2025 Update on the Q-cells Study

You can view this presentation at: youtu.be/GrG7Asnv1YY

[00:00:00] **Dr. Benjamin Greenberg:** Thank you to everyone for attending. I saw Dr. Clarice's great talk last talking about research activities. And happy to give an update on one of those and saw a question in the chat about research opportunities for individuals who are more than a year out. And that's exactly what we're gonna talk about today. And my name's Dr. Benjamin Greenberg.

[00:00:24] I'm a neurologist and a director of the transverse myelitis center at UT Southwestern in Dallas, Texas. And I'm here to give everybody an update on our study to investigate the safety of the transplantation of human glial restricted progenitor cells in transverse myelitis. Before we go on, I don't have any financial disclosures that are directly relevant to this talk.

[00:00:50] But I do wanna give a warning that there will be a couple photographs from an operating room. I'll warn you before they come up, for, so for anybody who is a little bit squeamish about seeing anything from an operating room you can look away at the moment. It's not anything too bad.

[00:01:06] I think it's pretty interesting, but I don't wanna make anyone upset with me. So, let's get back to the topic at hand, and that's the idea of stem cells. The notion of using stem cells to medically treat individuals with different disorders has been going on since the 1970s. So, we're really getting close to 50 years, definitely 40 to 50 years of discussions relative to the use of stem cells.

[00:01:31] And the reason that stem cells have been heralded for decades for therapeutic potential is because they have an incredible power to differentiate into any type of cell. Now, there are different types of stem cells in the world, and this causes a lot of confusion, both for patients and families.

[00:01:53] And frankly for practitioners, there are embryonic stem cells, mesenchymal stem cells, umbilical stem cells, and over the last decade of research induced pluripotent stem cells. And what this is taking an adult cell from an individual. So, we can take it from skin, for example, or from fat cells inserting specific genes.

[00:02:20] So genetically altering the cells to vac into a stem cell phenotype. But once a cell is in that stem cell biology, either naturally because of where it came from or artificially because we genetically engineer it, then the power is in the ability of those cells to differentiate into any other type of cell.

[00:02:44] You can make a liver cell; you can make a nerve cell. You can make a cell that grows new myelin for the central nervous system. And so, the power of stem cells is in that ability to differentiate into almost anything. The danger of stem cells is they can differentiate into almost anything. And we're gonna talk about that relative to safety in a moment.

[00:03:08] But while stem cells have been discussed since the 1970s and 1980s for their potential to treat individuals with different disorders, it was a seminal paper in 1999 by John McDonald, when he was at Washington University that looked at transplanted embryonic stem cells into an injured spinal cord.

[00:03:29] And this was a rat study where it showed that these stem cells could differentiate and promote recovery clinically of those rats in this model. And this really opened the door to lots of exciting conversations relative to the use of stem cells for neurologic disease and specifically for spinal cord disease.

[00:03:51] I'm gonna go through a lot of the research that's been done to get us to where we are with a phase one trial for individuals who've been affected by transverse myelitis. But it is no secret that you can go onto the internet and find advertisements for clinics all over the world with really impressive pictures and graphical displays around their stem cell therapy center and research center.

[00:04:18] And it's important to note the concerns that I have about these centers, both ethically as well as scientifically and from a safety perspective. So, you'll note in the first text, this stem cell center talks about advanced adult stem cell therapies, meaning they're really talking about mesenchymal cells.

[00:04:39] These are cells that can live within fat tissue or other places, and they make it sound extremely easy that you can harvest these stem cells from tissue, infuse them back into an individual, and they show wonderful videos and they give great interviews with individuals who have experienced dramatic improvements in their health from infusion of these cells.

[00:05:00] And in fact the center, which is located in Panama has been attracting visitors for many years. And most of you may have even heard of them, but there are a lot of concerns about the stem cell institute in Panama. I use them as an example. There are others. Their history goes back to 1975 when a psychiatrist started advertising the use of IV vitamin C treatments to improve human functioning.

[00:05:23] They opened a clinic in Kansas. Then there was a research institute in Dallas, Texas. Ultimately, after a lawsuit, there was a judgment against them for a variety of practices. Then they moved over time to Costa Rica. Then the Costa Rican government shut them down which I take independently as not a great sign.

