Update on the Q-Cells Study

You can view this presentation at: youtu.be/ZSaKJbA3TD0

[00:00:04] **Dr. Benjamin Greenberg:** So, I'm here to give everybody an update on where we are relative to stem cell therapies, specifically for our community in terms of rare neuroimmunologic disorders, and the ongoing study in transverse myelitis. I'll tell you where we are with that. But after the small breakout session we had the other day, I want to put this into context, and so, I am going to start.

[00:00:24] I'm going to warn you: late in the talk, there's a couple photos that come from the operating room where you'll see a surgical field. I will warn you before I show them in case anybody wants to turn away if it makes you squeamish at all. So, there is a lot of excitement about stem cell therapy relative to neurologic conditions. In fact, there's been a lot of excitement about it for decades. And yet, it still feels like we're not making the progress that I was promised 20-30 years ago.

[00:00:52] And so, the question is: Why? And if you look to the literature, there's actually progress being made. But the point I'm going to try and make is: around how studies are being done makes a big difference in how you interpret the data. Did anybody here see the news over the last year of a study coming out of the Mayo Clinic for stem cells being used for spinal cord injury? And it wound up on ABC, and CNN, and all these different things.

[00:01:17] And it was an important study. They used a certain type of cell that I'll explain. They injected it into the spinal fluid of individuals who had had a traumatic spinal cord injury, and they tracked their progress over time. And I just want to point out, there's a paragraph there. You don't have to read it.

[00:01:31] I'll tell you the summary of it, which is: they enrolled individuals who were within a year of their injury. They gave them the treatment, and then they tracked them over time. And what Christina Sadowski and others will tell you is: for people who keep doing therapy after the first year of their spinal cord injury, they continue to improve over time.

[00:01:53] And so, there were a group of patients here, and each of them are individual lines on that chart, whose function clearly improved. The videos are great to see and the data is wonderful to see. But what it leaves us asking is: Was it the cells or were they continuing to improve because they did everything Christina told them to do? And if you do listen to her, you're going to improve functionally.

[00:02:16] And one of the things that was underplayed was, as you follow the MRIs of these patients, you start to see swelling and clumps form on the nerve roots in the lower part of the spinal cord, and it's unknown what that is. Is it a reaction to the cells? And so, the two points I take away from this is: how we deliver the cells matters, and what group of individuals we choose to study matters when making conclusions about stem cells in general.

[00:02:41] So, the number one question I got, and I'm so glad we got in the breakout session, was: What about all these clinics we see around the world offering stem cell therapy? How many people here have seen a Facebook ad or a post, or family or friends sent you the advertisement of the brochure for a stem cell clinic anywhere? Anyone here heard of the Stem Cell Institute down in Panama? We got a hand over there.

[00:03:02] So, their website is spectacular -- I need their web designer -- because they will treat, and according to them, cure your child's autism, your autoimmune disorder, cerebral palsy, frailty of aging -- that's my favorite, by the way -- heart failure, multiple sclerosis, osteoarthritis, rheumatoid arthritis, sports injuries, wellness -- maybe just wellness -- and ask about other conditions. They are happy to hear about what ails you, and then take your $30,000 in order to treat you.

[00:03:33] You may see online lots of theories about why is the US medical establishment is so wary of these boutique stem cell tourism groups -- and I am not going to be unbiased, just for the record here. This is where I'm going to be very biased, and I want to walk you through the history of this clinic.

[00:03:52] It goes back to 1975 in Kansas, the Center for Improvement of Human Functioning, where a psychiatrist, Hugh Riordan, started offering high-dose intravenous vitamin C to treat cancer. Now, what's interesting is, if you go online today, these clinics are still using high-dose vitamin C to treat your cancer despite every double-blind trial showing not only does it not work, there are serious harms to it, but it is still offered as the cure offer, cancer and other disorders.

[00:04:23] So, they got renamed the Riordan Clinic of Kansas. Then, Hugh Riordan's son opened a clinic here in Dallas, the Riordan-McKenna Institute, that ultimately led to a huge lawsuit in the split between Riordan-McKenna -- I don't know the details -- and it got renamed the Riordan Medical Institute of Dallas offering all sorts of therapies.

