AQP4/MOG tolerization research

You can view this presentation at: youtu.be/oJA-fwn5r7Y

[00:00:05] **Dr. Benjamin Greenberg:** We're going to switch gears and talk about options to get rid of autoimmune disease without killing the immune system. And so, remember we talked about autoimmunity as being your immune system getting confused and going after a protein in you by mistake. What if we could teach it right from wrong? And in immunology terms, the word we use for that is tolerance. Can we teach an immune system to be tolerant again of that MOG protein or aquaporin-4 protein?

[00:00:34] So, I'm going to be introducing Dr. Peter Sguigna who not only did medical school and residency and fellowship here, but stayed. He was injected with a small serum that shall remain nameless and we convinced him in a back room to stay with us on faculty where he's taken a lead in our eye lab studies, which for many of you who've had optic nerve involvement, know this plays a critical role in these diseases and is taking a lead in a variety of trials.

[00:01:10] **Dr. Peter Sguigna:** Excellent. So, thanks for that introduction and I couldn't really have kicked it off better myself. So, I was asked to talk about AQP4 and MOG Tolerization. And I have messed it up from the beginning. And one of my disclosures is really, I have no idea what I'm talking about. So, I'm a neurologist, not necessarily an immunologist, but I've worked with the Department of Defence and a number of different collaborations over the years and I've kind of seen programs develop. And so, I'm taking this from perspective is this concept of inducing tolerance is kind of actively evolving. And I think it's going to be very applicable to both NMOSD and MOGAD.

[00:01:55] And so, I like objectives and I like trying to stay on time. So, we're going to go forward here. And so, I got to talk a little bit about what tolerization is and you really can't talk about tolerization without getting into the nitty-gritty of the immune system. We're going to talk about some of the things that have been done as far as immune tolerance in the history of medicine. What are we doing actively in NMOSD and MOGAD? And what does the future look like? And it's hard again to talk about an immune tolerance without talking about the role of the immune system.

[00:02:26] So, the way I like to explain it to people is the immune system is the part of your body that's always fighting viruses, bacteria and even cancer to a degree and it's constantly working, it's constantly encountering things and it's really got one job and one job only look at it and say, is this me, if it is, leave it alone, if it's not

me, we got to get rid of it. And fundamentally from most of the conditions that fall under the umbrella of the SRNA, we essentially believe that one's immune system has fundamentally become confused and sees something that belongs to you and thinks it does not belong to you.

[00:03:06] And whether it's part of getting caught in the cross fire in kind of a peri-infectious MOGAD or ADEM or, you know, something idiopathic to a different degree. We think that the immune system as it's encountering things is going to be playing a major role in the development, not only in the development, but also the continuation of these diseases, whether it's continued relapses or not. And really getting into the nitty-gritty is if you can learn about how one disease got confused, you actually learn quite a bit about how the other diseases may get confused.

[00:03:44] And so, most of these diseases, again, under the umbrella of the immune system getting confused, we think that each one got slightly confused in a different way. And so, one way may lead to MOGAD whereas another way might lead to NMOSD. And I hopefully don't get too much induction of PTSD by bringing up high school biology course, but basically when we talk about immunology and immunology 101, we talk a lot about B cells and T cells, B as in boy, T as in Tom. And this graphic here kind of shows about the education of each of these cells.

[00:04:27] So, as they're essentially born, they don't know anything and then they go different places in the body to learn what's me and what's not me. And looking at each of these cells individually, there are certain areas in their development where we think that they are getting confused. And so, we actually know quite a bit about where this is happening very particularly in NMOSD. And again, people are looking at these and saying, can we re-educate the immune system here or here or here. And again, most of the focus has been focused on B and T cells, but there's a third.

[00:05:08] So, now we're entering the 102 immunology course. There is a third cell called the antigen presenting cell often abbreviated the APC and each of these cells is talking to each other. And again, the role of the antigen presenting cell is to present it something to either the T cells or the B cells and they will decide is this me or not me. And there's a ton of chemicals and alphabet soup of proteins and signals that each of these are using to talk to each other. And some goes up, some goes down, depending if it's self or non self. And you know, it becomes kind of this intricate symphony of communication between the different types of cells.

[00:05:53] And so, the B cells, the T cells, the Myeloid cells, which are often antigen presenting cells are working together to create the symphony. And we're going to see if the sound works and it does not. Hold on. Bear with me. I want you to imagine you are hearing Mozart's KV 488. And so, each of these cells can kind of be thought of as a note in the symphony. And so, the string instruments enter as the wind instruments exit and everything has to go very smoothly. There it is. And a single note if it goes in the wrong place, may lead you to kind of the induction of autoimmunity. And around 10 seconds you may have heard this girl.

