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Exploring Stem Cell Research & Novel Options in Type 1 Diabetes

Dr. Anderson:

It's long been a goal of regenerative scientists to create and replace insulin-producing cells in patients with type 1 diabetes, but all efforts to do so have been unsuccessful, until now. Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and joining me today, to discuss this major breakthrough research is Dr. Matthias Hebrok, a Professor in Diabetes Research and Director of the Diabetes Center at the University of California, San Francisco. Dr. Hebrok, welcome to the program.

Dr. Hebrok:
Thank you. Thanks for having me.

Dr. Anderson:
So, to kick us off Dr. Hebrok, can you give us some background on type 1 diabetes? How did you set out to manage this condition with your research?

Dr. Hebrok:
Sure. If you strip everything away from, from patients that have type 1 diabetes, the underlying issue, essentially, there are two; one is the immune system that, for whatever reason has decided that the beta cells, the insulin-producing cells do not belong to ourselves, any longer and the other issues is the beta cells that is being lost. So, people have asked the question 'how can we provide a cure for people who are suffering from type 1 diabetes?', and as of today, the only way to survive, actually, on a day-to-day basis is to inject themselves with insulin. Now the problem with the injection of insulin is that what our body does so perfectly, which is to regulate the level of insulin, according to the level of sugars that we have in our blood, that is something that now needs to be done either by the patient him or herself or fortunately, we have now, new systems that allow us to essentially to inject them through a pump, as well as integrated system or closed-loop systems in which a sensor and a pump are connected. These are getting better and better over time but at the end of the day, you still end up with devices that you have to carry on your body and with tubes that have to connect to your body so that you can obtain the right level of insulin when you need it. For me, a cure would be different. And it can be defined in a number of different ways. For me it would be that a patient who has type 1 diabetes gets up in the morning and doesn't really think about what he or she does and have for breakfast, doesn't think about having a coffee without sugar. Essentially, getting back to the point that the body fulfills the function of regulating glucose levels. And so, how can that be accomplished? People have different ideas about this; one would be to ask our body to, what we call, regenerate our beta cells. What we have learned over the last years is that even in patients, type 1 diabetic patients, who've had the disease forv a prolonged period of time there still are some beta cells left, so, one of the questions would be 'can we just make more of those beta cells that are left?'. And this is possible but it's gonna be a tall order because the number of beta cells that are still residing in our pancreases is very, very small. And so, to increase that level and to, what we call, a replication of these beta cells is gonna be a tough thing to accomplish. The different way of doing this is what we decided to investigate and that is to find out ways to generate more of these insulin-producing beta cells. We all have done this, we have done this when we actually were in our mother's womb as embryos. The beta cells are formed during embryogenesis over a long period of time and then they expand after birth. So, we in my laboratory as well as other groups around the world have spent a long time to try and understand what kind of signals, often these are secreted molecules, what kind of these secreted molecules provide the guidance for cells to develop along the paths so that at the end you have a functional beta cell? That's something, a field that we call developmental biology where we essentially study these mechanisms that underly the differentiation of cells according along a specific path. And by then using this information that again have been gathered over decades, by using that information, we and others, we have set out to try see if we can capitulate this differentiation path under cell culture conditions. And that's where these human stem cells come in, either embryonic

stem cells or induced pluripotent stem cells that can be isolated from patients from somatic tissue like the skin, for example, or the blood. These cells, we call them stem cells, because they can differentiate in a number of different tissues. In our body, we have 250, or so, of different cell types. We all are starting out with one cell as humans and as mammals and over time, there are specific decisions are being made to take that cell and to turn it into a specific cell type, in our case, the beta cell. So, what we asked and what we decided to do, and it took us a very long time, more than a decade is to find out the right signals, give it the right time to a specific cell and then see how we can move that cell along towards the formation of the beta cell and that's what we think we succeeded, finally.

Dr. Anderson:
For those of you just turning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and I'm speaking with Dr. Matthias Hebrok about his breakthrough research on insulin-producing stem-cells. So, Dr. Hebrok, tell us a little bit more about these insulin-producing stem cells. I think you've done a really nice job of laying out how the stem cells are developed. But, from a clinical standpoint, why would using stem cells be preferable over things like pancreatic transplants, and islet cell transplants?

Dr. Hebrok:
So, it's a very good question. Why wouldn't we just use islet transplantation or pancreas transplantation. Pancreas transplantation is considered to be the golden standard and islet transplantation also has been around for decades, now and this is really a fantastic way of helping patients with type 1 diabetes. It's the gold standard because we are giving these patients an organ that is in its pristine form, it has undergone the differentiation that I just described before, in the formation, the organogenesis, as we call this process. But the problem with that is that it's just not enough of those around. There's only less than a thousand or so, islet transplants that, I believe, that are being done in this country and it has to do with the fact that the pancreas actually is, is quite a hostile organ. So, therefore, when we isolate a pancreas, if someone unfortunately has died, so an accident, for example, you would have to go in and isolate the pancreas very, very quickly and experts would have to do this because this, these cells types that are surrounding the insulin-producing cells, they about to release enzymes that can essentially lead to the digestion of the tissue that we're interested in. So, being able to get to a patient and being able to isolate his or her islets is something still that only few places have the been able to, to accomplish in a robust and reproducible manner. There are more than a million and a half of type 1 diabetic patients who live in this country alone. And many of those would love to have access to these islet transplants, therefore, we decided to go the route that I described before, using stem cells as the starting point for our differentiation to generate these beta cells because at least in theory, these stem cells can be amplified.

