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Is a Bioengineered Organ Going to Lead to a Biological Diabetes Cure?

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The Diabetes Research Institute (DRI) has been developing its BioHub mini organ, which looks to play a significant role in DRI's quest to get to the final destination: a cure for insulin-dependent diabetes.

By: John Parkinson, Clinical Content Coordinator, DiabetesCare.net

In March of last year, exciting news came from the Diabetes Research Institute (DRI) at the University of Miami. The DRI (**pictured here**) announced it was working on the Biohub, a bio-engineered platform technology that will house islets which will be transplanted into the omentum (inside lining of the abdomen) with the goal of restoring natural insulin production in patients with type 1 diabetes. [**Editor's note: check out our slideshow on DRI's technology here.**]

At the helm of this research is Camillo Ricordi, M.D. Ricordi (pictured below) is the Stacy Joy Goodman Professor of Surgery and Director of the DRI, and a leading scientist for islet transplantation. He developed the Ricordi Method, the procedure for isolating islets in large enough numbers so that the insulin-producing cells can be transplanted into patients. He is also credited with other islet-related discoveries and holds 11 patents. Ricordi has collaborated with scientists, clinicians, and surgeons from around the world to further islet transplantation research, and served on a number of panels and committees related to transplants, including being Chair for the steering committee for the Clinical Islet Transplantation (CIT) Consortium.

Ricordi and his team are using their breadth of experience in a multipronged approach to achieve their goal. While inroads have been made with islet transplantation, challenges remain. In the current protocol, patients who undergo islet transplants are required to be on a continuous regimen of immunosuppression (anti-rejection) drugs to prevent the patient's immune system from destroying the donor cells.

There are health risks to taking these drugs, including varying side effects and vulnerability to infections. These drugs can take an exacting toll on patients, so one of the end goals is to develop a transplant protocol whereby patients will no longer need them.

In addition, the long-term viability of transplanted islets has been another ongoing challenge. Patients can realize long-term insulin-independence, but at varying rates. Some patients can be insulin-independent for many years; whereas others may need to resume insulin therapy sooner. With this knowledge, DRI has identified three main challenges to long-term successful islet transplantation:

- Supply–the need for more insulin-producing cells for transplant;
- Sustainability–the need for the recipient to accept the cells long-term, without the need for anti-rejection drugs; and
- Site–the identification of an optimal site within the body to house the new cells. (1)

DRI is attempting to address these challenges by: using the BioHub platform, which will be surgically implanted; changing the transplant location in the body from the liver to the omentum; and gradually weaning patients off of anti-rejection drugs altogether.

DiabetesCare.net spoke with Ricordi about the two BioHub platforms, about transplant tolerance—what he calls the Holy Grail of transplantation—and the timeline for when clinical trials will take place.

DiabetesCare.net: DRI has developed two BioHub platforms, both the biodegradable scaffold and the bioengineered scaffold, to be used in the transplant procedure. Can you explain what these scaffolds are designed to do and the differences between the two?

Ricordi: One of the scaffolds (bioengineered) is a three-dimensional structure that is 90% air and 10% silicone. The silicone is a like a porous sponge that will house islets and keep them separate from one another and will be able to house other critical components that keep the cells healthy, viable and able to function long term. This material is compatible with the human body, but it is also a permanent material. The other option we are testing is a biodegradable scaffold that houses the islets, provides a similar structure and spacing, and allows us to add these same factors, cells, etc., but this scaffold materials is made from a patient's own plasma, and easily reabsorbed by the body. After a certain amount of time over the course of weeks or months the

scaffold will be gone, leaving the islets cells intact with their own newly-formed network of blood vessels supplying oxygen and nutrients.

DiabetesCare.net: One of the things you are looking to do with the BioHub, which is different from other previous islet transplantation procedures, is to place the bioengineered organ in the omentum as opposed to the liver, which has been the traditional transplant site. Why the change?

Riccordi: One of the concerns for regulatory agencies such as the FDA is when you develop something for mass distribution. If you put islets in the liver and anything goes wrong or you want to take them out, you cannot remove the liver. Also, with the liver location you are putting islets in a place which is a major detoxification station of the body. This can add stress to the islets over the years and lead to their eventual loss of function—as has been observed in some trials. Another issue with the liver is that when you take immunosuppression drugs by mouth they are absorbed through the intestinal tract, and the highest level of these drugs is witnessed in the liver.

