The State of MOGAD Science

You can watch the video of this podcast at: youtu.be/EJuZlJ59s4g

[00:00:00] **Announcer:** Hello and welcome to a special edition of the SRNA "Ask the Expert" podcast series, in collaboration with the MOG Project. This episode is titled "MOGcast: The State of MOGAD Science." SRNA and the MOG Project are co-hosts of this episode. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders, including MOG antibody disease. You can learn more about us on our website at wearesrna.org.

[00:00:38] The MOG Project is a U.S.-based nonprofit organization devoted to raising awareness, advancing research, and providing support and advocacy for the MOGAD community in hopes of finding a cure. You can learn more about the MOG Project on their website at mogproject.org. "Ask the Expert" is sponsored in part by Amgen; Alexion, AstraZeneca Rare Disease; Genentech; and UCB.

[00:01:06] Our guest for today's episode is Dr. Benjamin Greenberg. Dr. Greenberg is a professor in the Department of Neurology at UT Southwestern Medical Center in Dallas, Texas. He currently serves as the Vice Chair of Translational Research and Strategic Initiatives for the Department of Neurology. He is the Director of the Neurosciences Clinical Research Center.

[00:01:29] In addition, he serves as Director of the Transverse Myelitis and Neuromyelitis Optica Program and the Pediatric Demyelinating Disease Program at Children's Medical Center. You can view his full bio in the podcast description.

[00:01:44] **Julia Lefelar:** Welcome, everyone. It's MOGAD Awareness Month. And Saturday I want to remind everybody it's World MOGAD Day. In celebration of these two important proclaimed awareness events, we're going to welcome all of you who are connected to us today and connected to MOGAD. We have another fabulous collaboration with one of our community partners, the Siegel Rare Neuroimmune Association. You all know them as the SRNA—they're famous.

[00:02:14] In honor of MOGAD Awareness Month and the upcoming World MOGAD Day on Saturday, we have another great edition. It's this MOGcast series, and we've entitled it "The State of MOGAD Science with Dr. Ben Greenberg." And today we're speaking with Dr. Greenberg from UT Southwestern.

[00:02:34] Some of you may know me; my name is Julia Loeffler, and I'm the executive director and co-founder of the MOG Project, and I happen to be a MOGAD patient myself. Just a little bit about the MOG Project: we are a global nonprofit organization. We're devoted to raising awareness, advancing research, and providing support and advocacy as well, which includes policy work now for the MOGAD community.

[00:02:59] And it's really in hopes of finding better lives and a cure for MOGAD. We would like to thank Dr. Greenberg and GG from the SRNA, and the MOG squad and the SRNA team for their contributions to this

MOGcast. So, before introducing Dr. Greenberg, I'd like to extend a warm welcome to GG deFiebre from the SRNA. GG, please introduce yourself and tell us a little bit about the SRNA.

[00:03:27] **Dr. GG deFiebre:** Thank you, Julie. I'm GG deFiebre, Executive Director of the Siegel Rare Neuroimmune Association, or SRNA. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders, including MOGAD. So, we're very happy to be here today, and yeah, thanks for doing this.

[00:03:47] We're really excited to learn more about the research that has been happening. And so, I would like to introduce Dr. Benjamin Greenberg. Dr. Greenberg is a professor of neurology at UT Southwestern in Dallas, Texas. He's Vice Chair of Clinical and Translational Research for the Department of Neurology and directs the CONQUER program, overseeing collaborative research for neuroimmunology. So, thank you, Dr. Greenberg, for being with us today.

[00:04:14] **Dr. Benjamin Greenberg:** So great to be here.

[00:04:17] **Julia Lefelar:** This MOGcast is being recorded and will be available on the MOG Project and SRNA websites and YouTube channels. If you want to submit questions, please feel free to do so through the Q&A feature on the webinar. We're going to be periodically taking those questions and giving them to Dr. Greenberg. Welcome, Dr. Greenberg. We are really happy to have you here with us today and thankful as well. So, it's been a while—I guess it's been a while since we sat down and talked—and we thought we'd give you something to talk about from the past three years regarding MOGAD.

[00:04:58] And I think before we sat down, we had a discussion that was really from a therapeutics perspective. We'd love to know what main areas of research in MOGAD over that time have been, in your opinion, the most interesting and impactful? From any perspective, really, from diagnosis through disease management.

[00:05:24] **Dr. Benjamin Greenberg:** Yeah, so it's a big question because there's been so much that's been going on in a relatively short period of time. And I'll preface this by saying things never move fast enough in terms of going from scientific discovery to impacting individual patient lives. But in my experience, what we're seeing happen in the setting of anti-MOG associated disorder is really an accelerated track of work.

[00:05:51] And it really falls into what I would refer to as four "buckets," if you will. So, one is around diagnosis and recognition and understanding of the condition. The second is around basic science associated with what's happening to our patients. The third is in clinical trials, utilizing agents that we have available today to make an impact on patients by promoting health.

[00:06:19] And then the fourth is the future trials that are coming and the science around getting the world ready for those. And it's pretty unusual for a condition to have significant changes occurring in all four of those buckets at the exact same time. But essentially, that's what's happening in anti-MOG associated disorder.

[00:06:41] We can start in any of the buckets you want, but I think it comes as no surprise to this audience that with the release over the last couple of years and the beginning of the use of standardized diagnostic criteria, it opened the door for us to increase awareness and recognition of the condition, but also to start organizing our clinical and basic science research.

[00:07:02] And it can sound mundane, I think, to a lot of folks—diagnostic criteria. But it becomes really critically important so that as scientists and clinicians communicate with each other—"I had five patients, they had 20 patients, somebody had 50 patients"—were they all characteristically the same?