[00:07:04] And so, in that recording of the symphony, there was a note that didn't belong and this is a picture of who was responsible for that note. This is Penny, this is the face that she makes when she knows she has done something wrong. But the nice thing is we can teach penny, right? So, this whole concept is we can use education methods for the immune system to say, let's put this part of the immune system that is confused back in the right place. And so, continuing with this analogy and essentially this is the music sheet for the central nervous system on the right.

[00:07:45] And this is the same slide actually that I used to teach the second year medical students on the diseases of the white matter. So, not only is everyone an amateur immunologist, but now you're essentially entering the second year of medical school. Thank you. One of the reasons we asked you to sign in is so that

UT Southwestern can send you to the tuition bill. I'm kidding. You'll have to take that up with admin. And so, as you can see actually down on the top bottom, right, there is a very clear band where MOG protein is one of the major proteins that is easily found by the immune system in the central nervous system.

[00:08:29] And so, we know the note when it comes to MOGAD and we in fact know where it is in the symphony of the central nervous system. So, there's a very specific part of the neurons where MOG protein is involved in the communication between nerves. And so, we've actually very precisely honed down with molecular precision, not only where it is, but what it is. And the same is true for AQP4, right? And actually, Dr. Wang had actually a number of really good graphic slides up there. But what we've known is it's in certain parts of the central nervous system, the brain, the eyes and the spinal cord that actually correlate very well with what we're seeing in day-to-day clinics.

[00:09:10] So, if the immune system gets confused and begins to believe that the AQP4 protein is not you, you know, it will attack it and this would eventually lead to things like optic neuritis or transverse myelitis inflammation, those areas of the brain. So, this essentially leads credence to, we actually know quite a bit about how the immune system has gotten confused in both of these diseases. And again, the symptoms line up quite nicely. So, we've learned where it is or what's the bad note.

[00:09:46] So, what have we tried when it comes to inducing tolerance or re-educating the immune system? And actually, this was started in the late 60s and this was a complete accident. So, Dr. Sela, who was a great immunologist was studying mice who get multiple sclerosis like illness called EAE. And what he was doing is trying to see if he could re-educate the immune system. But to do that, you have to do the opposite. And actually he had the opposite of the intended effect. So, he actually by accident discovered a collection of proteins or small protein rather that actually protected these mice from this multiple sclerosis like illness.

[00:10:37] And so, he began to study it and he actually kind of honed in that he was actually probably re-educating the T cells to not be as excited about the white matter. And so, he said, great, let's try it in people. And so, they did a number of clinical trials and basically showed that when they gave this protein that was re-educating those T cells, it began to protect patients with multiple sclerosis. And then this was a graphic that came out in 1987 just to give you an idea of the timeline. Essentially Dr. Wang talked very nicely how things go through phases. And then the last phase in 1995 it was a successful treatment for patients with multiple sclerosis and it became known as Glatiramer acetate or Copaxone.

[00:11:26] And you know, this took a ton of work, a ton of people, the community came together to really make this reality. And of course, part of our jobs as physicians is trying to convince the people like the FDA that this is not only safe, but effective. And their full application to the FDA was actually 60,000 pages, right? So, it took us a ton of work and a ton of resources to make this a reality, but it worked, right? And so, this was really one of the fundamental tolerization successes in neurology. And it very nicely went through the phases to become a reality.

[00:12:05] So, it showed not only can we do it, but we actually learned quite a bit about how we did it and then how can we do better for the future. And at the risk of airing some dirty laundry, it takes time, right? Because safety is always our priority. And so, people have tried different iterations of this and it hasn't always gone as well. But with the success that we've had essentially at the turn of the century, we were able to go to the federal government and say, here's this idea, we want to be able to re-educate the immune system for multiple diseases.

[00:12:39] So, what came together was something called the immune tolerance network and that was the goal. And they decided to focus on a number of diseases. And this is the graphic that's very hard to read but

basically, they had quite a bit of success over the years in treating a number of autoimmune diseases and inducing immune tolerance. And so, type 1 diabetes, rheumatoid arthritis, lupus, organ transplant these are all situations where we think the immune system is fundamentally confused and we're trying to re-educate it. And so, again, I mentioned a little bit earlier in the talk that learning about how one immune system gets confused helps us to learn about another.

[00:13:29] And so, we kind of began to see synergistic progress throughout the course of the turn of the century. And a lot of the times I get questions from patients and they're very good questions. If I have a bad optic neuritis, can you replace the optic nerve? In my mind, that's a good question. And I can look at them and I could say probably not because they tried it in type 1 diabetes, right? And so, the idea is even if you replace that nerve, the immune system's going to still be confused and could still attack it. And they basically through the immune tolerance networks, they got a lot of tools and the toolbox are really good tools to understand how the T cells working and how the B cells are working.

