An update on study to investigate the safety of the transplantation of human glial restricted progenitor cells into patients with transverse myelitis

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[00:00:05] **Dr. Benjamin Greenberg:** You've heard about different research that's been going on, whether it's new ways to suppress your immune system or the very advanced science of retraining your immune system, all of that and if you remember the comments, Mike Levy and I had this morning, all of this that we've talked about today is about preventing new damage. Everything we've discussed so far. What we're going to end on is a study that is meant to reverse damage that's been done and try and restore function that's been lost. And this is work that's been going on now literally for 20 years.

[00:00:37] When I first got involved with the organization, I remember being at camp in North Carolina where Doug Kerr talked to families about the upcoming stem cell trials. And 20 years later, he's not in the room to explain himself but better late than never. So, just a warning. I will warn you when we get here, there are going to be a few graphic photos. So, if you are squeamish, I will warn you before they come. So, you heard from Doctor Wang and others about the processes that go into making a therapy a reality. And I'm going to go through this quickly in the interest of time, but you have to go through stages, the pre-clinical development of a therapy, the testing of it approval.

[00:01:25] I'm not allowed to do something to a human being unless the FDA gives me permission to try it in an experiment. And that's what's called an IND and then phase one and phase two, three studies. I've been hearing about stem cells since I was a kid. I mean, there's a lot of decades that people have been talking about stem cells from a restorative perspective, what the hell is taking so long? And we've known about the ability of stem cells to do amazing things for the human body for a long period of time.

[00:01:54] You can take an embryonic stem cell and it could make any other cell from the human body and they're extraordinarily healthy and extraordinarily active. The science the trick of this isn't the notion of a cell being able to heal a human. It's controlling it. As I like to say, you don't want a tooth in your spinal cord. So, for me to just put stem cells into somebody's spinal cord is not a good idea. And in fact, people have tried it and it's gone poorly. Tumors have formed, cysts have formed. Again, you don't need liver cells in your spinal cord. So, it's taken so long on the pre-clinical development is controlling what the cells do.

[00:02:37] So, these graphs of, if I only want a certain cell, how do I make that embryonic stem cell go just that direction so that when it's transplanted into a human, you don't get unwanted organs. And in the conditions of classic myelitis, whether it's related to anti MOG associated disorder or neuromyelitis optica or idiopathic myelitis. One of the goals, there are many, one of the goals is growing new myelin. And to do that, you need a cell that we call an OPC on the left hand side, that green cell. OPC stands for Oligo Progenitor Cell. That's the baby version of an oligodendrocyte that ultimately makes myelin that coats those axons in the spinal cord and allows signals to go through.

[00:03:23] So, you have to develop a stem cell that is only going to make a restricted number of types of cells. And then you have to test them, but you have to test them two ways. One is you have to put them into an animal model of demyelination. You put the cells in and you look to see does it make new myelin? That's what you want in a human. You need to make sure it happens in a mouse or other animal. But you also have to do a pre-clinical model for safety. This was about a decade's worth of work proving a negative, being able to say to the FDA we put these cells into tens, hundreds, thousands of animals and we never saw a tumor cell, we never saw a cyst, we never saw a tooth grow in the brain or spinal cord.

[00:04:07] So, how do you prove a negative? Well, you have to do enough experiments over enough period of time to be able to get as convinced as possible that the cells you're using are going to be restricted in what they do. And then you go to the FDA with safety data, toxicology data, manufacturing data. And you have to propose a trial. You can say to the FDA. Listen, I want to get these five people and give them stem cells and the FDA can say no, you can't pick those five. We don't like those five for the following reasons. It's not a well-designed study or an ethical study or a safe study.

[00:04:43] They can come with whatever reason they want. So, you have to negotiate and decide who's going to enroll in the phase one trial. So, let me tell you where we are relative to stem cells. So, the pre-clinical development. Groups, not me. I didn't do any of this work. Sort it out how to take a stem cell and push it into an Oligo progenitor cell and make sure that it doesn't turn into anything else. And it's like baking a really complicated cheesecake. You've got to put certain ingredients in at certain times and then you bake it at a certain temperature for a certain amount of time, then you change the temperature and then you let it cool. And if you don't do things in the right order, the right time, you don't get the right cell.

