Beta Cell Replacement

OVERALL VISION AND LONG-TERM OBJECTIVES

Replacing beta cell function via cell-based therapy remains the only approach with a clinical proof of concept that demonstrates insulin independence can be achieved in long-standing type 1 diabetes (T1D). While islet transplantation is an available strategy, its viability for the vast majority of individuals living with T1D is limited by the supply of donor cells and the need for chronic systemic immune suppression that keeps the cells alive after transplantation. Importantly, islet transplantation can reverse severe hypoglycemic events and unawareness, a serious consequence of T1D, as well as halt or stabilize other complications associated with T1D. Therefore, JDRF’s Beta Cell Replacement Program has prioritized moving beyond islet cell transplant toward commercialization of a product with a safe renewable beta cell source capable of restoring glucose control and delivering long-term insulin independence without the need for chronic immunosuppression therapy. The availability of safe and effective beta cell replacement therapies would restore the ability of people living with T1D to achieve significantly better blood-glucose control with little or no effort, thereby decreasing T1D’s daily challenges and avoiding many of the life-threatening complications of the disease.

The Beta Cell Replacement Program supports promising research that can go from basic discovery to translational studies and all the way to human studies to validate clinically meaningful therapies. While it is premature to make definitive statements, it’s likely that the ultimate beta cell replacement therapy will be comprised of several components, such as a genetically modified cell source, an implantable delivery device and administration of drugs to provide local immunosuppression. To support the developments across our pipeline, the Beta Cell Replacement Program will also include commercial commitment and regulatory activities to define and accelerate development plans that lead to product approvals. Lastly, the program will also help define target product profiles and commercial products that may be developed for specific T1D populations while considering patient access and clinician adoption issues.

In the long run, while current lines of investigation and commercialization focus on developing a product consisting of a replenishable beta cell or islet source in an immune protective device, there may be alternative strategies we will consider to position next-generation products to succeed. For example, induction of immune tolerance toward transplanted cells and organs may be an approach to allow the host immune system to accept grafts without the use of chronic immune suppression, obviating the need for encapsulation. Another potential strategy involves genetically modifying cells to (1) evade immune recognition and promote tolerance so that less or no immunosuppression would be required or (2) make them resistant to metabolic stress and hypoxia to enhance engraftment and cell survival.

RATIONALE

In the past two decades, there have been major advances in the islet replacement field as an approach to restore glucose control. Improvements in surgical techniques and immunosuppressive strategies have resulted in the introduction of donor islet transplantation with minimally invasive procedures. Phase 3
clinical data including the recent report from the Clinical Islet Transplantation Consortium (CIT) have demonstrated durable near-normal glycemic control and restoration of hypoglycemia unawareness after islet transplantation, and as reported by the Collaborative Islet Transplant Registry (CITR) up to 44% of recipients remained insulin independent after 3 years. However, due to the risks and side effects of the immunosuppression, the availability of these treatments is generally limited to patients with severe life-threatening hypoglycemia unawareness and increased incidence of hypoglycemic events. Several factors, in addition to the immunosuppression and unrelated to the immune response can also contribute to long-term failure including poor islet quality, insufficient islet mass, poor vascularization and hypoxia. The generation of replenishable alternative beta cell sources and delivery systems to support and protect such cell sources may address the shortage of human cadaveric donor pancreata and the requirement for lifelong systemic immunosuppression that restricts the availability of current human pancreas/islet transplantation to a small group of individuals with T1D.

CURRENT STATUS
At the present time, there is no commercially available beta cell replacement product. The priority effort is targeting preclinical and clinical product development. A first-generation replacement product could consist of insulin-producing cells in a delivery system that protects the graft from the immune system and supports long-term function. The various components of a beta cell replacement therapy are described below.