[00:07:24] Putting a flag in the ground and saying, "This is going to be the criteria we use to make a diagnosis, and you're in or you're out," allows us to have homogeneous patient populations that we can learn from. So that's been a major advance, if you will, in the field. Going from a day where MOG wasn't recognized as a condition to one where there's formal diagnostic criteria being used in trials is a big leap.

[00:07:52] **Dr. GG deFiebre:** Great. Thanks so much for that response. And so, we often hear from people that have questions about relapsing disease—whether they will have a relapse or not after their first attack of MOGAD. And we also get questions about whether research is close to predicting whether someone is going to have a relapsing disease course rather than just a monophasic disease course. Or whether there's a biomarker that clinicians can find to determine whether someone will have a relapse in the near future. Where are we in terms of research about this?

[00:08:27] **Dr. Benjamin Greenberg:** Yeah, so it's an area of a lot of intense research because we feel this is just a critical piece for patients, families, and clinicians to be able to predict who needs a preventative intervention versus not.

[00:08:41] The current standard is around holding back preventative therapy unless somebody has had two or more events. It would be great if we could sort through who is at high versus low risk. There's probably three parallel areas of work happening. One is we have already recognized that individuals who have a sustained positive antibody over time—more than a year—have the highest risk of going on to have future events.

[00:09:14] So, we know that after your first event, following that antibody level and determining if it's still there a year or more later splits an individual's risk of having events. There has been work published looking at risk-stratifying profiles by asking additional questions. Is there a difference in risk between male and female?

[00:09:40] Is there a difference of risk based on age of onset? Is there a difference of risk based on what your spinal fluid looks like? Is there a difference in risk based on if you got certain therapies at your first event versus not? And coming up with mathematical models to predict who's at the highest risk. And some of those have been published; there's some data to suggest that female sex—women and girls who have anti-MOG associated disorder—have higher risks of subsequent events.

[00:10:15] But it doesn't explain everything. So, there's work being done in that regard, but the most exciting work is happening through studies looking at the immune system of individuals who've had an attack and trying to understand at the most basic biological level what is going to drive that ongoing risk.

[00:10:34] And I want to highlight some of the work happening from one of my colleagues here, Linda Nguyen, who is a pediatric neuroimmunologist here at UT Southwestern and Children's in Dallas. Her work is focused on taking samples from the group I refer to as our "patient partners"—individuals who are willing to partner up with us and literally give of themselves through a blood draw and allow Dr. Nguyen and her team to start looking at their immune cells in ways nobody has done before to come up with biological predictive models of who is going to be at risk or not.

[00:11:15] I firmly believe we're going to get there, but that's going to be work that happens over about two to five years. And so, at this point, we're relying on the antibody titer and other epidemiologic or demographic features to risk-stratify people.

[00:11:31] **Julia Lefelar:** That's thrilling. As a community, that's one of the most important areas of research, I think. There are others, but that one definitely is something that would be life-changing for so many. And

the next question I have maybe came about as we read about recent Nobel Prize-level work, and also some people who are doing research are leaning in this direction.

[00:12:03] But we wanted to ask what the significance is of some of that gained understanding regarding regulatory T cells—also known as Tregs. Are scientists thinking about how this could be worked into any MOGAD research? And could you tell us a little bit about that, and if there's any research currently going on?

[00:12:26] **Dr. Benjamin Greenberg:** Absolutely. And so, you're referring to in the fall when Mary E. Brunkow, Fred Ramsdell, Shimon Sakaguchi receiving the Nobel Prize in physiology and medicine for work on what are called T regulatory cells and this role of a gene called FoxP3. Someday I want to have a chance to name a gene, but that's a whole other story. So, their work was Nobel Prize-worthy because it really explained the science of the difference between the "gas" and the "brakes" of the immune system. We've known for decades that every human being has immune cells that can react against self-tissue.

[00:13:24] So, let me explain what I mean by that and why it's important. If we go back over 125 years to the first discussions between the late 1800s and early 1900s about the immune system, there was a recognition that immune cells exist, and they were thought to fight off infections.

[00:13:48] And early on, Paul Ehrlich, who won a Nobel Prize in the early 1900s for his work, suggested that it is impossible for an immune cell to attack human tissue because the implications of that would be horrible. And he called it "horror autotoxicus." The dogma was that there is not a reaction.

[00:14:12] It is impossible for a human immune cell to turn on its host. And it wouldn't be until 50 years later, when Witebsky and Rose in New York proved for the first time that a mammal—in this case, it was a rabbit—could actually form an autoimmune disease. And so, it's really just in the last 65 years of existence that we've even accepted the concept of autoreactive cells.

[00:14:46] So, if you look from the 1960s going through the 1990s and 2000s, all of the work on autoimmunity was complicated by the fact that we were finding autoreactive cells in lots of people who didn't have autoimmune disease. In fact, the majority of humans have autoreactive cells—in fact, we probably all do if we look hard enough.

[00:15:11] But why on earth do we not all have an autoimmune disease? And it comes to the fact that an autoreactive cell can play one of two roles. It can be the "gas pedal," driving harmful inflammation directed at the protein, or it can be a "brake pedal," dampening inflammation against that protein. And that's the Treg cell.

[00:15:36] And that's why individuals won the Nobel Prize for their work in the early 2000s proving the existence of these "brakes" that had eluded us for so long. So now, all of a sudden, it opens up the opportunity to try and induce autoreactive Tregs—autoreactive cells that can apply the brakes in an autoimmune disease.

[00:16:03] So, if somebody with anti-MOG associated disorder has too much of a gas pedal, can I promote the brake in them—the Treg in them—and convert their immune system from one that's overactive to balanced? And so, there are lots of groups in the world of autoimmune disease in general who are exploring ways to induce Treg populations.

[00:16:25] And we think individuals who are in the MOGAD community would be a great population to study with this technology in terms of how we can induce those cell populations. The Treg avenue forms one component of a way to achieve something called "tolerance."