[00:05:44] And they move to Panama and open their doors there. They will state on their website that they have publications supporting the science. Many of those have been retracted in the literature or corrected in the literature or peer in journals that don't undergo peer review. And I really worry about the practices from this institute and others from around the notion of stem cell tourism, people spending tens of thousands of dollars to go down and get unproven risky interventions.

[00:06:14] Why is there risk to it? When you look at published literature in peer review journals at complications of stem cell tourism, which underreport the complications, these included spinal cord tumors, strokes, paralysis, cancer, worsening of underlying disease meningitis, and at least a couple patients who have passed away during or immediately after these interventions, those outcomes do not get advertised or in fact tracked.

[00:06:43] By the institutes who are offering these therapies. And so, I have an a, a significant bias, and I'm very open about that bias slash opinion, which is these stem cell tourism centers that advertise, are really preying upon individuals who are appropriately and understandably desperate for an intervention but are skirting around those regulatory steps that Dr. Clardy spoke about so eloquently that are necessary to not just show safety, but to show efficacy.

[00:07:15] And so, I wanna walk you through what we're doing to get to a world where stem cell therapies can be proven safe and effective for our patients in a rigorous and ethically sound manner. So how do we make a therapeutic possibility, a reality for all of us, again, whether it's stem cells or any other drug therapy?

[00:07:37] And, Dr. Clardy talked about this a bit. It starts with preclinical development, doing a lot of testing in a test tube, a lot of testing in cell culture to ensure that the drug or the cell that we are going to give to a patient, administer to a patient is gonna behave as we expect it to behave and doesn't have any contaminants.

[00:08:03] We then go on into preclinical testing. So, this is animal models, both to look for safety and for efficacy of the cells or drug that we're gonna administer to individuals. We then ask regulatory officials to review all the documentation we have about preclinical development, preclinical testing, and manufacturing, and for them to review that all of those steps, meet the appropriate requirements, and that it is reasonable and as safe as possible to move into a phase one clinical trial, which is a first in human clinical trial.

[00:08:38] And if the safety of the intervention is substantiated by the phase one clinical trial, it can never be proven in a single trial, but at least substantiated that we don't get a surprise signal of an adverse event or a bad outcome, then we can move on to what are called pivotal trials, phase two and phase three trials that allow us not just to document the safety we saw in phase one, but now really to look for signals of efficacy.

[00:09:06] And at the end of all of that, some very dedicated, very smart individuals from regulatory agencies, industry, academia, and patient advocacy organizations get together and in a multitude of ways, look at the data collaboratively to come to a conclusion. Is this intervention safe and effective to a degree that warrants its ability to be marketed in different markets for the FDA, it's the United States for the EMA, it's Europe and so on.

[00:09:36] So let's apply this to what we know relative to stem cell therapy and myelitis. So if we go back to this model that you can take embryonic stem cells and they can turn into anything I would argue, and I've said this in the past when giving the update that if we put embryonic stem cells into you to repair your spinal cord, you really don't want a liver to grow in your spinal cord or a tooth to grow in your spinal cord.

[00:10:03] You want to know that the cells we put in are gonna behave in a way that would be beneficial to the spinal cord. So, in our perspective, we want it to regrow, myelin, or someday regrow neurons. The focus of today's talk is gonna be on regrowing myelin. So, the first step is to take these stem cells these embryonic cells and differentiate them into what are called GRPs, glial restricted precursor cells.

[00:10:32] And it's those glial restricted precursor cells that will then never go back to form a tooth or a liver or muscle. They are only gonna differentiate into one of two cells that are normally found within the spinal cord, an oligodendrocyte or an astrocyte. And the thought is that you can develop cells in such a way you can incubate these cells in such a way that when we administer them to patients, we have a confidence that we're not gonna get an unexpected cell growth within the spinal cord.

[00:11:08] So we take this recipe and we move to preclinical testing. And the preclinical testing for remyelination when it comes to phase one trials is fascinating. So, the first is animal models of demyelination. You put in these glial restricted precursor cells and then you assess the animals for remyelination. You look to see whether or not the animals are growing new myelin, but that's not the only preclinical testing. The other preclinical testing is to try and prove a negative. You transplant the cells and you look for unintended consequences.

