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Critical Updates on Islet Transplantation and Clinical Trials of Stem Cell-Derived Islet Transplantation

Announcer:
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Dr. Ricordi:
Hello, my name is Camillo Ricordi. I'm a Professor of Surgery and Director of the Diabetes Research Institute Stem Cell Transplant Center, the University of Miami.

I have the pleasure to introduce today. Dr. Thierry Berney, who is a Professor at the University of Geneva, has been a pioneer in islet transplantation in Europe. And I had the privilege to collaborate with him for many years but has becoming president of all the most relevant society in transplantation in Europe and beyond from the European Society of Organ Transplantation to the International Pancreas and Islet Transplant Association and many others.

I'm happy that we can talk today and discuss a little Critical Updates in Islet Transplantation and Clinical Trials of Stem Cell-Derived Islet Transplantation. Welcome, Thierry and hello to everyone listening to this program. The first subject and question is, what are the strength and challenges of current transplantation technology for insulin-producing cells? Thierry, right now Europe move way ahead of United States because of the regulatory impediments we are facing in United States. But I'm looking for your view on this topic.

Dr. Berney:
Yes. So setting aside the problems that you just alluded to, i.e. regulation and we are talking specifically about islet cell transplantation. Type 1 diabetes currently is managed by two types of procedures, whole pancreas transplantation, which is very effective but it's a very heavy surgical procedures with a high morbidity rate but very good long term results. Islet transplantation is minimally invasive, has very good results that still have to match those of pancreas transplant, but has proven extremely efficient at controlling hypoglycemia unawareness, for example. Also, in quite significant proportion of patients, even achieving insulin independence.

These are the two modalities, I guess, that the two major hurdles that they face is one, the shortage of donors because you need organ donors to be able to do either of these two procedures. The second is, of course, the need for lifelong immunosuppression in order to prevent rejection and this is something that comes with a burden. Of course, it's better than living with the burden of type 1 diabetes, but it still is a significant burden.

Dr. Ricordi:
It's interesting that we actually recently published the 20 years cumulative survival data on patient receiving islet transplant and it is interesting that the survivor rate at 20 years was 85%. That seems even superior to the survival of insulin therapy in the absence of immunosuppression for that age range. Of course, you wouldn't do an islet transplant in a child or in a very young adult because of the requirement of lifelong anti-rejection treatment. But in this age range, if you're between 40 and 45 or 40 and 50, islet transplantation may even be considered a lifesaving procedure, in a way, despite the use of chronic recipient immunosuppression.

That is something that may, hopefully, change a little the perspective from endocrinologists on how to refer people to islet transplantation. But I would agree that the requirement for lifelong immunosuppression are severely limiting the applicability of islet transplantation at this time. We also have recent results in the first success of stem cell that are islet transplant that we can mention. Because as Thierry mentioned, the limitation of organ donation that if we have in the United States 1,000 suitable pancreases a year and millions of patients that would want an islet transplant once we will be able to do it without antirejection drugs, this clearly would impose a lottery system for who would get access to this precious resource. So the possibility to have stem cell-derived islets and potentially an unlimited source of insulin-producing cells is highly desirable.
I was honored to be able to present in Stockholm at a European Society on Diabetes, ESD, which is the largest congress in diabetes right now with over 23,000 delegates worldwide. We were able to present the first successful case of stem cell-derived islet transplant where a patient became insulin independent with normal hemoglobin A1C and 99 timing range of glucose levels. So if this will be confirmed and become reproducible, it will be huge advancement in the field, as far as availability for insulin-producing cells. Thierry, how do you see the hope of emerging technology to overcome this pitfalls, both the organ shortage and the immunosuppression?

Dr. Berney:
No, but you are spot on. I think the major point of stem cell-derived beta cell therapy is the fact that in theory, they are potentially going to represent an unlimited off-the-shelf source of insulin-producing tissue to be transplanted to patients whenever the need is. Of course, this is a major... It is not yet a major break breakthrough. We have had a result from the first three patients tested to be confirmed and reproduced in a larger scale. But it is extremely promising what we are seeing right now.

What will need to be done then, the next step will be to able to really have these off-the-shelf insulin-producing cells available for any type of patient, regardless of blood group and so on. Also, be able to move towards some kind of isolation of the cells from the attacks of the immune systems so that you would not only have an infinite source of tissue to cure diabetes, but also without the need for lifelong immunosuppression. Thus, you would address the two hurdles that I alluded to at the beginning of this module.

Dr. Ricordi:
Right. I think it's really encouraging the recent paper in Science Advances that was published by the group at Georgia Tech and University of Missouri and Harvard MGH using a Fas ligand microgel that showing nonhuman primate ability to support and maintain islets, preventing rejection for many months without the use of immunosuppression, thanks to a novel biotechnology that now iTolerance is bringing to the clinical trial for [inaudible 00:07:52] where you mix a microgel that present Fas ligand with the islets and this intercept the lymphocytes that will attack the islet transplant, inducing apoptosis or so-called programmed cell death and at the same time promoting regulatory T-cells to develop at the transplant site, maintaining operational tolerance.

So, this is really impressive because if you can combine then an unlimited source of insulin-producing cells with a way to induce immune tolerance without lifelong immunosuppression, it would be a major quantum leap for the field, in my opinion.

Dr. Berney:
I agree with that, Camillo and I think that in terms of isolating cells from the immune system, the field has been concentrated on encapsulating islets in physical, mechanical barriers for way too long and it has never really worked. I really think that with this type of study and also other studies that are being conducted, for example at the University of Geneva with novel types of hydrogels, I think we are moving towards a concept of encapsulation in which capsules are not physical barriers but are more of a immunomodulatory milieu in which the cells are embedded and in which they can be protected, made invisible to the immune system, be in contact with various molecules such as the Fas ligand you were alluding to, but also others that will confer some immune protection and prevent them from being distracted by not only immune rejection but also a recurrence of autoimmunity, which is a problem or could be in type 1 diabetes.

Dr. Ricordi:
Definitely. That, I would say, is a key challenge because if we don't have immunosuppression, if you don't eliminate immunosuppression as a need, then you don't need stem cell-derived islets because there will be enough, the islets from multiorgan donor if you have to use chronic recipient immunosuppression.
So, in a way, it will be the rate-limiting step to be able to use unlimited sources, to be able to transplant without lifelong recipient immunosuppression. Well, thank you very much, Professor Berney Thierry, for this brief discussion

Dr. Berney:
Thank you.

Dr. Ricordi:
And thank you, all of you, for attending.

Announcer:

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