[00:16:43] So, what Paul Ehrlich referred to with that "horror autotoxicus" comment was that our immune system should be tolerant against our body. Our immune system shouldn't damage our own body. And he was wrong that it actually can happen—he thought it would never happen—but he was right that that's the goal. Achieving that goal is termed tolerance. Achieving the goal of having an immune system that doesn't cause damage to self is the definition of tolerance, and inducing a Treg population is one of many different ways we're exploring to induce tolerance.

[00:17:22] **Julia Lefelar:** Got it. Thank you. Fascinating. I just wanted to interject a shameless plug that our Research for Rare program did fund a German group who's studying along those lines.

[00:17:33] **Dr. Benjamin Greenberg:** A great investment.

[00:17:37] **Julia Lefelar:** Thank you. GG, go ahead. I'm sorry.

[00:17:39] **Dr. GG deFiebre:** No, of course. So, Dr. Greenberg, you were talking earlier about what's been studied in terms of how we might be able to predict if someone will have a relapse. And so, we did get a live question about whether or not the severity of the primary attack has anything to do with the chance of relapse. So, if someone has a more severe attack, do they have a greater chance of relapse, or what do we know about that?

[00:18:02] **Dr. Benjamin Greenberg:** It is a great question, and we have been unable to tie severity of attack to the risk of relapse, at least in our look. And I'll also note that "severity" of relapse can be defined two different ways.

[00:18:19] Severity relapse can be defined based on, at your worst point during the acute event, what were your symptoms or deficits; or severity relapse can be defined on how much you recover. So, let's say we take somebody who, with their first optic neuritis, is completely blind, but they get back full vision six months later, which happens in anti-MOG associated disorder. Versus somebody who is not completely blind at their first event—maybe they go to 20/200 vision, but their recovery only gets them to 20/60 or 20/100. Who had the more severe attack?

[00:18:54] And so, one of the things the community does when doing clinical research is starting to come to a consensus around our vocabulary and our language on how we're going to start separating patients out. Because depending on how you define severity, there may be a role relative to risk of relapse, but at least as of today, when we talk about the first event at its worst point, it doesn't seem to reliably predict risk of relapse.

[00:19:21] **Julia Lefelar:** Always fascinating. Thank you for that question. So, I wanted to pivot and talk about the diagnostic criteria. It's another big hot topic always for MOGAD patients. And a while back now, a working group created these proposed diagnostic criteria; it's a very large working group and it's being used worldwide to the best of my understanding.

[00:19:49] Are there any updates to that criteria that are being developed that you know of? And could you tell us a little bit about maybe some of the gaps in that criteria that need to be discussed further or might lead to more changes in the future?

[00:20:10] **Dr. Benjamin Greenberg:** Yeah, so the criteria, which was published in Lancet Neurology in 2023, really, as I mentioned, put down the flag regarding what we're going to call anti-MOG associated disorder. And it laid out levels of data that were needed, and it always started with clinical events. So, somebody has

to have an event, a symptom, or a syndrome that is consistent with what we know to be in the plethora of anti-MOG antibody-mediated conditions.

[00:20:47] If somebody comes in and they have abdominal pain and an anti-MOG antibody, they wouldn't go into the MOGAD criteria because abdominal pain is not how patients with MOGAD usually present. You had to have optic neuritis, myelitis, or acute disseminated encephalomyelitis—known as ADEM—one of the multiple different options of a clinical event.

[00:21:09] And then you went into the testing, and this is where things get interesting and controversial. They indicated that the test needed to be done with the appropriate scientific assay—something called a cell-based assay. And then they separated out individuals who had a clear positive versus a "low positive" in these titers.

[00:21:33] This causes a lot of confusion for individuals around the world. If you'll indulge me, I just want to explain the concept of titers for a moment. The way we do this test—and I'm going to pull back the curtain, which may be a mistake; people may be disappointed when you learn about the science —but the way we do this test is, in the setting of a cell-based assay, we grow cells that express the protein of interest on the surface.

[00:22:03] So, in this case, we have cells that have the MOG protein on the surface. You give us some blood; we take the serum from the blood—which is where antibodies live—and we put it in the dish with the cells that have MOG protein on them. And we "bake" it in an oven for a little bit, and then we wash away your serum. If you had antibodies to the protein in your serum, they would stick to the cell. So now, all of a sudden, if you're somebody with the antibody, there's some of it left stuck to the cell.

[00:22:36] We add a second agent that then highlights the antibodies from your blood. So, we can literally look and we can say, "Oh, that blood sample must have had anti-MOG antibody in it," because even though we washed away the serum, there are still some antibodies sticking to the protein. It turns out, for reasons that are not completely understood, the MOG protein can non-specifically be like sticky flypaper to antibodies. And it could be antibodies to all sorts of other things.

[00:23:13] And so, even though we wash away a person's blood, if I just look after I put your serum on a plate, for lots of people it looks like there's something sticky sticking there, but it's not specifically an anti-MOG antibody. And so, there's this big conundrum of: how do we prove it's an anti-MOG antibody?

[00:23:31] So the way we do it is we then take your serum and we dilute it. So, instead of just putting your blood right on the plate, let's do a 1:2 dilution—meaning let's mix your serum with essentially "water" [it's not exactly water] and dilute it by 50%—and then let's dilute it again and again.

[00:23:53] So when you see the titers 1:20, 1:40, 1:80, 1:100, it means we diluted the serum a hundred times. So, 1%—a fraction of what's in the tube now—is actually your blood. And so, if I dilute your serum a hundred times, mix it with the cells, and there's still something sticking to the cells, we all agree you must have an anti-MOG antibody. No longer is it non-specific protein sticking to the cells.

[00:24:26] So, one of the discussions is what should the cutoff be for a positive test? And in the setting of the diagnostic criteria, what was decided was a "clear positive" was if your titer was 1:100 or greater. So, if I could dilute your serum 1:100, 1:1,000, or 1:10,000 and it's still positive, you have the anti-MOG antibody; and if you had one of those core clinical events, you have MOGAD. The issue is the "low positives."