Do those cells elicit inflammation? So, if somebody had myelitis, which is inflammation of the spinal cord, the last thing I want to do is put cells into the spinal cord and elicit new myelitis.

[00:12:04] So we're looking to make sure that these cells don't elicit an immune response, and we're looking to make sure that those cells don't grow inappropriately and form a tumor. With this data, you go to the preclinical testing data from a dish and from an animal. You go to the FDA in the United States, and you ask for approval of an investigational new drug application, an IND.

[00:12:32] You present to them data about preclinical efficacy. Preclinical safety, toxicology data, manufacturing data. The FDA literally goes and looks at the manufacturing facilities and says, is it clean? Is it safe? Have you tested what you're manufacturing for? Contamination? We don't wanna inject cells contaminated by bacteria or fungus because they weren't handled in the right way.

[00:12:58] And you also propose a phase one trial design. You say to the FDA, here are the individuals we wanna enroll in the trial. Here are the inclusion, exclusion criteria. Who would be in, who would be out? And here's how we're gonna monitor both for safety and for efficacy. And you create a structure for oversight.

[00:13:18] You create an independent safety monitoring board who doesn't work at the institution doing the trial, who meets on a regular basis to review the data, to give feedback to the principal investigator to tell them, is it safe to continue doing the trial? So, with all of this, let me now get to the point of the talk.

[00:13:38] And that is an update on where we are for turning stem cells into a therapeutic reality for our individuals with myelitis. So, the preclinical development that went into the study to date involved controlling what are known as Q cells. So, Q Therapeutics is a company that is not funding the trial.

[00:14:01] So here at UT Southwestern, we're not receiving funds from Q Therapeutics. But they are supporting all of the necessary costs of providing cells relative to that trial. So, they had to go to the FDA with preclinical data showing that they could take cells and expand them into oligodendrocyte, into glial restricted precursor cells.

[00:14:24] And what you're looking at here is not their recipe. This is an example of a recipe where you take embryonic stem cells and then on different days you expose them to different proteins. It's kind of like baking a cake or a souffle where you mix the ingredients and at different time points, you change the oven temperature.

[00:14:45] And over multiple days, the cells will differentiate from embryonic stem cells into glial restricted precursor cells. And what Q Therapeutics did was sort out the recipe for getting glial restricted precursor cells and then went on to studies to show that the glial restricted precursor cells could be implanted into animals.

[00:15:08] And these are pictures of axons from neurons. And the middle, black and white pictures are showing myelin growth. That black and white picture on the right, that looks like a wavy oval, if you will. That dark line that's concentrically going round and round is the new myelin that's growing from these restricted precursor cells.

[00:15:33] This was all done in a dish, but you then go with data from a dish, and you can do preclinical testing. From preclinical development to testing now means you're going into an animal model, and the Q cells were put into a mouse model known as the Shiverer mouse. So, this mouse is genetically engineered to lack myelin.

[00:16:00] So what you're looking at are three slices of brain. So, first on the left is a normal brain where the myelin is in blue, and you can see this big blue line across the middle. That's a big area of the brain where myelinated axons connect the left and right brain. And in the middle panel, this is the same slice from a Shiverer Mouse.

[00:16:22] You don't have that myelin. And these mice are very sick when they're born. They're having constant seizures and a lot of deficits. And so, what the scientists did with Q cells was inject the Q cells, these glial restricted precursor cells into the brain of a Shiver Mouse. And lo and behold, not only do the mice function better and their symptoms improve, but you can see the myelin creation that blue line is being restored.

[00:16:49] So this was preclinical data that was used as part of an FDA application to ultimately go forward with the trial, important in the regulatory approval. And what came up as a critical step for us with the trial, we're gonna talk about today is around delivery. So, when you look at stem cell tourism clinics around the world, often what you'll find is places that will.

[00:17:16] Quote obtain your own stem cells from fat or from blood, do something to them and then infuse them back through an IV into your arm. It turns out if I infuse cells into your veins, your liver and your lungs clear out the overwhelming majority of those cells, they never make it to the spinal cord.

