS, NMOSD, MOGAD, and other rare neuroimmune and neuroinfectious diseases.

[00:02:25] Thank you, Dr. Anderson for joining me today to talk about your research. To start, do you mind just talking about what transverse myelitis is?

[00:02:38] **Dr. Monique Anderson:** Okay, well, first, thanks for inviting me. So, transverse myelitis, really, the literal meaning is essentially inflammatory injury of the spinal cord. So, essentially this can be due to a number of reasons, including the immune system inadvertently attacking the spinal cord. It can be due to actually a virus or some other infectious agent going after the spinal cord and causing injury. Another potential mode

of injury would be where you can have neoplastics or cancers that can also cause this type of injury to the spinal cord. And then going from there, other rare causes such as vascular as in let's say you actually have something that's attacking the blood vessels within the spinal cord. So, that would be a vasculitis and that could also be a potential cause of that similar injury to the spinal cord but mainly when we're thinking of it, the two biggest causes are essentially immune mediated or infectious.

[00:04:06] **Dr. GG deFiebre:** Got it. And so, do you mind just talking a little bit about what you mean by immune mediated versus infectious?

[00:04:10] **Dr. Monique Anderson:** Okay, so, there's a little bit of overlap sometimes. I'll just pick viruses because those are probably the most frequent. There are certain viruses that have an affinity let's say for sort of neurons, herpes viruses, in particular, and they can just, by themselves, the virus itself can actually cause injury to the structures of the spinal cord. Then, basically, where you have immune mediated, that can be where, essentially, it's your own immune system that's attacking areas of the spinal cord.

[00:04:45] This can actually sometimes be the result or triggered by other things, whether or not that be infection as an example or it can also just be part of an overall autoimmune disorder but there's a little bit of overlap, even within that kind of definition. So, sometimes we see, and there's certainly a belief that the immune system can be triggered by stress, viral infections, other types of infections, to kind of rev up your immune system to then go and attack some of these structures.

[00:05:27] **Dr. GG deFiebre:** And then how did you become interested in researching transverse myelitis?

[00:05:32] **Dr. Monique Anderson:** So, my graduate degree is from the University of Virginia, but my most of my work was actually done at the NIH, the National Institutes of Health, up in Bethesda. I worked in the lab of Steven Jacobson, and that lab is actually focused on both multiple scleroses, but also a kind of rare disorder called HTLV-1 associated myelopathy/tropical spastic paraparesis. So, it's kind of a mouthful. It's called HAM/TSP and with this disorder, most of the injury that goes on is within the spinal cord.

[00:06:11] And I was very interested to understand why that was the case, what causes the immune system to target the spinal cord? How does the virus, how does it basically educate the immune system in terms of moving in that direction, if at all? So, all of those questions were a part of my project at that time, and I became very interested in just any inflammatory injury of the spinal cord. And that's kind of what helped me to figure out what direction to go in for my fellowship.

[00:06:47] **Dr. GG deFiebre:** And so, for your fellowship research, do you mind talking about the study, the background of it, and what led to the development of your particular research project?

[00:07:00] **Dr. Monique Anderson:** I guess back when I was still in residency and trying to figure out which fellowship programs I was applying to, I came across a program at Mass General Hospital and Brigham Women's Hospital, and they had an MS and neuroimmunology fellowship. And within that fellowship program, there were a few tracks that you could pursue and one of them was the neuroimmunology track with Dr. Levy. I was told that I'd actually get a chance to interview with him. During that whole process, I was looking through some of his ongoing research and I came across the paper that he had written on VPS37A and a family, a couple of siblings who both had transverse myelitis and that this was the mutation that was found. [00:07:56] And the reason why it became very interesting to me was this was a portion of a pathway that I was actually quite familiar with from my own prior research. VPS37A is kind of a long name, but it's basically a protein in a pathway that helps to form these extracellular vesicles that I had previously studied. So, I'll try to not make this too technical, but basically, the ESCRT pathway, which is the pathway that this protein

is involved in, what it actually stands for is the endosomal sorting complex required for transport and it's a major tool for the recycling and removal of proteins from cells.