[00:24:59] What do I do with somebody who at 1:40 is positive, but when I dilute it to 1:100, I don't see anything sticking anymore? Either they just have a small amount of the antibody, or they have a non-specific test. The

debate that's going on right now is whether the 1:100 cutoff is the right cutoff. It becomes more specific—so the people who meet the criteria overwhelmingly were accurate: you have MOGAD. But there are some people with "in-between" titers [in the 1:10 to 1:100 range] who have MOGAD but are not fulfilling the full criteria.

[00:25:36] So, a lot of the discussion that's going on now is: what do we do with those individuals? How do we follow them, and how do we prove which category they should be in? That was probably a much longer answer to the question than you wanted, but that's where the focus is these days.

[00:25:52] We had published some work—again, Linda Nguyen had led this here at UT and Children's—looking at our patients who are 1:40, and we find there are several of them who go on to prove they have anti-MOG associated disorder. So, we have a tough time with our 1:40 group. Our 1:10 and 1:20 groups, pretty reliably—not 100%, but pretty reliably—don't seem to have typical MOGAD features. But it's not a perfect system.

[00:26:23] **Dr. GG deFiebre:** Oh, that was a great explanation. I learned a lot even from that. So, I definitely appreciate it; it definitely is very clear. Treatments that target the MOG antibody specifically are of special interest to MOGAD patients. So, what are some of the strategies that are being explored that do this, if any?

[00:26:46] **Dr. Benjamin Greenberg:** Yeah. At this point, they're conceptual; they're all preclinical. So, the notion of getting rid of a specific antibody while leaving everything else intact —okay, so we can get rid of the MOG antibody. If I hook somebody up to a plasmapheresis machine and I do five treatments over a couple of weeks, I'm going to drop the antibody significantly. If you wait a couple of weeks more, it's going to come back.

[00:27:16] In terms of strategies to get rid of—and I should say I'm getting rid of lots of antibodies, not just the anti-MOG antibody. I'm getting rid of anti-flu antibodies and other things. How can we get rid of the anti-MOG antibody itself and leave everything else intact? There are only two ways to do that: you have to come up with a way to selectively bind the antibody and have it undergo destruction, or you have to shut off its production.

[00:27:46] Those are the options. So, years ago—going back probably now about 10 years—I was privileged enough to lend a little bit of assistance to a researcher here at UT, Sally Ward, who did a study on this in animals. Their team designed a peptide that put the MOG protein at the end of a peptide. Think of a lollipop. The antibody attached to it, but it then got sucked into the human cell's natural "trash compactor."

[00:28:19] All the circulating MOG antibody—this was in mice—got labeled for destruction and all the mice got better. They stopped having attacks. There are these theoretical ways to "tag" the antibody for selective destruction. Those, for reasons that elude me, have not gained as much traction in the biotechnology world as shutting off production. You can shut off production two ways: inducing tolerance to shut off production or remodeling the immune system into a tolerant state. Can you go in, wipe out the confused immune system, and let the person grow a new one with the odds that their new one will no longer have the confusion?

[00:29:11] And this is at the core of something called CAR T therapy in clinical research. CAR T therapy has been used and FDA-approved for treating certain cancers. The foundational technology is as follows: in general, the way it works is I'll take an individual with cancer. So, let's say I'm diagnosed with cancer and it's one that can be treated with CAR T. I go to the hospital, they put in an IV, they take out my blood, and from my blood, they take out T cells—part of the immune system. Those T cells go to a manufacturing facility, and my immune system gets a gene inserted into each of those T cells. They now become "contract assassins" for specific cells. They are now engineered to go after, let's say, B cells.

[00:30:12] So, let's say I have a B-cell cancer. A few weeks after I give my blood, I come back to the hospital, I get some medicine to get me ready to receive the infusion, and then I get my own immune cells back that

have undergone genetically engineered bootcamp training to be nothing but assassins for B cells. And what happens is they go into my body and they multiply, they grow, and they go to every part of my body: every organ, every lymph node, and every bloodstream. And anywhere there's a B cell, they kill them. Then they go away; those assassins die off. And what I'm left with is a body now without B cells, and then my bone marrow kicks in and I make new ones.

[00:30:57] So if I'm a cancer patient, I hope that I make new ones that aren't cancerous. And indeed, this has been a groundbreaking technology in certain lymphomas and leukemias where patients were literally failing drugs left and right but walked out of a hospital cured after receiving a successful CAR T.

[00:31:18] The technology has now shifted into the autoimmune world, where we have said: could we apply this technology to individuals with autoimmune disease, get rid of their B cells
[which are often driving the confusion], and allow a person who has lupus, multiple sclerosis, neuromyelitis optica, or anti-MOG associated disorder to get a CAR T therapy to wipe out their B cells, grow a new batch, and be in a long-term remission with a brand-new immune system that doesn't have the confusion? That is in clinical trials right now for multiple autoimmune disorders.

[00:31:58] And as we see both the safety—which I haven't talked about— and the efficacy, there is a significant interest in bringing that technology to bear in the setting of anti-MOG associated disorder. But it gets back to the very first question we started with: how do we know who's going to have a relapse? So, to undergo something like CAR T, we are really going to want to make sure we're selecting people who really need it.

[00:32:31] **Julia Lefelar:** Wow. That's a great explanation. Thank you. You're always so good at laying it out for us. We have some more questions on treatments, but I wanted to just go back a bit because I didn't ask this about the proposed diagnostic criteria. Do you have any idea if, anytime soon, there's going to be another release, or did you allude to that?