[00:17:39] And we've done this in animal studies over and over again. And so, part of the discussion with the FDA was not just about the cells themselves but was also around the delivery mechanism. How were we gonna get cells into the spinal cord in a reproducible way? And this is where a neurosurgical colleague, Dr.

[00:17:59] Nick Bullis, who's a professor of neurosurgery at Emory University stepped forward with a device which is referred to as the floating Derek Cannula as a way tied with a surgical procedure to get cells directly into the spinal cord. And there were a lot of barriers that Nick had to overcome when sorting out a spinal cord injection.

[00:18:27] So it turns out we can't just free hand inject cells into the spinal cord. Two reasons. Number one, if you put too much pressure on stem cells in a tube, they shear, they break, you kill the cells. So, you have to infuse very slowly and at low pressure, which means once a needle tip enters the spinal cord, we have to sit there for two minutes while just a drop enters the spinal cord.

[00:18:59] During those two minutes, our patients are breathing and their hearts are beating. And with every breath and with every heartbeat, the spinal cord moves. So, you do a surgery, you expose the spinal cord, but you can't hold a needle tip, a tiny, needle tip still for two minutes with all those heartbeats and with all that breathing.

[00:19:19] So the device that Dr. Bullis created allows this cannula to move with the spinal cord, with every heartbeat and every breath. The tip stays in the exact same position, and you can slowly infuse these cells over the two minutes, which are necessary to protect the integrity of the cell. And so, this was a part of the application to the FDA.

[00:19:48] It wasn't just asking for approval to move forward with the Q cells for transplant, but it was also approval to use this device and technique to actually transplant the cells. And so, this gets into some of the challenges in a phase one study. It's not just, then how do we do it? It's who do we include?

[00:20:09] There was a question earlier about the difference between individuals who are within a month of their event or a year or 10 years. And one of the questions is, where will cells be most useful? Is it better to give them earlier or can you give them to somebody who's more than a year, two years, five years out from their event?

[00:20:27] So part of the discussion with the FDA was who should be included? How do we deliver the cells and how do we judge the safety of the procedure independent of the cells? If somebody wakes up from surgery with a new issue, how do we differentiate? Was it the cell causing the problem or the surgery itself?

[00:20:50] How do we monitor individuals for safety? If we're enrolling individuals who have no movement and no sensation, how do we know if the cells are causing harm? How do we monitor for efficacy? Is it possible that cells could be making new myelin, but a person not show a benefit from it because their deficit was so significant?

[00:21:16] How long do we follow patients for? Is a month enough, two months, three months, a year, two years, 10 years. And then there are challenges to the transplantation procedure itself. So, the first is Dr. Bullis, who's an incredible surgeon and has been a great partner in this process, developed this device.

[00:21:35] Other surgeons have to be trained on it and then have to work with Dr. Bullis in order to get certified to do the surgeries independently. We have to find participants. Turns out that's harder than you might imagine, and we'll talk about that in a moment. And then we get to surgery day. The patient experience is interesting because once we get everyone prepped for surgery and we roll back into the operating room, we have to thaw the cells.

[00:22:04] And we don't want to put somebody under anesthesia unless we know the cells are viable. What if something happened to them during freezing and there aren't cells left in the tube to transplant? I don't wanna put somebody under anesthesia if they're not gonna have a surgery. So, we sit there while the thaws are, while the cells are thawing, having great conversations with our patients who have been amazing and our participants have been incredible.

[00:22:28] But we're waiting. And then the moment we know the cells are viable, we get somebody under anesthesia because the clock has started. We have less than four hours to transplant the cells based on what we know about their viability. This takes coordinating a huge team, the cell handling team, the anesthesia team, the operating room, the surgeons, the cell infusion team, the post-anesthesia care unit, the ICU, and so on the day of surgery, we're coordinating with approximately 30 different individuals to make sure everything runs smoothly, safely, and on time.

[00:23:01] And then we have to get the cells in. We can't speed up the infusion because the excess pressure will harm the cells. So, with all of that sorted out, we went to our phase one trial. We got alignment with the FDA on all of these issues and moved forward, and we opened the cells for screening just as COVID hit.

[00:23:24] So we had to hold for approximately a year while everything reopened from COVID. And at that point it was time to redo testing on the cells that had been frozen to show that they were so viable. So, in earnest the study didn't really resume until 2022, and it was in late 2022 at the end of the year that we were able to move to our first patient.