ALTERNATIVE CELL SOURCES
Recent advances in cell therapy have positioned cells derived from human embryonic stem cells (hESC) and human induced pluripotent stem cells (iPSC) and porcine islets as the most promising replenishable alternative sources of beta cells. As such, developing effective strategies for providing immunoprotection of these cell sources, such as encapsulation, is currently a major priority. The ultimate goal is to provide clinical proof of concept for the development of a renewable insulin-producing cell source from a human stem cell or porcine islet.
Allogeneic Human Stem Cells (hSC)
Progress in pancreatic development, beta cell differentiation and stem cell biology has resulted in protocols for deriving human pancreatic endocrine cell progenitors and surrogate beta cells from hESC and iPSC. There is still no clear data on whether the optimal commercial cell therapy product would incorporate a pancreatic progenitor cell population or a fully mature transplantable beta cell population. Both cell sources have advantages and disadvantages. Current cell preparations still contain populations that are not monohormonal and truly functional, and it remains to be determined whether additional non-beta islet endocrine cells will need to be produced to constitute a complete cell product. Development of stem cell therapies will also require long-term safety assessment such as the risk of uncontrolled growth and formation of teratomas. Overall, a well-manufactured source of beta cells should have a much higher quality control over cadaveric islet isolations such that beta cell survival and functional durability after transplantation will be improved. The yield, purity and consistency of these cell preparations will need to be optimized and scaled up under cGMP conditions. Several companies have applied this knowledge and are poised to develop hSC-derived pancreatic progenitors and functional surrogate beta cells as potential commercial beta cell replacement products.

Xenogeneic Islets
Islets isolated from clean defined pathogen-free pigs. Xenotransplantation using porcine islets has also advanced and is gaining acceptance as a potential readily available cell source. Key to the success of porcine islets as a source for replacement therapies is establishing which developmental stage (neonatal, juvenile or adult) will provide the best outcome, as well as overcoming the concerns about the transmission of porcine endogenous retroviruses (PERVs) from the pig genome. Advances in both assay development for pathogens and the ability to eradicate the PERV sequences using genome editing make xenotransplantation a promising option.

Encapsulation Technologies (Physical Barriers)
Developing effective encapsulation approaches for immune protection of cell sources to circumvent the use of immnosuppression is currently a major priority. Immune protection of islet cells via encapsulation could overcome allogeneic, xenogeneic and/or autoimmune responses against the foreign tissue. A successful encapsulation technology would increase the access of cell replacement therapy to a broader patient base by eliminating/minimizing chronic administration of immunosuppressive drugs. Encapsulation technologies use biomaterials to create a permselective immunoprotective barrier around islet cells and are thereby designed to limit and ideally eliminate undesirable immunological responses to the foreign graft. A permselective biocompatible material allows for exchange of small molecules such as oxygen, glucose, insulin and selected nutrients in and out of the device via diffusion, while blocking larger molecules, such as immune cells and antibodies. Devices under investigation differ by biomaterials, shape configuration and methods used in fabrication. Several synthetic polymer and natural materials including alginate, agarose, polysulphone, and polyethylene glycol (PEG) are or have been used to encapsulate islets. Encapsulation schemes can be broadly categorized into macro-encapsulation devices (one device containing a large mass of islet cells) and micro-capsules (each capsule containing single islets or small groups of islets). Newer technologies under development aim at
further reducing the thickness of the capsule wall: conformal coating uses novel co-axial flow apparatus to achieve uniform but thin coverage of islets; nano-encapsulation typically uses chemical and electrostatic interactions to deposit biomaterials via layer-by-layer assembly at the nanometer scale. Micro- and macro-encapsulation technologies offer different advantages and disadvantages. Due to the reliance on passive transport for nutrient, glucose and insulin exchange, the distance between the native tissue, its blood supply and the ability of a nutrient and oxygen rich environment poses a limitation on cell survival and proper glucose regulation, and this parameter is usually larger for macro-encapsulation. While macro-encapsulation devices enable retrievability of the entire graft, which may be a desirable feature for products using hESC/iPSC-derived cells, micro-capsules do not allow for complete graft retrieval but provide a larger surface area/volume ratio, maximizing diffusion of oxygen and nutrients. At this time, JDRF is supporting both design approaches to better understand the potential benefits and liabilities of each approach.

**Scaffolds (Open Devices)**
The Beta Cell Replacement program launched an RFA in 2015 to explore scaffolding technologies with the aim of developing devices that are more porous and permeable to enable vascularization and better exchange of oxygen and nutrients between the implanted cells and the recipient’s body. Scaffolds are also referred to as “open devices” as they do not use a physical barrier (membranes or capsules) to protect the transplanted cells. Scaffolds can be made from synthetic materials or using a natural matrix such as decellularized organ, and provide not only a tissue structure but the capacity to promote vascularization, local regeneration, as well as enabling localized protection from the immune system while ensuring easy retrieval and replacement. One potential approach to reduce the requirements of a full encapsulation system and help implanted beta cells to overcome the need for chronic systemic immunosuppressive therapy is to employ strategies for localized delivery of immunosuppressive drugs or immunoregulatory molecules to protect the transplanted cells or promote tolerance. One might envision engineering scaffolds to present or release such molecules, or as an alternative approach, one could leverage recent progress in gene-editing techniques, enabling cells to protect themselves from rejection. Finally, scaffolds that help create permissive environments, for example promoting vascularization in the subcutaneous space, could be combined with micro or nano-encapsulated cells.