[00:32:55] **Dr. Benjamin Greenberg:** I didn't. Usually, these diagnostic criteria will be "in the ether" for a solid five years before there's any attempt to revise. I will say there are always tweaks or discussions, but formal revisions take time to really understand how these things work. What is coming down the pipeline is a revised criterion for neuromyelitis optica.

[00:33:18] And there's likely going to be direct language talking between the criteria in terms of how we start to separate out the language because for so many years, individuals with the anti-MOG antibody could have been told they had neuromyelitis optica, and it created confusion. So, we're trying to separate out that language. There will be a new diagnostic criterion for NMO that will talk about anti-MOG associated disorder, but it's not going to redefine the diagnostic criteria for MOGAD.

[00:33:50] **Julia Lefelar:** Thank you.

[00:33:52] **Dr. GG deFiebre:** Thanks. And so, we know that Tolerization is something that's been talked about in the community, particularly in NMOSD. And so, we want to know what relevance this has in MOGAD at this time. So, can you give us a quick explanation about Tolerization and MOGAD and your thoughts on the state of this research?

[00:34:12] **Dr. Benjamin Greenberg:** Yeah, I think it's exploding. There have been meetings I've been to that have been dedicated to just the topic of tolerance—discussing nothing else, not talking about immunosuppression, not talking about other approaches.

[00:34:24] And so it's definitely got the attention of the field, and what's exciting about it is the just huge number of great ideas of how we achieve tolerance. I mean, everything from protein-based therapies to train the immune system, cell-based therapies like CAR T or inducing Tregs, and all sorts of things in between.

[00:34:48] And I think where the field is now is that there are different horse races going on in the preclinical stages—in animal studies and in dishes—trying to decide which is ready for primetime. And we're going to start to see phase one trials rolling out this year and next year over the notion of tolerance in these related conditions.

[00:35:11] For example, we're hoping to announce very soon a phase one trial for CAR T in aquaporin-4 NMO. So, an official trial to see: does it work there? And MOGAD won't be far behind. And so, we're going to see the tolerance induction strategies making it into human studies very soon. Some of the strategies around the Treg induction have to do with: can we put, in this case, a MOG protein into a human in a way that the human will generate Treg cells to it?

[00:35:46] Can we take advantage of underlying biology in a beneficial way? So, instead of suppressing the immune system or giving cells to remodel the immune system, can we just send it to summer school and teach it to induce Tregs in a much more gentle and benign way?

[00:36:02] And those strategies are in animals right now. There have been clinical trials for tolerance induction that have been successful in individuals with celiac disease. And so, we know that this is technically feasible in certain conditions. We're now trying to translate it to anti-MOG associated disorder.

[00:36:23] **Julia Lefelar:** You know, and then another shameless plug about that: we did provide mouse model funding for Steve Miller to do that. I did want to ask—it sounds like you said researchers were pretty close to getting some clinical trials started, correct?

[00:36:47] **Dr. Benjamin Greenberg:** So, in different conditions. For example, the CAR T in NMO should be coming in aquaporin-4—NMO should be coming very soon. There are clinical trials that are ongoing; some have finished in MOGAD-specific focused indications. I'm sure we'll talk about the exciting announcement that we heard recently on the Satralizumab study.

[00:37:09] And so there are studies that are in anti-MOG associated disorder, and then there are some coming to anti-MOG associated disorder. And what I want to encourage your listeners to do—and I've been so appreciative of the work of the MOG Project and the SRNA and the close relationship between the two.

[00:37:27] The SRNA model for many years had been what I called a "big tent" model. If you had a rare neuroimmune disease—whether your body was confused about protein X or protein Y—it's "let's form a community." And it's been highly instructive for everyone to stay in touch with each other because as we see what works in one avenue, it makes it easier for us to go another way.

[00:37:52] For example, with certain drugs, we're seeing them tried in anti-aquaporin-4 positive patients, myasthenia gravis patients, individuals with an acetylcholine receptor antibody. And as we see the experience there, it allows us to design and execute better trials for individuals with anti-MOG associated disorder.

[00:38:11] And so when I see tolerance studies being done, I lump them in with any neurologic autoimmune condition. We learn from them and decide: is it an appropriate intervention for our MOGAD community? Are the risk-benefits—do they make sense? And then launch the trial.

[00:38:36] **Dr. GG deFiebre:** Great, thanks. And you mentioned the Meteoroid study; Roche shared that it had positive results. And if the cosMOG study also shows positive results, we'll then have the potential for two choices for treating MOGAD approved by the FDA and potentially agencies worldwide. So, how will this change the thinking when it comes to what clinicians offer patients as the first sort of treatment against relapsing disease?

[00:39:05] **Dr. Benjamin Greenberg:** Yeah, so you mentioned it: the Meteoroid study, which is a study of a drug called Satralizumab sponsored by Genentech Roche, and the cosMOG study, which is a study of Rozanolixizumab—and everyone has to say it five times fast—which is sponsored by individuals at UCB, are really groundbreaking in a lot of different ways for a lot of different reasons.

[00:39:35] Number one is getting large pharma companies to invest in relatively rare diseases takes work. And it doesn't take work necessarily from myself or physician-scientists or institutions. It takes work from patient communities, and there are lots of rare diseases in the world, lots of rare disease patient groups in the world, who are all looking for help and support and an investment of interest and resources in drug development.

[00:40:17] And so to have, independently, two different groups coming to the table to see if their agent could be clinically beneficial and safe for individuals with anti-MOG associated disorder is a big deal. And I think one of the reasons they came to the table was the community.

[00:40:37] The fact that there is an engaged patient and advocacy community allows for the dissemination of information, recruitment of individuals to take part in the trial—a lot of things that go into drug development. My hat's off to the community for coming together and making this happen.

[00:40:56] Genentech Roche announced top-line results for Satralizumab, which means basically they've said to the world, "We did this trial and it worked." We're all going to be seeing that data, I suspect, at the end of the month. There's a large meeting of neurologists in Chicago this year called the American Academy of Neurology. It's where somewhere between 10,000 and 20,000 neurologists from around the world get together.

