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https://reachmd.com/programs/cme/advances-in-immune-tolerance-induction-and-islet-encapsulation-new-hope-for-t1d/14642/

Released: 12/19/2022
Valid until: 12/19/2023
Time needed to complete: 1h 14m

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Advances in Immune Tolerance Induction and Islet Encapsulation: New Hope for T1D?

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Dr. Ricordi:
Hello and welcome to this session on advances in immune tolerance induction and islet encapsulation, a new hope for type one diabetes. I'm Camillo Ricordi. I'm a professor and director of the Diabetes Research Institute and Cell Transplant Center at the University of Miami. I've been involved in islet transplantation and self-processing from the pancreas since the eighties, when we developed the automated method, so-called Ricordi chamber for human islet isolation when I was at Washington University, and then I led the first successful islet transplants at the University of Pittsburgh with Dr. Starzl and all the way to the successful completion of the phase three trial of islet transplantation type one diabetes that was funded by the NIH Clinical Islet Transplantation Consortium, which I had the privilege to chair, where I chaired the steering committee for over a decade. Now, the situation in islet transplantation has evolved in a way that the results are quite remarkable.

You can see you can have 96% time in range with no severe hypoglycemic episode, which is a reason why islet transplantation are performed with normalization of hemoglobin A1C. This has been quite remarkable. Now more recently, stem cell derived islets have reached similar results or even better than traditional islet transplants from organ donors. This paper was recently published, saying also that patient survivor at 20 years was quite spectacular in islet transplantation despite the requirement of chronic recipient immunosuppression. However, that remains a challenge and that's why we're addressing now tolerance induction and encapsulation immunization technology to try to eliminate the need [inaudible 00:02:06] to rejection drugs, which severely limits the applicability of islet transplantation to the most severe cases of type one diabetes. Recently, Vertex and many other entities are heavily investing and working on stem cell derived islets and we had some spectacular initial results that were first in human success of stem cell derived islet transplant in type one diabetes.

The results were presented at the ESD in Stockholm very recently showing in this patient how very unstable and metabolic control at baseline was corrected and led to insulin independence with a normalization of hemoglobin A1C to 5.2 at time in range of 99.9%, which was quite remarkable. To make stem cell derived islets appealing as an unlimited source of insulin producing cells, of course, you need to do this transplant without immunosuppression, otherwise, you may not need stem cell derived islets because this small indication would allow just the islet transplantation for multi-organ donor to be sufficient for the selected patient that may benefit. But if we achieve islet transplantation without immunosuppression, then it'll become like a lottery because we don't have enough pancreas to treat our patients that could benefit and that's why we need new technology. The two pillars in this direction are either islet encapsulation.

This is a very recent review from 2022, which show the different kind of nano capsule, conformal equation capsule, micro capsule, macro encapsulation, and 3D structure encapsulating insulin producing cells. These are all technology that are based on the concept that you can shield the islets on the immune response by some kind of physical barrier that is semipermeable, allowing glucose sensing insulin production and diffusion outside of the capsule as well as oxygen absorption and nutrient to maintain viability of the islets that are

encapsulated, whether in a micro capsule or in macro capsule that is a larger device. The challenges remain today is that if you develop any kind of fibrotic reaction around the capsule or the macro device, then the islets will shrink and suffer for lack of oxygen and nutrients. Let's also impart hypoxia and lack of nutrients has been why many of these encapsulation technology today have failed to produce long-term results in subjects with type one diabetes or in large animal preclinical model systems.

There is several attempt now to address this. There are new macro devices that are revascularizing with blood vessel that can grow through compartment that are immune isolated. There are new technique like a conformal coating like we're working at the Diabetes Research Institute with Alice Tomei that is trying to generate a very tiny coating around the islets so that the diffusion of oxygen and nutrient remains okay. And then there are also tolerance induction protocols like the one that rely on engineering of an intraabdominal endocrine pancreas in domain, and then application of a strategy like fast ligand micro gels that have been not published in science advances even in non-human primates, showing a hundred percent survival for six months in the absence of chronic recipient immunosuppression. That has been quite remarkable because it's the first example of tolerance induction without immunosuppression in a non-human primate that will be hopefully translated very soon in clinical trials.

This is based on fast ligand-induced apoptosis of the infiltrating effector cells that try to induce and destroy the transplanted islets and also use regulatory T cells expansion at the transplant site that are responsible for maintenance of tolerance in the long term. There are other trials, like anti [inaudible] ligand costimulatory blocker that have been approved also for clinical testing and will start in the United States this year. The jury is still out between encapsulation or tolerance induction, but I'm happy that there are so many approaches now being actively pursued and so far, none of them clinically has yielded long-term results of islet transplant without immunosuppression, but the path is very promising and I'm looking forward to update you with positive results in upcoming year. Thank you for your attention and have a great day.

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