[00:05:25] But then you have to prove in a cell culture and these are always pretty. I love using these pictures because none of us know what we're looking at. We're like, oh look, it's red and green. I like red and green. But what these red and green things are, are cells and myelin, the red here is the myelin basic protein that the Oligo progenitor cells are making. And you had to put it in a dish and you had to put it in and show that they could make myelin. So, we said, all right, we got the cells, they make Oligo progenitor cells. They make myelin in a dish. That's great. Now it's time to go to step two pre-clinical testing. Let's find a mouse. This is my second favorite because it's blue. I like red and green, blue is nice too.

[00:06:06] This is a mouse brain here called a shiver mouse that's been genetically engineered not to make myelin. They don't do well. The mice have seizures and they don't survive very long. Where there's normally myelin in the brain, you'll see it stained with blue and there's no blue here. If you put the cells in, they migrate all over the brain and they make myelin. This was pre-clinical testing in an animal model where there is no myelin. To say if I put this stem cell in, will you make myelin? This stem cell succeeded in making myelin. Then it was time and I'm skipping eight years of work to go to the FDA and say, can we talk about a protocol for a clinical trial?

[00:06:54] But one of the questions that was asked is how do you get the cells where you want them? And the first conversation with the FDA was well, just inject it into the vein and the stem cells will find their way,

doesn't work. I know there are clinics all around the world telling people to fly to, I think the latest is Panama. I could be wrong. I can't keep up. Where you'll get an infusion of stem cells. We tried really, really hard none of them make it into the brain or spinal cord. They get cleared by the liver and they get cleared by the lungs and they go all sorts of places, but I can inject tons of stem cells into you and then kill you and take your brain and I won't find any of the cells in the brain.

[00:07:38] And so, one of the issues was how to get them in. And we talked about Chitra was involved in this early on with Doug all sorts of sci-fi ways to program the cell to get into the brain. And in the end, a surgeon walked up and said, why are you guys fussing just directly inject it into the spinal cord. And we said, well, that sounds challenging. And he said it's not challenging, but you have to build an erector set to do it with this device because if I take you to the operating room and I want to inject something to your spinal cord every time your heart beats, your spinal cord moves. So, if I put a needle in the spinal cord, and I have to slowly and put cells in over 10 or more minutes through a tube. Because if you try and push too quickly, all the cells shear, they break apart. So, you have to go to very low pressure very slowly in order for the cells to get in.

[00:08:33] But if I'm sitting there with a needle and I did this with animals, the needle was all over the place because the spinal cord is bouncing. So, a surgeon out of Emory, Nick Bois came up with a device that you could clamp to the patient and it floats with the spinal cord. So, every time the spinal cord moves, the catheter moves with it, so we can all sit there twiddling our thumbs for a couple of minutes while cells are going in, but the needle never moves from its target. So, we developed this device. The device needed its own FDA approval. Yes, welcome to our world. So, the device went through its FDA approval. So, now you have a device now you can go to the FDA and say, look, we have a way to get cells in but you have to decide who to enroll.

[00:09:18] Should I take somebody who just developed myelitis last month, in the last six months, in the last year, five years? How soon is too soon? How late is too late? How do you deliver the cells? Is it one injection, five injections, 10 injections? How do you monitor for safety? Imaging? I'm not going to do biopsies of this model cord afterwards. How do you monitor for efficacy? So, what if I took somebody one month after their event and I took him to the operating room and I put stem cells in and six months later they were walking. Was it the stem cells or the physical therapy that they've been doing for the last six months that got them better? How do I know when the cell is working versus anything else I do as a clinician?

[00:10:04] How long should you follow the patients? The first response from the FDA was the patients need lifelong follow up? I said, well, I'm going to die at some point. I don't know how to swear to you that somebody else is going to follow people for life. What's a reasonable amount of time to follow patients and understand the long term implications of putting an artificial cell or a transplanted cell in. And then there are the challenges of a transplant procedure. You need a surgeon who knows how to use a device. The FDA said, well, that's great Nick, you made this device and you've proven that you can do this in animal surgeries and cadaveric surgeries, but you don't work at Ut Southwestern.