**Gaps and Challenges**
It is expected that encapsulated beta cell replacement products will evolve over a multi-stage development pathway. Each next iterative product using either encapsulated hESC/iPSC-derived cell products or porcine islet cells is anticipated to demonstrate improved immune protection and glucose control performance over previous versions to increase function and durability as they further reduce and eventually eliminate the burden of immunosuppression. However, several challenges remain and must be addressed in order to make cell replacement therapies applicable to a wider number of individuals with T1D. They can be grouped into four categories:

**Technical**
- Identifying the best cell source and composition
Reducing the cost of goods: cell source manufacturing (stem cell or porcine islets) remains expensive

Determining an adequate balance between immunoprotection and integration with the host to promote graft survival and function (encapsulation vs. alternate forms of immune protection)

Determining the best method to protect the cells (encapsulation, local immunoregulatory components or genome engineering)

Methods for delivery and for measurement of oxygen in the local microenvironment are not sufficient to address this important concern and novel strategies are needed

Reduction of inflammation, scarring and fibrosis hurdles from the device design

Poor translatability of rodent studies, increasing the risk for success

Cost, complexity and expertise needed for large animal studies

Lack of success criteria from preclinical studies to translate into human proof of concept studies

Availability, variability and cost of high quality human cadaver islets as a comparator for cell quality assessment

Disparate Expertise

Beta cell replacement is both a cell biology and engineering/biomaterials challenge

Multi-disciplinary collaboration from a number of scientific disciplines is required to achieve a successful beta replacement cell product

Devices are being developed independently of cell sources, slowing optimization of a final device-cell combination product

Teams use different models, protocols and experimental designs that complicate evaluation and comparisons and there is limited standardization and reproducibility across laboratories

Traditional islet transplant centers are motivated to develop beta cell replacement programs but we may benefit from additional medical programs that deal with related challenges such as vascularization and device implantation (plastic surgery, vascular surgery, orthopedic surgery)

Design of Target Product Profiles (TPP)

Based on the state of the science and what is currently known of the effects of islet and pancreas transplantation, there are several TPP for existing and future beta cell replacement products. These profiles attempt to capture the anticipated improvements in the potential succession of next generation products. As the science matures and improves, the immune protection from better encapsulation technologies and alternative strategies is expected to reduce and ultimately eliminate the burden of immunosuppression for next generation products.

- Cadaveric islet transplantation with chronic systemic immunosuppression
- Porcine islets with chronic immunosuppression
- Encapsulated hESC/iPSC-derived beta cell product or porcine islets with transient/no immunosuppression
- Limited encapsulation and targeted immunosuppression approach with a hESC/iPSC-derived beta cell product or porcine islets
Each TPP has safety and health outcomes considerations. Additional considerations for porcine products are the source (neonatal, young piglet and adult pig islets), while hSC-derived beta cell preparations might differ in term of differentiation stage and cell compositions (i.e., progenitors vs. fully mature beta cells).

**Regulatory Considerations**
- No “one size fits all” regulatory approach
- Clinical trial designs will be based on cell source, need for encapsulation, site of implantation and need for immunosuppression
- Maintain close interaction with investigators and regulatory agencies; JDRF is committed to clarifying the regulatory pathway

In order to address these key challenges in the field, JDRF established an Encapsulation Consortium involving academia and industry partners to create a research network to accelerate and advance research and development in strategic areas by encouraging collaborations among multi-disciplinary experts (bioengineers, chemists, immunologists, transplant researchers, etc.), building a robust technology pipeline, and fostering protocol standardization and independent replication of promising results. The main purpose of the Consortium is to exchange project updates, discuss strategies to address key challenges and identify the missing gaps that impede progress to better position our resources and gap-filling initiatives.

