Immunology of Rare Neuroimmune Disorders

Part 3

You can watch the video of this podcast at: youtu.be/j9a0vOR5-9o

[00:00:00] **Dr. GG deFiebre:** Hi everyone and welcome to the SRNA's “Ask the Expert” podcast series. This podcast is titled “Immunology of Rare Neuroimmune Disorders Part 3.” My name is GG deFiebre and, I moderated this podcast. 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. Our “Ask the Expert” podcast series is sponsored in part by Horizon Therapeutics, Alexion, AstraZeneca Rare Disease, and Genentech. 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.

[00:00:48] Alexion, AstraZeneca Rare Disease is 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're committed to ensuring that patient perspectives and community engagement is always at the forefront of their work. Founded more than 40 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures, and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche group, has headquarters in South San Francisco, California. For additional information about the company, please visit gene.com.

[00:01:28] For this podcast, I was joined by Dr. Benjamin Greenberg. Dr. Benjamin Greenberg received his Bachelor of Arts degree from Johns Hopkins University and his Master's degree in molecular microbiology and immunology from the Johns Hopkins School of Public Health in Baltimore, Maryland. He attended medical school at Baylor College of Medicine in Houston, Texas. He completed an internship in medicine at Rush Presbyterian St. Luke's Medical Center in Chicago before going on to his residency in neurology at the Johns Hopkins Hospital in Baltimore. He then joined the faculty within the division of neuroimmunology at Hopkins and became the co-director of the Transverse Myelitis Center and director of the Encephalitis Center. In January of 2009, he was recruited to the faculty at the University of Texas, Southwestern Medical Center where he was named director of the new Transverse Myelitis and Neuromyelitis Optica Program. That same year, he established the pediatric debilitating disease program at Children's Medical Center, Dallas. He now serves as the director of the Perot Foundation Neurosciences Translational Research Center within the O’Donnell Brain Institute and Vice Chair of Translational Research for the department of neurology. Dr. Greenberg is recognized internationally as an expert in rare autoimmune disorders of the central nervous system.

[00:02:41] **Dr. GG deFiebre:** So, to start, do you mind talking a bit about what we mean when we say repair in the spinal cord, the brain, or the optic nerves?

[00:02:51] **Dr. Benjamin Greenberg:** Yeah, GG, it's a great question and something we get asked in clinic all the time and when patients or families ask me about opportunities for repair pathways for repair research about repair, I actually always push back and ask a somewhat rhetorical question, which is, "Are you interested in repair or recovery?" Because it's actually important to recognize that functional recovery can occur via mechanisms that have nothing to do with repair of the spinal cord or brain or optic nerve. So, it's possible to have residual physical damage of the nervous system, but yet be functionally perfectly intact. And this is where rehabilitation comes in. And this notion of plasticity where you can recover function, your body can adapt to damage and get back function even if not fully repaired. But admittedly, there are many patients, a lot of patients who have residual symptoms or reach a plateau who would benefit from structural repair of damage that's been done. And when we're talking about repair, the context is around what's been damaged. And we think about two different categories and then within them they have subcategories. So, on the one hand, we think about the actual neurons, the actual wiring that connects point A to point B, whether it's brain, the spinal cord or spinal cord to muscle, but the actual neuron itself. And then we also think and talk a lot about the myelin, the protective coating around those wires, if you will, those neurons. So, when people have had damage, it's possible that they damage the myelin, the wires, or both, and depending on what was damaged would dictate what needs to repair.

[00:04:38] **Dr. GG deFiebre:** Got it. And so, is this the same for the spinal cord, the brain, and the optic nerves? Or do these areas differ in some way from each other?

[00:04:46] **Dr. Benjamin Greenberg:** Yeah. Grossly we lump them all together. We said that a neuron in the optic nerve in the brain and the spinal cord is a neuron and myelin is myelin. That's probably too simplistic on our part. The types of neurons that exist in different places are different and what would be needed for repair would be different. The best example in our community is we serve lots of patients with different forms of myelitis. Sometimes the myelitis happens as part of ADEM, as neuromyelitis optica, sometimes it's idiopathic, we don't find the cause, and sometimes patients have the acute flaccid myelitis variant. And if we compare the idiopathic myelitis patients to the individuals with acute flaccid myelitis, they have each suffered damage to neurons to some degree, but there are two totally different neurons. The idiopathic myelitis patient has suffered damage to what's called the upper motor neuron, the connection from the brain to the spinal cord, but the patient with acute flaccid myelitis has had damage to the lower motor neuron going from the spinal cord to the muscle. Now, not to get too complicated, but it's worth noting about half of acute flaccid myelitis patients have damage to both upper and lower motor neurons but what they all share in common is that lower motor neuron damage. And what's needed for repair of a lower motor neuron is different than what's needed for repair of an upper motor neuron. Remyelination strategies will not recover function in someone who has a lower motor neuron damage. So as people are looking at clinical trials and research around repair of the brain and spinal cord, it's important for everyone to know their diagnosis, their location of damage, and whether or not any of the work being done or research being offered would actually be of benefit to them.