[00:08:50] So this can either help the cell to just kind of gobble it up and essentially almost like a trash disposal. And it'll be gobbled up within the cell, or it can actually take those tag proteins and dump them into the extracellular space in these extracellular vesicles, some of which are called exosomes. And these exosomes are what I'd been studying previously. And so, the whole idea of proteins that are within the cell, potentially one going outside of the cell, and two, that they might actually be getting misdirected from where they're actually supposed to go by mutations became interesting to me especially since we're always trying to understand what triggers the immune system to go after the spinal cord, especially in the case of transverse myelitis. So, is it the case of proteins that aren't necessarily supposed to be there actually now being available and present for the immune system to respond to? So, that's part of the reason that this whole project came to be.

[00:10:05] **Dr. GG deFiebre:** And so, what is this broad research kind of question that the study is attempting to answer? Are you looking at people specifically with what we describe as idiopathic transverse myelitis with no known cause? Or are you looking at people with MOG antibody disease where there maybe is that pathway for why there's inflammation in the spinal cord? Do you mind just talking about that kind of broad research question?

[00:10:29] **Dr. Monique Anderson:** Yes, because there's the broad question of transverse myelitis. So, we're including both patients with idiopathic transverse myelitis where we do not have a cause and then we're also including patients with MOG antibody disease, NMO, and MS because these are also the three inflammatory disorders that all involve injury to the spinal cord. And so, one, there's a question of whether or not there are any shared mechanisms between those diseases, but also because for at least NMO and MOGAD or MOG antibody disease, we actually have the antigens or those proteins that we know that the immune system is responding to. And so, if we're able to actually see the presence of these proteins and exosomes, if we're able to see that these proteins in exosomes are able to kind of trigger or inflame, activate that immune response in patients, it might be possible for us to find a similar protein or antigen within the exosomes of idiopathic transverse myelitis patients, and see what their immune system might have been triggered by or going after.

[00:11:55] And then there's the piece of going back to the whole idea of that ESCRT pathway, how these vesicles were even formed in the first place. If there are similar mutations occurring in the different patient populations that might give us a clue of something that's actually occurring through all similar diseases. So, it gives us an idea of, one, are there additional genetic tests that we should be doing for patients? And two, is this a potential therapeutic target for these patients?

[00:12:35] **Dr. GG deFiebre:** Yeah, and I guess in a way, would this then help explain potentially some of those idiopathic transverse myelitis patients and the cause then might be more explained?

[00:12:48] **Dr. Monique Anderson:** Exactly. And especially because at this point, idiopathic pretty much just means that we've looked at everything else and we haven't been able to figure out why it's occurred so if we're able to further parse out that population and actually see, even if it's not necessarily VPS37A, but let's say that we actually find additional components of this pathway that there are additional mutations or variations in those proteins and genes for those patients, then at least I would find it very important because it's something that we could certainly look further into and hopefully find therapeutic targets.

[00:13:35] **Dr. GG deFiebre:** And as you said, that's how people were being diagnosed with transverse myelitis and then we didn't necessarily know that about aquaporin-4 and then when the testing for that came about,

they got separated into a different category based on that. And so, as you said, parsing out this big category that we don't really know, that's very exciting. And then as you said, potentially diagnostic and then treatment pathways. So very exciting. And so how is this study actually set up? Are you doing testing in actual patients in cells? How is it set up?

[00:14:14] **Dr. Monique Anderson:** Okay. So, I guess think of it in two parts. So, part one is mostly tissue culture. So within where most people think of in the lab or under the hoods working with cells. We have basically a way to express this particular gene as well as that gene mutation and a way to knock down or decrease the expression of that gene within the cells. So, that's first part, looking at cells in culture and seeing what happens with this mutation. Do we see any changes in what the cell looks like and how it functions?

[00:15:05] Getting a better understanding of what the consequences might be. The other part is we have continued to collect patient plasma, as well as the cerebral spinal fluid, the CSF. And we're looking at exosomes, which is one part of the end of that pathway that I was discussing before and looking to see what changes we're seeing in the protein contents of those exosomes. Are there variations? Are there shared proteins, especially within those idiopathic transmission myelitis patients? Are we seeing anything that's shared? And if so, what do we do with that? So, that's part two of it. So, I guess to answer that, both. So basically, both the most basic stuff, tissue culture, and then also working with patient materials.

[00:16:01] **Dr. GG deFiebre:** Got it. Are you finding people in the clinic or is this through other testing that they get done, then you use samples or how does that work?