[00:10:44] UT Southwestern would have to send a surgeon to Atlanta to train and then Nick, you've got to come to UT for two surgeries to oversee the surgeon. Nick doesn't have a license to practice in the State of Texas. We have to get him a medical license to practice in the State of Texas. Then he needs privileges at the university which have to be redone every year. If we don't pay attention to, oh, crap, he was due on October 1st. We have to redo the whole packet. These are the types of things that come up. Finding participants. We have a large clinic here at UT but not everybody in our clinic qualified. We put out word for individuals. But how do you get here? How do you stay here for weeks on end, months on end possibly to take part in a procedure.

[00:11:27] So, we partner up with the SRNA to help fund individuals who are coming from a distance to take part in the study. And then there are the practical issues surgery day. This is fun and I'm going to walk you

through it. So, we have to thaw the cells and then check that the cells are still viable. You don't want me putting dead cells into your spinal cord. So, we do a little test to make sure they survived the freeze stall, they have survived freeze stall hundreds, probably over 1000 times now. And yet, every time we still check, we don't just assume, but I'm not going to put you under general anesthesia until I know they survived. But from the moment I thaw them, I have four hours to get them into you where they're no good because that's as far as we tested.

[00:12:13] So, if you're a patient in this trial and for those of you on my team who are part of this you know the fun. We're in pre-op, we say, okay, let's go and we all go back to the operating room and there's dozens of people standing around and you in a cold room with those really attractive gowns on just laying on a table and you get to pick the music we listen to and we all sit there for about 45 minutes waiting to hear are the cells viable. And then we put you to sleep really quickly. We say good night and then we have a clock ticking to get the cells in a certain amount of time. And so, coordinating the teams which include the people thawing the cells, the people driving the cells from that location to us and hopefully not getting into traffic because they're not on site.

[00:12:57] The surgeons, the anesthesiologist, the OR team, the radiology team for taking X rays before and after, the cell infusion team, the ICU team for afterwards, there's about 30 individuals all touching this four hour procedure that all have to be coordinated. And then you got to get the cells in but you have to use a low pressure pump and put the cells in very slowly. So, we sit there and we say, okay, the pumps on and we all sit there waiting and I have the really glamorous job of watching this little bubble in this long, very small tube to make sure that it's advancing, that the cells are actually getting in. Because if the needle is put in a certain position, a certain way we may hit the pump on, but no cells actually go in because it's such low pressure. And I'll come back to that in a moment.

[00:13:54] Where do we stand? Well, the phase one study opened and it was very exciting. It was many years of work. It opened just at the end of 2019, beginning of 2020 just in time for COVID to shut down everything. We spent 15 years getting ready for this, we launched, we were ready, we started getting patients interested and then all research and elective surgery stopped, not just at UT but around the country and around the world due to COVID. We waited. COVID paused the study until 2021. And right as we were ready to get going by the timeline, we were due for an FDA update on were the cells that had been in deep storage still viable? Which required a whole series of experiments in order for the FDA to re-clear us to keep going.

[00:14:44] So, that got us into 2022 when we could actually resume. So, in late 2022 this was the scene for patient one. So, the neurosurgical team on the left Trisha plum and I on the top right, neurosurgical team in the middle, flashing the gang sign is Nick Boles, the inventor of the device. He's a wonderful neurosurgeon out of Emory. And one of my daughters saw this picture. She says, you're in the operating room for the surgery. I said, yeah. And she looked at the picture and she said, well, which one is you? I can't really tell. Is that you? I said, no, that's doctor Bagley. Is that you? No, that's his fellow. Is that you? I said, no, that's a scrub nurse. I said, I'm over here and she said, well, what are you doing? I said, well, there's this pump and a bubble.