[00:23:49] And these are gonna be the pictures that I gave you a warning about. There are gonna be a couple pictures here from the operating room. No patient identifiers are shown but for three slides if you're squeamish, please look away. I'll warn you and I'll tell you when it's done. But just to show you what's happening in the operating room.

[00:24:05] So shown here is the operating field. The surgeons on the left Tricia Plum, and myself on the top right. Bottom right there is Dr. Bullis. He is not a member of any gang but likes to flash his signs from Emory. And as we look closer, what you're looking at is that floating Derrick Cannula.

[00:24:30] It is lying over the patient over the incision. And this is how the needle can stay safe and stable with that spinal cord as heartbeats and breathing occurs while we're infusing. One last image is the most graphic, and that is the spinal cord itself. What you're looking at now is after we've incised through the spine, through the dura to an actual human spinal cord, that thick white line going from top left across the middle of the screen is a human spinal cord.

[00:25:04] And what it is being prepared for first injection of stem cells into the cord. So graphic pictures are done. If you looked away, you can look back. It is safe. And now I just want to give you an update on where we are with this trial. The first cohort of patients for safety has been completed and the data from those cohorts was submitted to the FDA, and they gave clearance to move to cohort two, which is well underway.

[00:25:33] We have patients nine to 24 months and beyond out from the procedure, and there have been no procedure or cell related serious adverse events. We have had adverse events, and we have had things that we expected, for example, postoperative pain at the site of surgery. We expected it and there was some, but we have not seen any tumors formed, any infections or any events related to the cells that raised any concerns.

[00:26:05] Likewise individuals in this trial have immunosuppression in order to prevent inflammation from occurring. And overwhelmingly that immunosuppression regimen has been well tolerated and unfortunately, I am not yet sharing efficacy data at this time in order to protect the integrity of the study.

[00:26:23] Generally, in some subjects we have seen evidence of a clinical response to the cells. I'm not gonna go into more detail unfortunately, until we complete the phase one trial. Importantly, with the safety data we had in hand we approached the FDA and got clearance to expand the cohort of individuals we're recruiting.

[00:26:48] So the original cohort was limited to individuals who could not walk. We have now gotten clearance to enroll individuals who have limited walking capabilities. So, if somebody's walking with a walker, but for a limited distance, they can now be considered for enrollment in this trial. If you would like to learn more, there are study details on the SRNA website.

[00:27:15] As well as a link to a survey if you want to participate, and you can answer the questions on the survey, and then we call you back. And we are happy to talk over the phone to see if you would be a candidate. We are actively enrolling individuals who are non-ambulatory and individuals who have some ambulation.

[00:27:33] And we appreciate all interest in the study. Please feel free to reach out to us if you'd like more information. Acknowledgements: the University of Texas Southwestern Foundation through donors have supported the cost of this trial at a huge sum, and we are very grateful to them. The Siegel Rare Neuroimmune Association has helped patients and families with travel costs to make it to and from the study and could not be more grateful to all of the donors big, medium and small to the SRNA who make this research possible.

[00:28:06] The Q Cell Therapeutic Team, who's given us the cells and supported regulatory costs relative to the trial. My colleagues, Dr. Nick Bullis, Carlos Bagley, and Sala Aoun, who is our current neurosurgeon performing these surgeries at UT Southwestern, an incredible debt of gratitude and thanks to patients, caregivers, and families who have both offered themselves to be considered for this trial, as well as those who have volunteered to be early participants in this trial.

[00:28:38] There's a huge team within the Conquer Program at UT Southwestern. Taylor Hinojo, Patricia Plumb and Paula Hardeman are among several photographed here who make the stem cell protocol happen. Taylor, who's on the right side, second from the top she's wearing glasses there is overseeing the vast majority of everything that happens with this trial, and it could not happen without her leadership.

[00:29:06] Then I always like to end with a, thanks to my family. And just a note that when starting down this path, my girls, Rebecca and Hannah here, were quite young. They've grown up into incredible, amazing, intelligent, beautiful young women. They give me a hard time every year that we haven't completed the study.

