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From Stem Cells to Insulin Producing ß-cells: How Do We Get There?

Announcer:
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Dr. Ricordi:
Hello and welcome to this round table From Stem Cells to Insulin Producing Cells. How Do We Get There? I am Camillo Ricordi, a professor of surgery and director of the Diabetes Research Institute and Cell Transplant Center at the University of Miami Miller School of Medicine. I'm pleased and honored to have a Dr. Melena Bellin from the University of Minnesota, professor and now master and commander of the field of islet transplantations.

I discover I used to be ranked number one or 12 between 2008 and 2018. And then I check this expert skip and said, "Oh my God, there is this Melena Bellin, number one," and I slide to the number five in the top five position. Still pretty good. But congratulations, Melena, for your achievement, is a truly remarkable leader and pioneering the field of islet transplantation. And now moving to our stem cell, that is the topic of this round table. What do you think are the current strategies and mechanism? How do you see the field evolving, Melena?

Dr. Bellin:
Thank you Dr. Ricordi for having me. So as you know, we've both been long involved in the field of islet transplantation for type one diabetes. And we know we can take a patient who has long-standing type 1 diabetes, usually with complications like severe hypoglycemic episodes and give them human islets from another person, a deceased donor, and very successfully restore stable blood glucose control.

The cells do much better than any technology we have at providing for stable blood glucose control. And in many cases, especially if you have the participant or the patient under the right immunosuppression regimen, you can actually get them off insulin. Of course, one of our big hurdles there is that we only have so many deceased donors who can actually provide islets to treat the many, many patients who have type 1 diabetes, but hopefully eventually other forms of diabetes might be amenable to cell therapy.

This is where the question of how do we get another cell source in? How do we treat enough people comes into play. I think what's really exciting right now is that there are a couple companies, a couple trials that are underway in the US and Canada and elsewhere that are using islet cells that instead of coming from a deceased don't actually come from a stem cell line. And what's nice about these stem cell lines is they can be maintained in perpetuity. So you can really create as many cells as you need to provide therapy to everyone.

I think at five, 10 years ago there was some skepticism. Could these stem cell derived islets work like native islets? Could they make enough insulin? I think that's what's been really exciting recently with a couple of these trials as we've seen in indeed that these cells that are manufactured cells instead of deceased donor cells can work like typical islets. I think we really now are on the horizon of having the potential to get that supply to treat everyone.

Dr. Ricordi:
I think there have been also very major advances in different direction because it's not only from embryonic stem cell derive islets, but also from iPS, inducible pluripotent stem cell, generating islets from different sources or taking intermediate tissues like islets or pancreas.

And also, from pathic stem cells, European groups have been concentrating, also deriving insulin producing cells from adult stem cells that can be found in the liver.
I think we still have to determine and define which one will be the best source of insulin producing cells, but I'm glad that at least we're moving to clinical trials and pilot clinical trials, so we'll learn a lot in the next few months or years.

Dr. Bellin:
I agree. And I think the challenge we have still is the immunosuppression aspect, which is not necessarily alleviated by these current cell lines that are in trial, but something like induced pluripotent stem cells where you might have more personalized, maybe, medicine approaches of driving cells for specific patients or genetic editing of these manufactured cells really offer some promise to address that barrier a little bit better.

Dr. Ricordi:
I believe also the recent approaches, like the recent science advances paper on Plos and micro trial on how you could possibly induce local tolerance and increasing regulatory cells at the transplant site, are very hopeful for clinical translation.
I think it is indeed, as you said, is a quantum leap we have to reach because if you still need lifelong immunosuppression, you may not need an unlimited source of insulin producing cells because then the organ donation pool may be sufficient with the limitation imposed by lifelong immunosuppression.

But you really are two parallel tract that will be critically important to the next quantum leap in biologic replacement. On one side you have to develop an unlimited source of insulin producing cells and on the other be able to transplant them without chronic recipient immunosuppression. How do you think the success have been so far in the initial therapeutic approaches?

Dr. Bellin:
I think the place where we have a longer ways to go is certainly in the immunosuppression area. I don't think we yet have a approach that is robustly successful in people. I think most conventional approach that has been tried is the encapsulation approaches, and I think, maybe they can get somewhere that is okay, I'm not convinced that you're going to get optimal cell survival or diffusion of glucose and insulin across that capsule barrier for those to function as ultimately we might like them to.

I think that's where these other approaches with genetic editing or local immunosuppression, as you mentioned, with more of a bio scaffold approach because of course you could give immunosuppression that is much safer than what we give patients right now, which is a systemic immunosuppression if you're able to just regulate the local environment instead of suppress the entire immune system. I think that area has a long ways to go, but I think it's really, there's some innovative potential on the horizon. I think there's actually the potential to get there.

Dr. Ricordi:
Yeah, definitely. It's so important because using immunosuppression may also affect long-term survival of the transplanted insulin producing cells because the open imposed immunosuppression of much higher metabolic demand on the transplanted islets, whether they're organ donor derived or stem cell derive.

This can trigger problems than for long-term functional integrity and or exhaustion of the transplant, Besides the problem of rejection and autoimmune recurrence. The tolerance induction, whether it is biological approaches scaffold or encapsulation that unfortunately super immunoisolation barrier have not been successful. But there are more and more design and technologies also in this field that may be tested clinically very soon.

I'm encouraged by the fact that we have indeed obtain insulin independence with a stem cell derived islets transplant even with immunosuppression. Because often at the beginning you want to see do the stem cell work with the immunosuppression the same that we use in islets transplantation and then move to non immunosuppression approaches. Because if they don't work, then you don't know is it because of the wrong immunosuppression or is it because the cells were not working? I think it'll be critically important what we do in the next several month, years to come. Melena, what do you think will be the best? Do you think will immunoisolation micro devices win or tolerance induction in biological?

Dr.Bellin:
I guess it remains to be seen. I'm optimistic of the potential for genetic editing combined with some other strategy. I really think it's maybe more on the local immunosuppression or tolerance side as opposed to a full encapsulation approach just based on the data to

date. But I think that addition of being able to genetically manipulate the cells combined with some other immunoregulatory approach may have great promise.

I would also argue you don't necessarily need to get rid of all immunosuppression. There are many people who are not transplant patients but have other conditions where maybe they get intermittent or very low dose single medication immunosuppression and do actually quite well. So it may not be getting rid of everything, but I think we can make a lot of progress from where we're at with full immunosuppression.

Dr. Ricordi:
Definitely in the combination also of decreasing the immunogenicity and of the transplant with some kind of tolerance induction, they may actually be synergistic because we will be much easier in use, long-term, stable, at least operational tolerance.

Dr. Bellin:
That's right. And we always have to remember in type 1 diabetes specifically, we are overcoming two barriers, both the alloimmune, the sort of donor islet barrier, but also the autoimmune barrier.

Dr. Ricordi:
Yeah. Great. Thank you so much, Professor Melena Bellin and all of you for attending, and thank you for your attention.

Dr. Bellin:
Thank you, Dr. Ricordi. Thank you to the audience.

Announcer:
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