[00:04:42] And when they were told, “Hey, you really can't do this,” they opened the Stem Cell Institute of Costa Rica until the Costa Rican government shut them down, which I'm just going to say, “Probably isn't a great sign.” And they moved to Panama, where you can now go and spend $30,000 from your hard-earned money or a GoFundMe campaign and get stem cell therapy on the beach in Panama.

[00:05:08] And you will see their website list all the publications that they have supporting it. You're like, “Wow! They are a published group.” Read the publications. The majority of them are commentaries, and review articles, and opinion pieces. There is no prospective data whatsoever in the publications. And in fact, the couple papers that had prospective data, have since been retracted or corrected, and that is not to be found on their website.

[00:05:33] You have to go to the journals and realize that those studies have since been re-reviewed and pulled. So, they're doing this without data, without formal study, without prospective follow-up, and nowhere on their website will you see the rate of adverse events, or serious adverse events, or outcomes. It is not tracked. It is not published.

[00:05:50] A group of colleagues -- I was not involved in this -- tried to get a point estimate in the United States of individuals who have traveled there, who don't have YouTube videos talking about what happens. And the

only people with YouTube videos are the ones who say their life changed. But when they did an accounting of the adverse events, here's the list on the left in too small print, but I give you a fun summary of more than one tumor, strokes, paralysis, cancer development, worsening of their disease, meningitis, and at least four fatalities coming out of the clinic.

[00:06:22] This is not advertised or discussed in any way, shape, or form because this is a for-profit entity. This is not about trying to find the best way, safest way to treat patients. So, I'm going to shift gears now and talk about how we're trying to do this, albeit slower than we want. And I will fully own that and admit that this is going slower than we want, but we're trying to do it the right way.

[00:06:45] Why was I promised stem cell therapy 30 years ago and we're still talking about it today? And the answer is: It's really hard. A stem cell by definition -- you would think every stem cell would be the same -- and by definition it would mean it can turn into other cells. That's actually not true. There are different types of stem cells. There are embryonic stem cells, you'll hear about mesenchymal stem cells quite a bit, umbilical cells, and induced pluripotent stem cells. These are all very different with different risks and different capabilities.

[00:07:22] The embryonic stem cells are truly, truly totipotent. They can become any cell you want in the body. The key is: you want to control that differentiation. I've joked for years and I'll joke again, you really don't want a tooth in your spinal cord. That is not of value to you, whatsoever. What you want is a stem cell that is going to repair the spinal cord, so you have to control the development.

[00:07:45] Twenty years of research has gone into making sure that when a stem cell goes into a human, it only turns into what you want it to. So, you had to spend two decades proving a negative -- proving after and billions, and billions, and billions, and billions of cells were differentiated, there wasn't a liver cell, or a tooth, or a heart cell there, and that takes a lot of time.

[00:08:06] Induced pluripotent stem cells are very exciting to me scientifically. We take your skin cells; we then have to mutate or reprogram four genes to turn it back into a stem cell. So, on the one hand, it's your cell, that's exciting. On the other hand, what happens when you mutate those four genes over the long run? We're going to need a lot of time to figure that out.

[00:08:29] And so, where the work has focused is on the most pluripotent or totipotent cells, and I'm going to talk about those. Taking a stem cell and you can differentiate it into cells, and the one I'm going to talk about are these glial-restricted precursor cells, meaning the GRPs. They are only going to form one of two cells that are naturally found within your spinal cord, and those are the cells we're focusing on in our study.

[00:08:54] So, how do we go from this being a therapeutic possibility to this being a therapeutic reality? It's not easy. It starts with preclinical development. Lots and lots of years spent in a lab making sure the cells do only what you want it to do. Then, after you're done testing in a dish, you go into preclinical testing, putting it into animals, and making sure that the cells do only what you want it to do, and understanding dosages and understanding: How do you get the cells in? Can I put it in your vein? -- which is what a lot of the clinics do in Panama or elsewhere.

[00:09:27] It turns out, if I put stem cells in your vein, your liver and your lungs clear out the overall majority of those cells. They never make it to the organ of interest. So, then people said, “Well, let's put it in the spinal fluid.” Well, they float and then they clump along those nerve roots at the base of the spinal cord.

[00:09:45] And so, the question is: How many of them actually get to the site where you want them? Once you have all that data, you talk to the FDA here in the United States, and they issue what's called an Investigational

New Drug Application approval or IND, and that means, you're allowed to test in humans. You go to a Phase I study and then, ultimately, Phase II or Phase III, in order to get approvals.