[00:06:27] **Dr. GG deFiebre:** Got it. And then in the central nervous system, does repair occur naturally? Is that something that your body just does after an inflammatory attack or issue that occurs and what inhibits that sort of repair and what might facilitate that repair?

[00:06:46] **Dr. Benjamin Greenberg:** Yeah, it's such a good question with bits and pieces of data. So, let's start with the two major co-variants around repair, what was damaged and the age of the person that had the damage. So, if we're talking about damage to myelin and the question is does your body naturally remake myelin? The answer is yes. Does it do it better in a young person then--I won't say old because I'm in that category now--an older person? Yes. So, if I have a child with myelin damage, they're gonna have much more repair than an older adult with myelin damage. And so, it does happen naturally. We consider it incomplete. The best data we have says that remyelination that occurs naturally is not the same as the

original myelin that was there but there is remyelination that occurs. And there has been intense focus on why doesn't it remyelinate better or more completely. And there are molecular signals within the cells of the brain or the spinal cord of the optic nerve that sends stop signals to myelin formation that are left over from our embryologic development. And so, some of the research that's done is in how do we temporarily turn off that stop signal to allow people to remyelinate more. Now that's very different than damage to neurons. We have very limited data around regrowth of neurons in the brain, spinal cord, or optic nerves. The general sense is once the neuron is gone, it's gone. Now in the peripheral nervous system, when a neuron is damaged, neighbor neurons can sprout and grow and take over some of the function but that's different than the primary neuron regrowing. To-date, evidence suggests that once a neuron is damaged, the axon is cut, it does not regrow and can't regrow in the same way it was there. And so, we're really looking for other parts of the nervous system to take over.

[00:08:52] **Dr. GG deFiebre:** Okay. And then we hear people often ask about how they've been told they have an astrocyte scar or that there--Can you talk a little bit about what that might be?

[00:09:03] **Dr. Benjamin Greenberg:** Yeah. We do hear about a lot and it's in the literature a lot. And I think it's a sometimes-hard concept for us to absorb until we take a very normal routine event in our lives, like cutting our hand in the kitchen, which I've done too many times. For the record, you can't see it on the video, but the mark here is from a mandolin and if nobody on call knows what a mandolin is, look it up and don't use them. After slicing a part of my finger, it healed but I'm left with a scar. My fingerprint is different than what it used to be. The cells that grew back to fill in the wound did not remake the original tissue of my skin. They formed a scar to prevent bleeding and to prevent infection and to allow the rest of the finger to function. The same thing happens in the brain and the spinal cord and the optic nerve after an injury. And the scar we refer to as an astrocytic scar because of the types of cells that fill in that wound, which is exactly what this is. It's a wound. It's tissue damage. It just so happened to occur because of the immune system or something along those lines, but that scar forever changes the architecture of the brain and the spinal cord or the optic nerve. So, some of the work that's being done around repair is actually fascinating in terms of the focus. There are groups that have been working on medications to prevent a scar from forming. So, imagine a world where your body actually could repair quite a bit and maybe naturally it can, but its full recovery, its full repair potential is limited due to scar formation. If we were to give people medicine during their acute illness that prevented scar formation, then their body may have a much better chance at repair. Or if we had a medication that could get rid of a scar, natural tendencies of the body may lead to greater repair. So that astrocytic scar is an area of focus for a lot of researchers and for good reason.

[00:11:06] **Dr. GG deFiebre:** Okay. And then I actually have a question about imaging and so if someone has an MRI and they were told something like the area of damage is smaller or has been healing or something like that. Do you mind talking a bit about that and does MRI kind of correlate with how much function someone gets back. Can you measure repair in some way?