[00:15:32] She says, wait, wait, wait, wait, wait your job is to watch a bubble. I said, yeah, it's a very important job. Shut the hell up. Bubble doesn't move. So, the next set of pictures are not overly for squeamish graphic, but it will get a little graphic and I'll warn you before the graphic one. So, what you're looking at here is that floating cannula system. And so, this tube which has the really little bubble in it somewhere that you can't see. I had to train to see this bubble. It's very, very difficult. They line it up and then any time the patient moves, this catheter would move with the patient allowing us to slowly infuse cells over time. And then this picture is the graphic one. If you get squeamish, there's a little bit of blood in this picture, a little bit of tissue so look away.

[00:16:24] What you're looking at just to get you oriented. This white right here is a human spinal cord. This is the tube holding the needle just making contact with the spinal cord. And what's going to happen is once we're in this sheath gets pulled back and all that would be left is a needle inserted into the spinal cord three millimeters and we'd be told, all right, ready to go. And Trisha turns on the pump and the cells slowly go in and we do a series of 10 injections into the cord going usually from top to bottom based on a person's anatomy right into the level where the lesion is. So, we know that the cells get to the site of injury. So, what's happened since then? So, we've completed two transplants. Patient one and two have finished, I'm happy to report that both are doing well.

[00:17:19] This is a phase one study, by definition is a safety study and we are happy with the safety we are seeing thus far. Unfortunately, I am not going to share specific FC data at this time. This trial is still ongoing. There are certain regulations about sharing data when a trial is still ongoing. So, I can't come in and report specifics. I will just say that people are doing well and we're happy with how things are going. For anyone here, either yourself or others. You can always go to the SRNA website. There's a link for a survey where you get asked questions and these questions relate to the entry criteria. We are enrolling people ages 18 to 70 inclusive. You have to be less than 10 years from your event.

[00:18:08] So, if you're 20 years from your event, not a candidate for this study, you have to be more than a year out and you have to have lost the ability to walk. If you can stand and walk, you're not a candidate for the first study. We are hoping with the safety data we get here to expand the individuals who we can enroll. So, what have we learned so far? Just a few last slides and then we're done. So, many patients who contacted us who couldn't stand or walk when we got their records and reviewed them, we realized they didn't have myelitis. A lot of patients had, had a vascular event to the spinal cord. And so, for a lot of patients, we were giving them an update in their diagnosis.

[00:18:51] And the reason for that is over the last 20 years, our acute treatments for transverse myelitis have gotten better, more people are getting steroids earlier, better recognition, more plasmapheresis. And so our outcomes are getting better than they used to be. There's an old statistic about a third, a third, a third. A third get better, a third partial, a third don't improve. It's completely wrong today. Far less than a third are left with long standing paralysis. And so the number of patients who fit our criteria has gone down dramatically. It's a good problem to have, but we now need to revise the trial. We can enroll up to nine individuals. So, seven more to go. And the criteria are listed there.

[00:19:32] We got the FDA to agree not to lifelong follow up, but 10 years of check ins. So, I've told Tricia she can't quit for 10 years. So, by way of just a couple of acknowledgements. So, this trial was funded through philanthropy this was not funded by Pharma. So, the manufacturer of the cells is giving us the cells for free, but we are not taking any funding from them at the institution. We are funding this internally. So, I have incredible thanks to the UT Southwester Foundation. The SRNA has stepped up massively which is you and whether it's a walk and roll or a bake sale or a before the end of the year help your income taxes, donation to the SRNA. Those funds have gone a long way to supporting families who want to travel here.

[00:20:21] The Q therapeutics who gave us the cells, we are indebted to them for the cells. The patients who volunteered for this and volunteered to be screened. I am forever in gratitude towards. And then their caregivers and families are incredible. This is a lot of work for families, a ton amount of work to come from a distance to take part in this. And then the team I get to work with day in and day out. Many of whom you've met during this conference do an incredible job at supporting not just our clinical mission, but our research mission as well. Cindy had a series of pictures in her talk that I really appreciated about kind of the passage of time and the personal journey.