[00:14:05] And it's actually funding a number of clinical trials. Again, CR attempts to re-educate the immune system and some have worked and some have not worked. And so, this is another example of trying to re-educate T cells in a different way and it didn't work. So, in a sense it was a failure but we actually learned quite a bit by this failure essentially. That this part of the immune system was probably not the way that those T cells got confused. And this becomes really pertinent to both NMOSD and MOGAD, because in both of these diseases, we have molecular precision in knowing what it is we're trying to re-educate the immune system on.

[00:14:47] And so, NMOSD tolerization trials in a sense are underway and MOG in my mind is not far behind, you know? As Dr. Wang had mentioned we didn't really get the commercial assays in the United States till 2017, but we've actually kind of known about it all along. So, if again, we're kind of re-examining things and trying to get the pieces together, because I kind of get a clear picture of what the future holds. And this molecular precision really helps us, right? Because if someone comes to us and they think they've got the cure for these diseases, right? Nine times out of 10, they don't, right? And that's for a number of reasons.

[00:15:25] But if you know what it is you're trying to do with very good precision, then you really streamline this process into the most successful therapy that we're going to bring to patients. And so, what are we doing to do that? So, people have looked at this in very recent history and said, okay, the immune system has suddenly gotten confused. Should we start over, right? So, you hear this note, and we tried to make penny read and she didn't really do a good job. And so, we're going to just start over. And the way they go about this is essentially a stem cell transplant.

[00:16:07] So, people use this word differently for different contexts. This is a bone marrow transplant if you will. So, what's called the Hematopoietic stem cell transplant. And that's started from the top. So, the immune system has gotten confused should we wipe it clean and allow it to re-educate itself? And so, we've tried this in neuro-immune conditions by autologous or when you give it to yourself. So, basically, we take some of those cells, we wipe out what's there, we give the cells that we took back to you and your immune system is reconstituted. And this is mostly studied in multiple sclerosis.

[00:16:46] So, again, this is not a new concept. People have done this and people are continuing to do this particularly from multiple sclerosis and we're tweaking a number of things again to see if we can have essentially perfection, right? It is one of our most effective ways to treat multiple sclerosis and most effective is about 80%. And then you take a disease with multiple sclerosis and we talk a lot about cures and essentially, they can't, the definition of a cure in multiple sclerosis is often referred to as NEDA or no evidence of disease activity. So, about an 80% chance with multiple sclerosis, but it's actually been tried in NMO.

[00:17:24] So, this is the Northwestern group where they did this stem cell transplant. And this was kind of their own regimen that they took. And this was a small number of people. And again, you've got to always take this in context. So, this is people with different types of NMOSD and differences in how aggressive each one was and what we saw was basically what we saw in multiple sclerosis, roughly 80% effectiveness with about five years follow up. It turns out that it might not be that good if you follow them a little bit longer, but it at least lended credence to this. We were on the right track as far as re-educating the immune system.

[00:18:05] And, for NMOSD, we've got this AQP4 antibody blood test. And basically, if people go negative, we are cautiously optimistic about their prognosis in a good chunk of them and eventually turned negative. But some of these people stayed positive and that typically, those were the people who had relapsed. And again, with this molecular precision, we're always asking us with these two diseases. Well, we know a lot about how the immune system is confused. Can we re-educate it, right?

[00:18:41] And so, I wanted to highlight some of the work that was done by our colleagues at UCSF where they basically were able to induce immune tolerance to AQP4, specifically by targeting the T cells, but not against MOG. And so, they basically had mice that were developing NMOSD or MOGAD and they were able to re-educate their T cells and it seemed to have worked. So, we're always fighting is that B cells or T cells. This was a pretty good argument that paradoxically the T cells might be a good target in a disease like NMOSD.

[00:19:20] And this is an NMOSD or MOGAD, but it's actually, well, it was called multiple sclerosis. And so, this was actually the same company that made one of the more popular COVID vaccines. And they basically tried to re-educate the immune system by targeting MOG itself, so the MOG protein. And they called it multiple sclerosis, we're going to have to re-educate them a little bit about that. But basically, they showed by using a vaccine, they were able to make the immune system less excited about that MOG protein. So, we're excited about some potential future developments on that progress side.

[00:19:59] And there's even something called cell therapy. So, this is a little bit weird, but stay with me. So, sometimes it's off what we call off the shelf or sometimes we'll do a blood draw and we'll take parts of your immune system, we'll change them a little bit and then we'll give them back to you. And it's looking at the antigen presenting cells, which I showed a little bit earlier on the immunology slide. So, if we were to take an antigen presenting cell and say, hey, this MOG protein or this AQP4 protein that's you and then give it back to him. Could we use that as a therapy in these diseases?