So the decision was made to engineer a micro-organ that is retrievable but keeps all the insulin-producing cells in a confined space that is either completely dissolvable (biodegradable BioHub scaffold) or can be easily removed (bioengineered BioHub scaffold). One of the key challenges we need to address is the successful implantation of the cells without the continuous use of immunosuppressive drugs. The advantages to confining the islets to a specific location is that we have the ability to manipulate the cells and the area itself by providing local agents to block immune attack, provide agents to boost oxygen levels and vessel growth, dampen inflammation and overall more closely mimic the native organ.

The BioHub is an emerging technology that brings together the pieces of the puzzle. It's being developed in parallel with other research elements such as stem cell and immune therapies. We plan to phase in, in subsequent clinical trials, the various components to further improve the cells' micro-environment. Our goal is to arrive at a complete biologic cure without the continuous use of immunosuppressive drugs. There might be some temporary immunosuppression required, but we want to eliminate the use of these drugs altogether.

One of our technologies to protect islets includes the development of protective barriers, referred to as cell encapsulation, which provides semi-permeable, protected membrane that allows the insulin to defuse but shields the cells from the immune system. That alone might not be sufficient, so if we are using a tolerance induction product, like the one I'm studying with Suzanne IIdstad. [**Editor's Note: According to DRI's website, Ricordi and his team are collaborating with Dr. Suzanne Ildstad of the University of Louisville who is performing bone marrow transplants using a new protocol in kidney transplant patients. To read more about it, go here.**] (2)

The use of anti-inflammatory agents will play a key role in islet graft acceptance. In any transplant model, and in this we're speaking of islets, if you have inflammation at the time of the transplant it is very difficult to induce permanent islet survival because the immune system is waking up and you have this amplifying effect induced by the inflammation.

DiabetesCare.net: How is DRI planning to counteract immune system attacks on islets?

Ricordi: That is the key question we are now addressing. We are developing and testing different approaches to achieve permanent acceptance of the transplanted cells. This is known as donor-specific tolerance. In addition, we are developing strategies to reset the immune system to prevent the recurrence of autoimmunity.

One of the most exciting approaches that we are going to test is something we are doing with Dr. Ildstad, who has been a collaborator of mine since we were at the University of Pittsburgh in the early 90s.

We are investigating an approach that utilizes donated bone marrow derived cells in order to reconstitute the immune system of the recipient—so that the host immune system becomes a combination of both the donor and the recipient—which has led to the acceptance of tissue from the same donor source because it is recognized as "self."

The exciting thing is this procedure is already in clinical trials for kidney transplantation at Northwestern University in Chicago and at Duke University. The results are very exciting and were presented at the World Transplant Congress in San Francisco a couple of months ago. They now have patients out five years with transplant survival in the absence of anti-rejection drugs. This is unprecedented in transplantation.

DiabetesCare.net: How would this bone marrow procedure work with transplantation? Would a patient go through this procedure first and then go through islet transplantation?

Ricordi: The islet transplant would be first and then this procedure a few months later. In the beginning, it will require some immunosuppression that will be tapered during the year. And there would be no more anti-rejection drugs at one year post-op.

We also have other approaches for tolerance induction. Hopefully, we will be in clinical trials for them in the next year.

DiabetesCare.net: DRI has received FDA approval to begin a phase I/II clinical trial for the first step toward developing the BioHub. Can you talk about the specifics of this trial and what you hope to accomplish?

Ricordi: The biological scaffold trial has been approved, and in this first trial we are looking to test a new site in the body— the omentum—as a viable location for a BioHub. The goal of the trial is to compare this site to the liver. While much of the work is focused on the engineered site, on a parallel track, our team is developing and planning to test strategies for tolerance induction, so we don't have to wait years to add another component to the research. The goal is to merge these research tracks so they converge towards this ultimate biological replacement goal.

DiabetesCare.net: You have said that you are confident the BioHub could move cellular therapies and biological replacement strategies towards a final goal. What is it about this project that makes you so hopeful?

Ricordi: This project makes me incredibly hopeful because of the convergence of technologies that we have been working on for the past 20 years; seeing all the components coming together and fitting like a puzzle. The recent advances made in clinical trials are really encouraging. For us working in the field, this has been an exciting time.
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Read more: http://www.diabetescare.net/up-close/is-a-bioengineered-organ-going-to-lead-to-a-biological-diabetes-cure#ixzz3IyOXiOX1