[00:11:31] **Dr. Benjamin Greenberg:** Yeah, this is one of my favorite topics. I get the question a lot and I have to admit that our MRI technology is not where we want it to be relative to quantifying damage and repair, particularly in the spinal cord. And so, there is no good correlation meaning no concrete correlation between what happens on the MRI and somebody's function. And it has to do with a lot of different features. One is imaging the spinal cord is extremely difficult. The spinal cord itself is relatively small. It's encased in bone and that bone is surrounded by lots of tissue and every time your heart beats the spinal cord bounces. So, we're trying to take a picture of a moving target that's very small. And so, getting really accurate data on MRI right off the spinal cord can be quite difficult. Secondly, what the MRI measures is water content, water in the cells, water out of the cells, water flowing between the cells. And so, when you have damage, we're using those water molecules as a surrogate for how intact is the tissue or not. And we don't yet know how to tell

the difference between repair versus repair with scar versus just scar. They may all look about the same on an MRI And so, there are advanced technologies that are pushing the envelope for us being able to track this. But to date the MRI is a poor correlate for most patients to their outcome. Are there patients with really bad looking MRIs and bad outcomes? Yes. Are there patients with really bad looking MRIs who are doing great? Yes. And so, it's hard on the individual person to do a 1:1 correlation between the two.

[00:13:17] **Dr. GG deFiebre:** And then you talked a little bit about research for repair, but is there any other research on repair that is currently ongoing that you'd like to talk about?

[00:13:26] **Dr. Benjamin Greenberg:** Yeah, there's a lot of work happening in different ways. We've been working as you know on our remyelination stem cell trial in collaboration with the SRNA and a group, Q Therapeutics, and with COVID, and all sorts of other things. We are finally hoping to have our first surgery this year and keep working towards achieving that. So, we're hoping to help individuals who have damage to myelin in their spinal cord. These cells are not going to make a difference for regrowing neurons, for example. Are there groups that are looking at options to regrow neurons for our patients and families affected by acute flaccid myelitis where you need a new neuron to go from the spinal cord to the muscle? And indeed, there are. And so, this is being approached in a lot of different ways. It is challenging. There are a lot of obstacles, and the obstacles aren't just in the science. The obstacles are in the clinical trials. How do you design them to show that these interventions are safe and effective, but the field continues to move forward, both with cell-based therapies and medications that hopefully will promote repair. There are multiple oral and infusible medicines that are under study to try and enhance the body's remyelination potential. So, there are a lot of things that we're going to see, and I'm firmly convinced that at some point we will have these technologies working but it's still a road ahead of us to get there.

[00:14:50] **Dr. GG deFiebre:** Got it. And then just briefly as well, we do get questions about stem cells frequently. There are stem cell clinics that exist. Are those kind of based on any sort of research or what is the general experience with that?

[00:15:06] **Dr. Benjamin Greenberg:** The stem cell clinics that exist, some in the U. S. although there are fewer than there used to be, and then a lot internationally, have raised a lot of concerns for different reasons. Often the question is around not just the source of cells, but what exactly is being injected. A lot of these clinics are very cagey about releasing exactly what's in their proprietary formulations. We have had unfortunately patients who traveled overseas for stem cell therapies who passed away and we never get full detailed information about what happened. And it's important to note that even in clinical trials where stem cell-based therapy has been tried, we've seen some adverse events. We've seen the immune system react to those cells in some situations. And so, these are not therapies to be taken lightly and jumping into, these are things that we need to be careful with and be methodical about and take time. And so, in general, I caution people against doing off label or unapproved cell-based therapies, because there are a lot of risks involved.

[00:16:22] **Dr. GG deFiebre:** Got it and then any final thoughts or anything we didn't cover on this topic?

[00:16:27] **Dr. Benjamin Greenberg:** No, I think I'd just bring it back to the beginning, which is to make sure people realize the goal is restoration of function. And there are lots of things that can be done to restore function even before the technology is available for repair or enhanced repair. And the other thing to keep in mind is a lot of the things we recommend for our patients from a rehabilitation perspective isn't just around restoration of function. A lot of what we do is recommend certain interventions to keep people healthy from a bone density perspective, a muscle mass perspective, a cardiovascular perspective so that when we do finish our jobs and succeed in a cell-based or drug-based therapy to promote repair, the rest of the body is ready to receive that repair. I've had conversations with a lot of my patients where I've said, "Wouldn't it be sad

if we finally prove a cell-based therapy to remyelinate late your spinal cord, but your muscle has contracted so much?” Even a new spinal cord won't get you back function because the muscle now has independent damage. And so, a lot of the work we ask our patients to do may not lead to dramatic changes in function but will keep them to be ideal candidates to receive technologies in the future. So even while waiting for the promise of technology to come through, we shouldn't do so idly. We should be active in pursuing different interventions.

[00:17:55] **Dr. GG deFiebre:** Got it. Thank you so much

[00:17:57] **Dr. Benjamin Greenberg:** Appreciate it.