[00:20:43] This is essentially their phase one trial of where they did essentially just that. They did it in a handful of patients with multiple sclerosis as well as NMOSD. This is the results and I've got a lot of graphics here. I don't want you to worry too much about them, but limited numbers, quite variable disease. Basically, it seemed to be safe and they looked at how the immune system was reacting to each of these proteins that they tried to induce tolerance to. So, they looked at how the T cells were reacting and the results were a little mixed.

[00:21:18] They looked more specifically at those NMO patients that they tried to induce tolerization. Again, the results were kind of mixed. And they looked at some of these very specific proteins that were communicating. How excited are these cells about these different proteins that are found in the nervous system? And actually, it's hard to interpret, but actually, the results over here were kind of suggested that it may be working, there's room for success, but maybe this entire strategy is not only safe, but an effective way to move the field forward when it comes to multiple sclerosis and NMOSD.

[00:21:59] And on the topic of cellular therapies, some of our colleagues have actually tried a different approach. So, we talked about the antigen presenting cells giving those back to you. There's something called car T

cells, which is very similar. So, if we took your T cells and we changed them a little bit to be, let's say, not excited about the AQP4 or the MOG protein, but actually, to be excited about those cells that were excited about AQP4 or MOG protein. So, have those T cells tried to take out those specific cells that are essentially autoimmune and give those to you as a therapy itself.

[00:22:39] So, they did this in NMOSD and this is basically how sick these patients were at the onset. So, these are NMOSD patients that were actually having relapse, a number of relapses despite conventional therapy. So, essentially some of these FDA-approved therapies Dr. Wang was telling us about they didn't seem to be doing a good job by reducing the risk of relapses and then they basically started the infusion and followed them. And the results that we see here essentially kind of mimic the earlier study. So, it was safe, there was a number of issues that they ran into, but they were able to overcome these.

[00:23:18] And with NMOSD, we have that protein that AQP4 antibody and they looked, you know, in the top right, did it go away? And it looked like that most of these patients were converting to sero negative essentially. Essentially, we were getting rid of that part of the immune system that was confused. And so, this is all very exciting. We're seeing this essentially almost in real time. I think the last two papers I showed you were published in the last three months. So, what does the future hold, right?

[00:23:53] So, again, these are really good diseases when it comes to convincing others to study them because we know what we're talking about. And again, if we can develop this therapy with molecular precision, we can develop a very safe and effective therapy to re-educate the immune system. And so, in a more broad sense, actually, there's about 288 actively recruiting clinical trials and that immune tolerance network that I showed you a little bit it is continued and they're funding about 16 active immune tolerance studies.

[00:24:26] And again, I showed you some of the results that indicated that the NMOSD trials are underway. And essentially in a way, we're actually all trying to re-educate the immune system. So, for NMOSD people are targeting those B cells that are very specifically producing these AQP4 antibodies. There's something called the BTK inhibitors, which essentially in a way are trying to re-educate those myeloid cells and the B cells to be less excited about these antigens. And then we're specifically targeting certain types of CD20 antibodies that are better at reducing those antibody producing cells.

[00:25:08] And again, Dr. Wang had very shown very nicely actually that we've got actively going clinical trials which in a way are kind of re-educating the immune system that are looking for people and to help move the field forward. So, with that, I'll take any questions. So, his question was, is there a way to measure the grade or grade someone's, you know, the strength of one's immune system. Yes and no.

[00:25:45] I would say it's very similar to using the symphony analogy. You can measure, let's say the overall volume, but it doesn't give you an idea of each of the components or the frequencies. And so, there's a number of standard clinical ways one can do this, but it's very hard to get into the nitty-gritty without doing really advanced testing.

[00:26:11] **Audience Member 1:** You said a lot so I'm not sure I quite understood everything. Is there going to continue being research on stem cells with MOG? That's my first question. Second is what about with umbilical cord cells?

[00:26:25] **Dr. Peter Sguigna:** Yeah, so there's two types of stem cells, right? So, there's the like Hematopoietic where it's purely immune based. So, they're not trying to like restore any sort of function in neurological disease. And then there's the other one and actually, Dr. Greenberg is going to present next. So, I'm going

to let him answer your second question. But as your first question, when it comes to the MOG, what I didn't really talk about there is the process of the stem cell transplant is actually quite intense.

[00:26:55] So, most of the time it involves the chemotherapy, most patients are hospitalized for roughly a month. And so, we try to get people in tip top shape before they undergo that process. And there's actually a very extensive testing that needs to be done before someone is essentially declared by a candidate, which is often done by committee. So, there's a quite a bit of process, you know? Most of the effort is, can we make that process safer, right? And so, that's where most of the research is focused.

[00:27:30] So, with the original MS studies, yes. The whole conditioning regimen is quite intense, you know, and again, and even in the recent additions of the stem cell transplant studies, we're trying to get rid of that select group of autoimmune system. And so can we do that without getting rid of everything is the question.