[00:41:20] And let me tell you, it's nothing but a party. When you put 10,000 to 20,000 neurologists together in one city, they usually have to call out the riot police to make sure we don't get out of hand. But we fill a convention center for the week, and it gives us a chance to meet with our global colleagues and to hear all the latest and greatest things going on, and we expect to see the detailed data there.

[00:41:39] What was done with this drug, Satralizumab—which is FDA-approved for aquaporin-4 positive NMO patients—was a placebo-controlled trial to show that individuals who got this drug
[which interferes with a communication protein that the immune system uses to instigate an immune attack] would prevent relapses. At least in the press release and what we know in terms of the trial design, the fact that they met their primary endpoint means that it did just that: it prevented relapses.

[00:42:15] What they're going to share with everybody is the degree that it prevented the relapses—was it a lot or a little?—and the safety. What's nice about this drug is we've already been using it for years in patients with aquaporin-4 associated disease. And I have to say, in my experience and some of the work we've published, the safety profile holds up quite well over the long run.

[00:42:42] And we've been overwhelmingly very pleased with it, and I'm hoping to see the detailed results are hopefully quite good, giving us an option to get the FDA to approve it specifically for anti-MOG associated disorder. And I'm going to come back to what that means in one moment. I do want to, as you mentioned, talk about the cosMOG study.

[00:43:06] The drug that everyone has to pronounce, Rozanolixizumab—which is an FDA-approved drug right now in myasthenia gravis—works differently. This is an antibody that operates the "human garbage disposal" for antibodies. So, it basically creates an "on" switch. So, if you have an autoantibody floating around, we start really sucking them out.

[00:43:34] So, it allows your cells to just start breaking down those antibodies. We do this with plasma exchange right now: I hook you up to a machine and I suck your antibodies out, I put them in a bag, and we either throw them away or take them to a research lab. What this drug does is it turns on the garbage disposals in each of your own cells to get rid of the antibody.

[00:43:57] And so that's under trial now, again in anti-MOG associated disorder, and we're going to wait on the results for that. So, let's assume one or both have good enough data to support the Food and Drug Administration in the United States or the EMA in Europe giving approval or a label for anti-MOG associated disorder.

[00:44:18] Man, it makes everything easier. One of the biggest barriers to access to care, access to drug access to therapy we have in the US and elsewhere is through payer systems. The interventions, whether they're FDA-approved or not, are expensive. And often we hit barriers where we have to justify to a third-party payer [whether it's an insurance company or a government] why we want a certain drug if it hasn't been proven or FDA-approved. The moment we have FDA-approved options, access to care improves across the board.

[00:44:51] And having drugs that have been proven to work in well-designed and executed trials allows me to look patients and families in the eye and say, "There is reliable data to say this intervention is worth it." And right now, we don't have those randomized prospective trials. We have open-label trials, natural history trials, or observational trials.

[00:45:15] So I can say, "I really think this intervention is helpful; all the data suggests it," but I can't say it with the level of confidence that I could using data out of studies like Meteoroid and cosMOG. So, we are ecstatic to see these trials get to the finish line, more ecstatic to see the drugs work, and very hopeful that there'll be FDA and EMA approvals so that we can start to make them available to our patients who may not be responding to other therapies that we're using in an off-label fashion right now.

[00:45:47] **Julia Lefelar:** I just have a follow-up to that. Do you anticipate that when those things are FDA-approved eventually, some of us who might be on something like subcutaneous IG or something that's working for us that we're comfortable with—do you feel like the insurance companies will switch and say, "You have to take these other ones?" Just a thought.

[00:46:11] **Dr. Benjamin Greenberg:** Yeah, it's a great question. I don't expect that to happen. So, if somebody's on a drug that's working for them and well-tolerated, it would be unusual for a forced switch to occur. But I'll tell you what I'm more concerned about. So, funny story. And you can ask neurologists around the country and you'll get similar stories.

[00:46:28] For years, even before we knew MOGAD existed, when patients were lumped in and we called everybody NMO, we were using Rituximab off-label to treat patients with aquaporin-4 disease and seronegative NMO. And often we would get pushback from insurance companies, and they'd say, "This is experimental; it's unproven." And we'd have a lot of trouble getting it approved.

[00:46:56] Then three, and now four drugs have FDA-approved labels for neuromyelitis optica. They are all dramatically more expensive than Rituximab. And now, often that exact same insurance company that said I

can't use Rituximab because it's experimental is telling me I have to use Rituximab first before one of the other drugs. I had a meltdown on the phone the first time I was told this; it was like a psychic fracture occurring because I literally said to the person on the phone: "It wasn't six months ago that you were telling me I could not use this drug because it's experimental, and now you're telling me I have to use an experimental drug instead of an FDA-approved drug." There may have been a few profanity-laced words that came out and some letters written.

[00:47:46] But what we're expecting, frankly, in the setting of drugs being approved for MOGAD is: are we going to have barriers to prescribing it for newly diagnosed individuals? Because if I have somebody who's on a drug and they're doing well, great. I'm not looking to rock the boat.

[00:48:04] But if I have somebody who's new to the diagnosis and is in need of starting a therapy, and now I have data to say that drug X worked very well in a population and I want to start with that, we're going to wait to see if there are barriers to going down that road. But for individuals who are doing well and stable and don't have a reason to switch, I don't suspect there's going to be a push from anybody to make big changes.

[00:48:31] **Julia Lefelar:** Thank you for that. That's not surprising, and I think you always follow the money on that one. I have a community question, and they're asking: in your experience for MOGAD specifically, are alternative Rituximab regimens—like 500 milligrams every six months, or CD19-based dosing, or CD27-based dosing—as effective as the most common treatment of 1,000 milligrams every six months?