[00:20:59] I will point out when I started, there was no gray in my beard whatsoever. At that point in time, my daughters, when I started this were about this size and then as they transformed to this size, all of my gray hairs came in. Whether it's been the trial or my oldest daughter, one or the other, they got me gray, but we're excited for where we are now. We're actively working on patient three. I hope when we come back next year, we will have done a variety of patients and be well on our way with talks with the FDA about what the next trial would look like.

[00:21:36] With that, I'm happy to take just a couple of questions because I know we were in late. I want to thank our sponsors again for the incredible support, our SRNA colleagues and my partners at UT for stepping up and being here on a Saturday. Finally, all of you for toughing it out to the end. We really appreciate your attendance and look forward to chatting. I'll take two questions and then we can go have a reception. Thank you.

[00:22:11] **Audience Member 1:** That was for TM?

[00:22:13] **Dr. Benjamin Greenberg:** So, thank you for saying that. The first cohort to enroll are people with idiopathic myelitis. They are negative for the aquaporin-4 and negative for the MOG antibody. And so, these are folks with idiopathic myelitis and here's the reason. One of the concerns from the FDA was, I take you to the operating room I put stem cells into you. What if six months later you have myelitis. Did the cells induce the immune response or not? If you have anti MOG or anti-aquaporin-4 disease I won't know if that myelitis is just a random attack of your disease or if the cells attracted the immune system.

[00:22:53] So, the agreement was to use individuals who don't have an underlying ongoing autoimmune disorder so that if there is inflammation in the spinal cord, we're going to blame it on the cells. That was the reason for the phase one decision. Yes.

[00:23:09] **Audience Member 2:** [Inaudible]

[00:23:21] **Dr. Benjamin Greenberg:** Yeah, so in the end where we want to get to with these cells in this procedure is for individuals who had immune mediated spinal cord damage. Very specific, not going to use this for traumatic patients. That's not the goal. But for immune mediated. So, whether it's anti-MOG or aquaporin-4, or multiple sclerosis, or idiopathic myelitis, our goal is to be able to use this in all of those patients. But the safety, the first set of safety had to be done in people who had idiopathic disease. Okay, one last question.

[00:23:53] **Audience Member 3:** My spinal cord is less than half the diameter of the normal one. So, I'm figuring it needs more than just myelin. So, where are we at in regenerating axons because I've only heard about it as far as traumatic injury?

[00:24:14] **Dr. Benjamin Greenberg:** Yeah, let this be a lesson. I should have stopped at two questions because that's, that's a really fantastic question and it really cuts to the fact that we have a lot more work to do. So, the question was about, what I'm presenting is about regrowing myelin. What about the actual axons? I can tell you what I know and what I don't know. What I know is that for individuals who've had immune mediated spinal cord damage, there has been damage both to myelin and to axons. I know that to be true.

[00:24:49] In any given patient, I have no way of knowing how many axons are left that would benefit from Myelin. There is no MRI measure in the spinal cord to predict who would be a great recipient for remyelinating cells. My suspicion is we assume that everybody's long term deficits are from axons being cut and that's not true. In even individuals with the most severe injury, even with an atrophied cord on MRI, there are axons there that would benefit for remyelination. The question is, what will it get you functionally? And so will it lead to, for example, improved sensation, but no motor benefit? Motor without sensation?

[00:25:39] If you take part in this study, one of the longest parts of the consent process is where I explain how the cells could get into you. They could do their job, they could grow re-myelin and the impact be pain. If you haven't felt anything below your waist in five years and all of a sudden I bring back a sensory pathway, but incompletely, you may have had no pain all these years, and all of a sudden you're left with pain. So, even in a success story of the cells remyelinating, I could do harm to an individual based on their underlying anatomy and I can't tell who's who.

[00:26:15] There's a huge group at the university who's spending their time and money and efforts on imaging the spinal cord to try and get me to be a better doctor to be able to pick who's who and we shall write them letters to hurry up because they're taking their damn time. And so, until then we're left not being able to predict who's who, but to your point there are many of you and many of your loved ones who not only need remyelinating therapies but need ways to grow new axons and that's separate work that's being done. So, with that Chitra, do you have anything you want to say to close? Thank you all.