[00:10:08] So, if we're talking about the preclinical testing of cells for remyelination, there are two parts to it. One is: an animal model where there isn't myelin, you put the cells in and you say, “Does it work?” That is a straightforward experiment. You start it on a Monday. Over a period of a few months, you get your data, but then you have to replicate it. So, it takes a while.

[00:10:30] But then, there's this study where you have an animal model of demyelination, you transplant the cells, and you have to make sure nothing bad happens. Well, it turns out the FDA wants us to do that over, and over, and over, and over. It's not one and done because they want you to change the animals, they want you to change the situation, because what I don't want to do is put cells in and give somebody a tumor because those cells divide in an unusual way. And both of these are required for regulatory approval.

[00:10:58] And when you go to file an IND, there are a lot of requirements. The preclinical data, the safety data, the toxicology data, the manufacturing data, and then you have to propose a Phase I trial. You have to say to the FDA, who are you going to enroll. So, remember in that example from wonderful colleagues -- great work, important work from the Mayo Clinic? They enrolled individuals who were still within the first year of their injury and took them to study stem cells.

[00:11:27] One of the questions is: Is that the right place to start or not to look for efficacy and safety? A big question. Who do you enroll and how do you deliver these cells directly to the area you want? So, let me give you the summary of what we've achieved in myelitis relative to stem cells. Preclinical development -- and I'm going to focus this talk purely on the cells that we're currently using at UT Southwestern known as Q cells.

[00:11:52] So, the preclinical development was done through labs outside of UT and all around the U.S. And there have been publications showing as you're growing these cells, the exact substances you have to expose them to on the exact right day, at the exact right time, to make them turn into those glial-restricted precursor cells and nothing else. It's like baking a souffle. You've got to do certain things at certain times or it just doesn't work.

[00:12:19] And so, that was a lot of hard work to get to that recipe, if you will, in order to get cells that work. And then, you put them in a dish -- and these pictures will be meaningless to many of us in the room, but I'll point out the middle, those black and white rings. What you're looking at is electron microscopy. This is a microscope that can get down to the cellular level, the myelin level. And those concentric rings, that oval in the middle, that is myelin wrapping around an axon that was produced by these stem cells. So, you show in a dish that you can create new myelin.

[00:12:56] And then, you go to this next phase, the preclinical testing. So, the ideal mouse to test in would be one that doesn't have myelin and is having a lot of symptoms because it lacks myelin. And in that case, the mouse that was used was called the shiverer mouse. My favorite named mouse in all of science: the shiverer, because they look like they're shivering, and it's actually probably seizure activity because they genetically don't have myelin.

[00:13:21] And so, their brains develop. What you see on the far left of the screen, the blue, is basically a normal brain and the blue is myelin through the tracks of the mouse. The shiverer mouse is in the middle, you don't see any of the myelin. And on the right is the shiverer mouse has used transplanted stem cells. So, they go throughout the brain, and they make myelin, and the mice stop shaking, it stops seizing. And there's both a clinical benefit and a tissue benefit to transplanting these cells into the mouse.

[00:13:49] So, equipped with preclinical testing, preclinical screening, development data, and a lot of other things, you can go to the FDA and ask for approval. But one of the biggest questions was: how to get them in. We didn't want to inject them into the vein, we tried it for years, it just didn't work. We didn't want to inject them into the spinal fluid, we didn't think the cells would get to the site of injury.

[00:14:11] I spent over a year at Hopkins trying to develop an injection technique through the skin with a needle into the spinal cord to inject the cells into the spinal cord. And it turns out that every time your heart beats, your spinal cord moves. That's a problem. It doesn't matter how steady I am. The target is moving, and we're talking about millimeters that make a difference, relative to the target. The other thing is, if I inject like this: if I put the needle on and I just go, whoop, and I give you the dose, all the cells break apart in the tube. The pressure that's created breaks the cells.

[00:14:48] So, you have to push them in very slowly, over a couple minutes, to give a dose into the spinal cord. And over a couple minutes, your heart has a few heartbeats to give, and so the spinal cord is moving that whole couple minutes. So, there was a neurosurgeon, at Emory, by the name of, Nick Boulis, who developed a device that can actually attach to the patient in the operating room. We call it a floating cannula derrick. It's like an oil derrick. It lowers the needle down. It puts the needle through the cord, but then the needle moves with the spinal cord.