Dr. Anderson:
OK. So, talk to us about the clinical implications of this. It sounds like a great solution. How far away do you see this being an actual clinical reality for patients, potentially? When will this maybe be a treatment option for people with type 1 diabetes?

Dr. Hebrok:
Yeah, this is also, of course a great question. Before I do this, I should point out that I do think that this is something that's gonna become available to patients in the not-too-distant future and the reason why I believe that is because there are a number of companies who essentially are going full-steam-ahead in trying to use this technology and essentially helping patients with type 1 diabetes. Now, the challenges that they're facing are there are several of those. Starting out by just saying that of course, the most important thing is that we know that whatever we would give a patient is something that is safe. So, we need to ensure, that's the first thing, that the beta cells that we're generating from the stem cells are so close to our counterparts that we have in our bodies that they are safe for transplantation. That's the first thing. Second thing is we need to ensure that there are no other cell types present once you do this transplantation that essentially could interfere, either with the activity, the functionality of the beta cells that we're putting in or some other cell types that, for example, would have tumor-formation capacity. Now, this is something that slowly residing into the background as a concern because these differentiation conditions and protocols have been optimized and are continuing to be optimized in a way that we now have a pretty good understanding that we can generate functional cells, again, very similar to those that we have in our body, as well as we are liking these other cell types that we would have unwanted effects.

But, there are some other problems that are still exist, and that has to do with the fact that we, of course, all of us, are different. What does that mean? It means we are genetically different and therefore our immune system is very different as well. So, if we were to just give someone the cells that we have generated, the, their immune system would go in and eliminate these cells because they would be identified as something that doesn't belong to themselves. Now, in the context of a patient who has type 1 diabetes, it's even harder because not only would that person recognize cells that do not belong to him or herselves, the immune system is unfortunately primed because this person has an autoimmune disease to destroy any kind of beta cells, so even if we would give that person his or her own beta cells back, the immune system would just get reactivated and eliminate the beta cells. So therefore, we need to think about how we can protect these beta cells from the immune system when we put it back in And a more sophisticated way of doing this is something that we in the lab are doing as well as others, of course, is to try to modify the molecules that are being presented to the immune system

on our stem cell-derived beta cells. The general idea behind this would be to cloak our beta cell, stem cell-derived beta cells in a way that the immune system would allow them to stay in the body and therefore not harm them.

Dr. Anderson:
So, as we wrap this up, Dr. Hebrok, talk about next steps for your research team, what are you working on now, what do you see yourself working on in the next year?

Dr. Hebrok:
There's a number of things I'm really excited about. The ability for us to think about how we can cloak cells against an immune attack, I think is really important one. I think this has to do with our ability to use these gene-editing tools that have become so prominent over the last several years, 5 or so years, many of your listeners will know that, there's this system that called CRISPR that essentially allows very precise gene-editing and this CRISPR system now also is capable of actually, working in human embryonic, on human IPS stem cells. That's something that is a game-changer because we can now end, and almost at will, activate or de-active a specific set of genes that we choose and therefore we do think that it will be able to modulate the expression of molecules on the cell surface of the stem cell-derived beta cells in a way that the immune system is not being able to recognize them.

The other thing that we're doing right now is the, the beta cell is actually almost a wimpy cell, it's teetering on the brink because it is so highly sophisticated, it produces a million or so insulin molecules a minute, it's a factory that is working on full steam. But at the same time, that comes at a cost and so if there is any kind of stress that essentially pushes these beta cells then they can we call this exhaust, they can essentially stop working and therefore would lose their functionality. So, we are, are working on identifying these critical elements in these beta cells that we can target using these CRIPSR or gene-editing tools to make these beta cells more robust, hoping that therefore also for cell transplantation if you put cells in there would be "super beta cells" that would essentially withstand these stresses that they would face upon transplantation. Then we would hope that the transplant by itself would last longer and would be functional for extended period of time.

The last thing that I'm really excited about is, is something my lab is, I always tell my members of my lab we are in the business of taking fiction out of science fiction we are hoping to essentially put sensors into cells that would allow, the reporting of biological processes within our cells and then essentially send these signals back out to a device that patients could have, either in the doctor's office or possibly even in, you know, at some point might be incorporated into our phones and therefore you would have after transplantation the ability to read out how your cells are performing. These kinds of things I think would go a long way of us opening up this black box that currently exists after transplantation of any kind of organ.

Dr. Anderson:
Wow. Well, this has been a fascinating look into one of the most groundbreaking findings in the field. And I want to thank my guest Dr. Matthias Hebrok for joining me to discuss his research on insulin-producing stem cells. Dr. Hebrok, it was great having you on the program. Thank you.

Dr. Hebrok:
It was very fun. Thanks so much for inviting me.

Dr. Anderson:
I'm Dr. John Anderson. To access this and other episodes in our series, visit ReachMD.com/DiabetesDiscourse where you can be part of the knowledge. Thanks for listening.