[00:49:05] That's the first part. But this person is really worried because the doctor chose these 500 milligrams for them despite them tolerating the drug really well, and in each cycle, the B cells end up returning back to about 1% to 3% before being wiped. So, the concern is: is that good enough, and why that decision?

[00:49:33] **Dr. Benjamin Greenberg:** This is an area where there are more questions than answers. I can tell you things that we have reasonable data to support. Number one is—and this is data we published 15 years ago—the amount of dose you get of Rituximab, for example, dictates how long your B cells will stay depleted.

[00:49:57] So, if I give somebody 100 milligrams, 500 milligrams, or 1,000 milligrams: the people who got 100 milligrams, they're going to repopulate in a couple of months. At 500 milligrams—and this is for adults, I should say average-sized adults—some of them will go six months, but not all. At 1,000 milligrams, overwhelmingly, people go at least six months before they repopulate. So, there is a relationship between the amount you get and the duration of loss of B cells.

[00:50:26] The next thing we know relative to this is when I'm measuring that B-cell count, I'm doing it in your blood. There are a lot of places in the body where B cells will live that I'm not measuring. I'm not doing a lymph node biopsy every six months to track other B cells in your lymph node. So, even though a person's level might be zero in the blood, there may be B cells elsewhere in the body.

[00:50:48] So, measuring the blood is an incomplete analysis of somebody's B-cell population. So, at the point that somebody is repopulating the blood, they're repopulating elsewhere. We have learned in other autoimmune conditions—and the most informative has been in aquaporin-4 antibody-positive NMO patients—that it is the repopulation that likely is associated with risk of relapse.

[00:51:13] So, in general—and there are exceptions, so I need to make this very clear, this is not a one-size-fits-all—but in general, in my practice, I've been giving every adult at least 1,000 milligrams and not been doing B-cell based dosing because I don't have a way to predict or know who's who.

[00:51:37] So, if the dose is tolerated, we're giving it. I understand the idea of wanting to get away with as little drug as possible. I'm not looking to overmedicate people or give doses they don't need, but we're still figuring this out. And what I say to patients is, yes, the risk and the efficacy are tied. If I'm going to keep you fully protected, there's going to be risk of being B-cell depleted.

[00:52:01] If I let your B cells come back, does that lower the risk of infections? Yes. But it increases the risk of a relapse. So, why are we doing the drug if we're going to allow for that risk? And so, we don't have a great way to walk that fine line yet. I fall into the camp, probably, of the aggressive side. I have colleagues who want to try and find the "sweet spot."

[00:52:22] But as long as we're being transparent with the most important decision-maker—the patient—then I think it's fine because it's not a one-size-fits-all, and I have patients who prefer to try and find that sweet spot, knowing there are risks to it.

[00:52:39] **Dr. GG deFiebre:** Great. Thank you. And then again—so we've talked a bit about my antibodies and seeing if someone will have a relapse, but do we know why someone might develop the antibodies in the first place? So, do we have any understanding of the predisposing factors for developing the antibodies to begin with? And this was from the community.

[00:52:59] **Dr. Benjamin Greenberg:** Yeah. As I've gotten older, I've decided I'm going to blame the music my daughter listens to. That is just what I've decided because it's really just as good an explanation. "I wish I knew" is the answer. You'll remember, as we were talking at the beginning, this notion of autoimmunity.

[00:53:18] Everybody has autoreactive cells, and part of this may not be this issue—we like to think that there's an exposure that confuses your immune system. That's one possibility. If that's the case, it might be diet-related or infection-related. If I had to pick one, it'd be infection-related as the most likely, but we can't prove it.

[00:53:45] But there's another theory, and that is: everybody has these cells, and then there's an event where we lose our ability to control them; we lose our tolerance. So, in some people, it's not that they develop the autoreactive cells; it's that they lose the regulation of them. If that's the explanation, then it's a very different model of exposures that could explain why some people have this clinical condition versus not.

[00:54:15] **Julia Lefelar:** That's a great answer. There's another person that has a question about an initial attack presenting as optic neuritis. What are the chances that any future attacks are going to present differently?

[00:54:35] **Dr. Benjamin Greenberg:** It's a great question. We get asked it all the time. And so, there's the statistical answer, which is that the most common subsequent event in patients with MOGAD are optic neuritis events. That's just the most common event, especially amongst adults with anti-MOG associated disorder. But, as some people say, statistics only get you so far. I can say that's the probability, but it's not the definite.

[00:55:06] So, in our patient population here, the two most common events are optic neuritis or myelitis, with either an encephalitic or meningoencephalitis—headaches, seizures—those types of events being a third-place finisher. But it seems to be equal opportunity. It's not restricted to people who first had optic neuritis. So, if your first event was myelitis and you asked me, "What's most likely next if I'm going to have another event?" the most common is the optic nerve.

[00:55:46] **Dr. GG deFiebre:** Thank you. And then we've talked a bit about CAR T. So, how does Rituximab or other B-cell therapies differ from CAR T-cell treatment?

[00:55:57] **Dr. Benjamin Greenberg:** Yeah, so the antibody therapies—we give an anti-B-cell antibody into your blood. It attaches to B cells and marks them for death. And they can be killed by your body through a protein system called complement or cells called natural killer cells. And we deplete your B cells and then you have to wait for your bone marrow to make new B cells.

[00:56:21] Ande give a dose of the antibody and that's all the antibody you get. The antibodies don't replicate, so once they saturate all the B cells and they're gone, that's it, and you're just waiting to repopulate. CAR T cells will divide and grow in your blood and traffic everywhere in your body.

[00:56:42] So, let's say there was a B cell sitting in your brain or in your lymph node and the antibody never made it there: the CAR T cell will get there. And so, the depth of B-cell depletion in the tissue is dramatically different with CAR T therapy than antibody therapy. And so, we think it leads to a very different impact in terms of the immune system regrowing after the therapy.