[00:15:24] So, the tip never moves. Every time the heart beats and the spinal cord moves, the needle's moving with it; it's just floating with it. And we can attach it to tubing, and very slowly put the cells in. This needed its own FDA clearance. So now, all of a sudden, it's not just the cells in the preclinical development, but the device needs FDA approval. Before a device, such as a human in a medical setting, we have to make sure it's not going to spark and start a fire, or it's not going to give an issue. So, it had to go through its own approval process.

[00:15:56] Then in the IND submission process and discussions with the FDA, we had a lot of challenges. Who do you treat? Do I take people who are within a year of their injury? And if they all get better, was it the cells? Because it would make for some great videos. There are some people in this room who started off unable to stand or walk in the hospital, and you were able to get out with a walker out of rehab.

[00:16:19] If I treated you in the hospital with stem cells, I'll tell you what I would have claimed. It was my stem cells that got you all. Christina's great, but my cells are better, and I probably would have been wrong. So, there was a discussion about who to include. How do you deliver the cells? How do you monitor for safety?

[00:16:35] How do we track people over time? How do you monitor for efficacy? How long should patients be followed? And one of the notes here is, also around the fact of how do you prevent a person's immune system from attacking the cells? It's like an organ transplant. If you get a new liver, you have to go on immunosuppression.

[00:16:56] What happens if your immune system attacks the cells? That would be the worst irony ever. I'm trying to treat transverse myelitis with stem cells and I induce transverse myelitis with stem cells, that would be bad. So, we had to have a regimen to put people on immunosuppression to prevent that. How do we assess the safety of the regimen? So, if somebody feels sick a month in, is it the drugs? Is it the surgery? Is it the cells? And we had to agree to all of this with the FDA before we could proceed.

[00:17:26] So, what about the procedure itself? So, Nick Boulis invented this device. He knew how to use it. Nobody else knew how to use it. So, you have to qualify surgeons. You have to get them trained. And how many procedures do they need to do before they're allowed to do it?

[00:17:43] Who here wants to sign up for somebody's first time trying the stem cell transplant device with spinal cord? I didn't have too many takers. Finding participants. Once we defined a cohort, we have to find very selfless individuals who are willing to take part in clinical trials. It's a sacrifice.

[00:17:59] And then, surgery day itself. So, turns out this is a total ballet of organizing large groups of people, and it takes a lot of people. And so, from the moment the participant arrives at the surgical center, there's a surgical team, the anesthesia team, the nursing team, the research team. There's a separate stem cell team thawing the cells, and then when they thaw them, they have to tell us, "Yes, those cells look viable."

[00:18:28] And from a moment they tell us that, the participant is put under anesthesia, and we have four hours to get them in or the cells aren't viable. So, from that moment, the clock starts, and we're doing a series of 10 injections in the spinal cord, each injection taking a few minutes, and we want to be careful about it. So, things are moving at a very organized pace in order to achieve all of this the day of. All right. So, we have to do this slowly.

[00:19:00] So, now let's talk about where we are in terms of the Phase I study. So, we opened the study for screening. It was great. We were very excited right at the beginning of 2020. And literally, it couldn't have been eight weeks after we opened for screening that all research at Nationwide shutdown relative to COVID. So, everything that was elective was put on hold, and this was felt to be elective.

[00:19:28] This wasn't an emergent or life-saving event. So, we were able to reopen in 2022 to screening. And it was at that point that the FDA wanted its update on viability of the cells that had been in the freezer. So, we had to hold to give them the update that the cells were still viable in the freezer. So, it kept getting pushed and pushed. And then, in late 2022, we went to the first patient.

[00:19:54] So, this is my warning now: In the next few slides, there'll be a couple graphic slides. I'll tell you when it passes in case anyone's worried. The first slide is not graphic. The first slide is, what you're seeing here is the picture of the operating room for patient number one, in terms of a big day in history for the first stem cell transplant into somebody who was paralyzed from transverse myelitis.

[00:20:17] The next two pictures will have some graphic detail. This, you can see the derrick, the floating cannula derrick, on your right side, and it attaches to the spine, and that derrick moves every time the spinal cord moves. The most graphic of the photos is the next one. I'm going to show you a human spinal cord in the surgical site. I'll give you a moment to decide. Okay. Here we go.