[00:16:11] **Dr. Monique Anderson:** So, we have patients that had been recruited previously, through the clinic, as well as an ongoing study where we're able to additionally ask patients to donate materials. Then also, we do have access to biobanks that had previously been established here at Mass General Brigham where we're able to access certain materials generally, more so plasma, that had previously been donated by patients.

[00:16:45] **Dr. GG deFiebre:** What is the status of the study at the moment? Are there any results you can report or is it still too soon?

[00:16:52] **Dr. Monique Anderson:** I have some preliminary results, but I guess at this point it's hard for me. At this time, I don't necessarily feel comfortable with making conclusions based off of those results. So, I'm able, at this point I've actually been isolating exosomes from patient samples, mostly plasma at this point. I don't have any results yet from CSF. I have done a few CSF samples, but not enough to really say anything. I can say that certainly from the NMO patients, I'd say that I've actually found the aquaporin-4.

[00:17:34] Again, I think I haven't had enough patients to be able to say, definitively. I'd love to have a larger number before I actually start saying I'm able to see this and I'm able to basically conclude this. But what I can say is that we have dug a little bit further in the patient subsets to see what additional mutations, variations are in that pathway I was discussing before and we actually have found a few, I think it's about five other genes within that pathway that shared between transverse myelitis, and I believe it was MS and NMO. So, we're going to look at those as well. And see whether or not they also carry similar implications as VPS37A. So, I can at least say that. So, I guess what I'd say is that I have some preliminary data, but not enough to actually make any conclusions. I'd feel a lot better once I have added all my numbers.

[00:18:41] **Dr. GG deFiebre:** Definitely. So, when is the study expected to finish or be at the next iteration of the study?

[00:18:53] **Dr. Monique Anderson:** So, I certainly hope that by next summer or fall, I'll have the numbers that I want in terms of especially patient samples to be able to start to actually really piece together the story. And the same is true on part one of it, more of the tissue culture-based portion. That portion probably a little bit earlier, just because it's not necessarily so much dependent on the additional samples coming in but I'd say probably summer. Optimistically, I think next summer.

[00:19:42] **Dr. GG deFiebre:** Great. And we'll definitely check in with you then as well. And so, what potential impact does this study have on those diagnosed with transverse myelitis or other rare neuroimmune disorders?

[00:19:55] **Dr. Monique Anderson:** So, the part that I think was most exciting when I was and continue to do the research in this area is that that same ESCRT pathway has been implicated in several other neurologic disorders especially in the realm of repair and recovery. So, it's unclear if this is also going to be the case with transverse myelitis, but this is something that we're hoping to answer as well. And especially because a lot of my main interest is understanding what triggers disease and essentially what is that initiating step. If this does indeed really determine what antigens or what proteins the immune system may or may not be responding to, again this could be sort of something for early intervention.

[00:20:59] **Dr. GG deFiebre:** Got it. And so, by repair and recovery, are you saying that the knowledge gained from this might help figure out ways to repair and restore the spinal cord?

[00:21:10] **Dr. Monique Anderson:** It feels lofty to state, but when I came across that and the fact that this does seem to be a pathway that's been cited again and again with other neurologic disorders, it has certainly brought up the question. Especially if it's involved in sort of the recycling of proteins and the recycling of membrane or surface proteins, then maybe it actually might have a role in that recovery and repair, especially in terms of myelin. If this is something that's potentially on the surface, can this actually help with repairing that damage that has occurred? I don't know. It would be really cool if that were the case.

[00:22:06] **Dr. GG deFiebre:** Yeah, for sure. And then in terms of early intervention, is that what we talked about earlier with the potential diagnostic piece of being able to identify a genetic mutation or something that then could lead to treatments?

[00:22:19] **Dr. Monique Anderson:** [Nods yes.]

[00:22:20] **Dr. GG deFiebre:** Anything else that you want to mention that I didn't ask about or anything else?

[00:22:27] **Dr. Monique Anderson:** I think another piece of, and honestly this is something that's being pursued by really a lot of other neuroimmunologists, is just trying to figure out not only what triggers but what's the difference between monophasic, or this happens once, versus this happens again, or this then leads to progressive disease, or this then leads to basically, additional flares. So, that's another portion of this project, trying to figure out how do we put the brakes on things going further.

[00:23:15] **Dr. GG deFiebre:** Got it. Thank you. It's all very exciting and we appreciate you taking the time to chat with me today about your research and doing the research as well and contributing to the knowledge of our community. So, thank you so much.