[00:57:09] **Julia Lefelar:** Thank you. I want to move on just because we're getting towards the end of the time here and just give you an opportunity to talk about what research has been happening at your laboratory at UT Southwestern for MOG antibody disease specifically, and what you consider the most potentially impactful? And also, I'll add in: how can patients support your research?

[00:57:35] **Dr. Benjamin Greenberg:** Great questions. I'm going to highlight the work of two junior faculty in the nation whom I've had the pleasure of working with because I want to show that there's a diversity of work going on. Linda Nguyen here, whom I mentioned already, is doing really incredible work trying to interrogate the immune system to predict who's going to have a relapse and who isn't.

[00:57:57] And a great way to be involved in her work, or work like hers, is if there are opportunities—if you're ever asked to fill out a survey or if you're giving blood for a clinical reason and you don't mind giving more. See if your clinicians or the places where you are receiving care will take those extra samples. We learn more from the human sample than any mouse any day of the week.

[00:58:24] And hopefully, we'll see good results with her work. The second person is a clinician-scientist at Johns Hopkins, Hi-Wen Chen, who is looking at anti-MOG associated disorder in a very different way, which we haven't talked about. And that is: how could the antibody affect the brain independent of causing inflammatory lesions? Could the antibody actually affect cells in the brain and the function of cells in the brain without causing a lesion?

[00:58:55] She's been part of an NIH-funded grant to dedicate her career to this cellular biology and is really looking at this in a way that very few other people are. I highlight both of them to show not just that there are lots of people doing great work—and it's great to have a generation behind us who are doing amazing work— but also the diversity of questions that have to be asked and answered.

[00:59:24] And it gets to your point of being involved. There are several ways to be involved. So, one is people can go onto a website, clinicaltrials.gov, and look for any clinical trials that are recruiting. Some of those are non-drug studies. Some of the studies are asking for people to give a blood sample or fill out a questionnaire.

[00:59:46] I'll give a shout-out to both the MOG Project and the SRNA that will reach out to members on a regular basis with surveys. If anyone hearing my voice has survey fatigue through email, please fill out the survey. I cannot stress that enough. cosMOG, Meteoroid, investments from drug companies can go to a lot of different patient communities.

[01:00:14] They like to invest in communities that are engaged. As the MOG Project and SRNA can go back to biotech companies and say, "We have a 90% response rate on our surveys," it is dramatically impactful for getting that company to write $100, $200, $300 million checks, or even $500 million checks to fund research that will directly benefit our community. And it's as simple as being engaged and responsive. It goes a very long way.

[01:00:49] **Dr. GG deFiebre:** Great. Thank you. And to just end on a hopeful note, is there anything you want to pass on to MOGAD patients about your hope for a cure or a remission for this disease as we move forward?

[01:01:03] **Dr. Benjamin Greenberg:** For all the variety of conditions that I've been involved in—patient groups, families, the people I've had the privilege of caring for myself—if I had to think about which of the conditions is most likely to be fully cured in my lifetime, or even on a shorter horizon, I would actually put anti-MOG associated disorder at the top of the list. There are lots of things about it that make it very attractive for curative interventions.

[01:01:34] We need the investment of time, resources, and attention. But from a biology perspective, it has all of the features we would want to do things like inducing tolerance or immune remodeling—things that will lead to a durable, long-lasting, or curative intervention. So, I would encourage everyone to be extremely hopeful.

[01:01:54] What I tell pediatric patients over at Children's is: whatever drug we're starting now, you are not going to be on forever. This is definitely going to be a disease we conquer. It's just a matter of when and how, not if.

[01:02:09] **Dr. GG deFiebre:** Great. Thank you. Thanks for ending on that hopeful note; it's very encouraging to hear. And so, yeah, we want to thank you, Dr. Greenberg, for your time and commitment to the MOGAD community. SRNA is happy to have joined the MOG Project for this podcast—or "Ask the Expert" MOGcast, as it's called.

[01:02:31] You can also go to our website to find this recording, our YouTube channel once it's done, and additional resources and information, as well as our SRNA registry, which you can find under "Shaping the Future Research." There, you can contribute information about your experience with your diagnosis and treatments and kind of how you're doing now. And so, yeah, we'll include that in the link as well. But thank you, Dr. Greenberg, so much. We really appreciate it. Julie?

[01:02:58] **Julia Lefelar:** We'd like to thank you, GG, for bringing the SRNA together with us for this important month that I think means a lot to people. And your involvement with this MOGcast has been really great.

[01:03:17] We also encourage everyone to visit the SRNA website at wearesrna.org and the MOG Project website at MOGproject.org. Hopefully, we'll have that in a banner on the recording. In addition, follow the MOG Project for updates to our educational materials and events. And you can connect with us through email on our connect page at mogproject.org/community/connect.

[01:03:46] I can't thank Dr. Greenberg enough, also. It's always a pleasure to have you join us. This is the second time you've joined us. I know you've been in one of our patient summits—the International Patient Summit—and it was absolutely fabulous.

[01:04:00] If anybody wants to see that video, please go to our YouTube channel and look on the playlist for the international MOGAD Patient Summit, which happened last April. Anyway, thanks everybody for this discussion. Happy MOGAD Awareness Month! And I guess we'll close off.

[01:04:17] **Dr. Benjamin Greenberg:** Great.

[01:04:18] **Dr. GG deFiebre:** Thank you.

[01:04:20] **Dr. Benjamin Greenberg:** Thank you both. Appreciate it. Thank you. Alright, thanks.

[01:04:21] **Julia Lefelar:** Thank you.

[01:04:24] **Announcer:** Thank you to our "Ask the Expert" sponsors: Amgen; Alexion, AstraZeneca Rare Disease; Genentech; and UCB. Amgen 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. Amgen believes science and compassion must work together to transform lives.

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