[00:20:42] So, what you're looking at in the field, on the far left in the center of the red, you can see a white cylinder structure. That's the spinal cord. And it's going from left to right on your screen. As it gets to the right, you see a silver tube touching it. That's the derrick, and the needle's being inserted into the spinal cord. And then, that silver tube will retract and the needle stays attached to the spinal cord as it moves.

[00:21:08] And what you're witnessing here in this picture is, the first ever administration of stem cells into a patient with myelitis into the spinal cord. So, that's the photo of that first injection. All right. You're safe now. You can all turn back. All we have are blue and yellow.

[00:21:23] So, we have three cohorts that are FDA-approved. Cohort 1 has been fully enrolled and is being followed up. We then had to go to the FDA to get approval for Cohort 2, and we have gotten our clearance for Cohort 2. All of our patients now are six to 18 months or more out from the procedure.

[00:21:44] We have had no procedure-related or cell-related serious adverse events. So far, from a safety perspective, we're hitting our milestones, and we're keeping in touch. We have an independent Safety Monitoring Board that watches all of our data, and then we have regular reports to the FDA.

[00:22:00] The immunosuppression regimen that I mentioned we're using, has been well tolerated. We're still tweaking some of it, but we haven't had any serious events with it. We are not sharing efficacy data at this time in order to keep the integrity of the study. We're not looking to sensationalize what we do in any way, shape, or form. We want to finish the study before we present it in its totality.

[00:22:22] So, if anyone here is interested in participating, it's on the SRNA website. It's on clinicaltrials.gov. There's an online questionnaire. One of the things you'll see there is that second question: Are you less than 10 years out from your onset? We elected to enroll individuals who are more than a year from their event. They're not within the first year of their event, but they're less than 10.

[00:22:46] And the idea was that we didn't want to ride on the coattails of early improvement. We want people who are relatively stable so that if we see improvements as best as possible, we can know whether or not it's the cells. So, a lot of work goes into this.

[00:23:01] The funding for the clinical trial actually comes from the UT Southwestern Foundation. Partnership with SRNA that puts in funds that are critical for helping patients and families get to us. Q Therapeutics, Steve Borst is here, and he can raise his hand, if you have questions for the group that has graciously provided us with the cells at no cost, and supports a variety of aspects of the study and the FDA work.

[00:23:24] Nick Boulis, the original surgeon. Carlos Bagley and Salah Aoun, are the surgeons we trained. Cannot say enough to our patients, caregivers, and families who have taken part in this. This is a huge sacrifice of time with lots of travel to our clinic. And for those of you at the travel session, for those of you who live with us, travel is not easy. And so, to come back and forth to Texas is a huge deal, let alone taking part in a clinical trial.

[00:23:48] And then, our CONQUERTM team, Taylor's, here. Taylor, in the back room is in charge of everything that happens with this study, and is just one of the best coordinators I have ever worked with, and does an amazing job of coordinating all of these cats that have to be herded, throughout the trial.

[00:24:07] Patricia Plumb, who I don't think is with us today, who's a research nurse. Paula Hardeman, our PA, who I'm not sure is still here, are critical for the study. And then, a large portion of the team shown here and could not do this without the whole group.

[00:24:25] And then, I always end with a couple of updates relative to my daughters. So, when the study was being discussed in terms of how to design it, how to do it, they looked like the left side of your screen. And around the time that Patient 2 was being dosed, they looked like the right.

[00:24:45] On the way here this morning, I put the younger one, the one on the right on a plane to go back to college. She was here for fall break this weekend. And I said, “Well, I'm going to drop off and then I have to go give a talk.” “What's it on?” I said, “It's an update on stem cells.” She's like, “You have got to finish that study.” And I said, “I think I'm going to hear the same thing in the room. Love you so much, honey. Get the hell out of the car.” So, I know we're running late on time. I'll be here through the end. I'm happy to take questions at the end, but I want to make sure other speakers get to get through their talks.

[00:25:17] I appreciate your attention. I want to say thank you again to the SRNA. It's been a tremendous weekend. Chitra, GG, and the entire team, just an incredible job. And thank you to our sponsors who have made all this possible. If you need any other representatives, please thank them on our behalf. So, thank you all. Appreciate it.