[00:29:27] My wife Kim is very patient with the time it takes, but we are all equally excited to get this study done past phase one and move on into expanded cohorts and determine whether or not these stem cells will help individuals with myelitis and MOGAD, ADEM, neuromyelitis, optica and beyond. So, I appreciate the attention, and I appreciate the ability to give you the update and to the SRNA for hosting this symposium.

[00:29:53] and as people are considering questions you can reach out to SRNA if you have questions, and they can put you in touch with Taylor, myself or again to our website, which we'll get you directly to Taylor. Taylor. Stacy Clardy in the last talk mentioned this community is critical for recruitment.

[00:30:22] So even if you yourself don't qualify or aren't able or aren't interested in taking part in a phase one trial, you are connected to the community abroad to raise awareness so that there may be individuals who could qualify, who may not be aware of this going on. So, talking about this in your support groups, talking about this with your friends, Facebook posts connecting them to SRNA you're an incredible ambassador for raising awareness, and we appreciate any and all referrals of interested parties. None of this can happen without the community involvement.

[00:31:03] **Dr. GG deFiebre:** Let's see. We've got one question that says any research you're familiar with regarding some specific peptides for spinal cord injury repair, I'm assuming?

[00:31:13] **Dr. Benjamin Greenberg:** Yeah, it is a great question. There, there is work happening on peptides to, to try and limit the scar that forms after an injury or to help if, for lack of a better term, dissolve a scar.

[00:31:27] And, those have been moving from animal studies, hopefully to human trials. Part of the issue is for anybody who has a deficit. So, if you're listening today and you have symptoms after myelitis or optic neuritis or, ADEM, what explains your symptoms? And there's really three things that explains your symptoms.

[00:31:49] A loss of myelin, a loss of axons or neurons, and then a scar that may block a signal. And so, depending on what percent of your symptoms come from any of those three camps, different interventions may be more or less helpful to you. So, if I enroll a patient who isn't moving after a myelitis event, but it's because they've lost axons, our myelin repair strategy will be of limited value to them.

[00:32:15] And so it turns out that we really can't differentiate patients with an MRI that it's near impossible for me to tell a patient what percent of their symptoms come from demyelinated axons versus lost axons with any reproducibility. And we're working on those technologies right now. But likewise for these peptides that may affect a glial scar.

[00:32:38] Without knowing how much of a scar somebody has, we, it's hard to design the trial to see if those peptides would, work there. There're also proteins and peptides to try and promote endogenous stem cell repair. So far, those have had limited value, but there are some agents that are in clinical trials to promote remyelination without a stem cell.

[00:33:00] And some of them have a lot of promise. And so, I think you're gonna see different strategies coming in to promote repair cell-based and drug-based, whether they're protein or other things. When you type in remyelination, you see a plethora of things that are understudy.

[00:33:17] **Dr. GG deFiebre:** Got it. And then another question came in. So how do you decide where to target the cell insertion location? Is it standardized? Is it based on the patient?

[00:33:26] **Dr. Benjamin Greenberg:** Yeah. I love this question. Thank you for asking. And I should have mentioned it. So, for our clinical trial the power of a surgical implantation is we implant directly to the side of the injury.

[00:33:40] So we do an MRI and we can see where the injury was. And that's the part of the spine where we do the surgery. Now, we are limited right now in two ways. So, one is for the initial phase one trial, the FDA wanted us doing the surgery below the neck because there are breathing centers in the spinal cord of the neck, and they didn't want the surgery risking those breathing centers.

[00:34:03] I completely understand the concern in ALS trials, they have done surgical transplantations in the neck already, so we're acquiring data to say the procedure's safe, but for our first patients, they wanted us to do it below the neck. So, we're limited to individuals whose myelitis event was in the thoracic spine, not the cervical spine.

[00:34:24] So below the neck. And then the largest area surgically we can open up is three spinous processes. So, the bones related to three levels, which is a pretty long area. It gives us access to about more than 10 centimeters of cord. So, we can cover a longer lesion but it's in the thoracic cord, but we are directly injecting to where the injury occurred.

[00:34:52] **Dr. GG deFiebre:** Got it. Well, thank you so much.

[00:34:53] **Dr. Benjamin Greenberg:** Pleasure. Thanks so much.