**MID-TERM GOALS**

**Preclinical**
- Advance development of technology and bioengineered therapeutic strategies for beta cell replacement that promote graft survival and function
- Define success criteria and identify preclinical animal models most predictive of human responses
- Accelerate IND-enabling projects
- Renewable beta cell source (porcine islets, hSC-derived cells) with an encapsulation device
- Renewable beta cell source (porcine islets, hSC-derived cells) with an immune privileged scaffold
- Genetically engineered beta cell source (porcine islets, hSC-derived cells) with an encapsulation device or immune privileged scaffold

**Clinical**
- Establish methods for manufacturing replenishable cell sources, long-term banking and shipment standardization of stem cell-derived beta cells
- Define meaningful clinical endpoints for 6–12 month efficacy (reduction of HbA1c, insulin dosage, severe hypo events)
- Proof of concept for a product capable of delivering insulin independence for 12–24 month without chronic systemic immunosuppression therapy
JDRF FY18 Program Strategy Roadmaps: Beta Cell Replacement

Regulatory
- Additional IND(s) approved for human studies using human/porcine islets, hSC-derived cell sources
- BLA submitted and/or approved for cellular/biomaterial/engineered final product
- IND(s) approved for first-in-human study of genetic engineered beta cell source and immune privileged scaffolds

Business Development
- Development of commercialization plan
- Support equity investments in early stage companies (device, combination product and/or engineered cells)
- Establish industry partnerships leading to human trials for replacement products

SHORT-TERM OBJECTIVES AND PRIORITIES

Cell Source
Differences between beta cells from adult islets and beta cells derived in vitro from human stem cells still persist (function, insulin kinetics, structure, access to vascularization, matrix composition and contact with other cell types). Initiatives to increase translatability of human stem cell sources include:

1. Explore the human islet microenvironment as an approach to improve in vitro function of an “islet cluster”:
   a. Identify and characterize other pancreatic cell populations that may contribute to beta cell function and improve glucose control in vivo (endothelial, exocrine, neuronal).
   b. Identify the role of extracellular matrix signals and factors that could potentially improve beta cell/cluster survival and function.
   c. Identify and validate gene modifications (both loss-of-function and gain-of-function) that protect beta cells from immune-mediated damage while maintaining normal glucose-responsive insulin secretion.
   d. Identify and validate gene modifications (both loss-of-function and gain-of-function) that enhance beta cell resistance to harsh environments (i.e., hypoxia, oxidative stress).

2. Reprograming of somatic cells in vitro to functional insulin-producing cells.

3. Improve differentiation/maturation protocols:
   a. Elucidate mechanisms of beta cell differentiation and maturation from studying pancreas development to apply to in vitro protocols.
   b. Screen for specific transcription factors for governing beta cell maturation and target in novel protocols for complete in vitro differentiation of human stem cells into functional beta cells.
   c. Identify key missing functional proteins that correlate with imperfect function.

4. Assess impact of co-transplantation of, e.g., mesenchymal stem cells, that provide an immunomodulatory and/or regenerative milieu, thereby facilitating engraftment, function and long-term survival.
Delivery Systems
Design, create, and validate bioengineered delivery devices.

1. Identify agents, membranes, hydrogel formulations and novel biomaterials that prevent or mitigate host response to implantable material (foreign body response). Current approaches are testing the efficacy of several approaches in reducing fibrosis, providing efficient vascularization and improving graft function.
2. Validate methods for increasing oxygenation and measuring oxygen levels in vivo; bring in experts in oxygenation of tissues from outside of the beta cell replacement field.
3. Demonstrate long-term cell survival with the appropriate glucose regulation and insulin kinetics.

Clinical Path
1. Development of a complete replacement system that pair a renewable beta cell source with supportive scaffolds or protective devices.
   a. Encapsulation devices with hESC/iPSC-derived beta cell or porcine islet products that have demonstrated functional competence.
   b. Improve durability and function of encapsulated beta cell sources, including but not restricted to: adequate oxygenation, glucose-stimulated insulin delivery kinetics, long-term cell density maintenance, etc.
   c. Modification of cells and/or associated materials to optimize local immune modulation for long-term beta cell/islet survival and function without systemic immune suppression.
2. Leverage early clinical trial data to improve next generation products.
   a. Analyze data from current clinical trials aimed at validating human stem cell-derived beta cells.
   b. Establish clinical proof of concept for 3 months of detectable implanted cell function (insulin staining, stimulated c-peptide production, improved glucose tolerance).
3. Implantation site.
   a. Comparison of sites: subcutaneous, omentum, skeletal muscle, intraperitoneal.
   b. Engineer extrahepatic implantation sites to promote engraftment via scaffolds.

Standardization and Sharing
1. Implement standardization, encouraging head-to-head comparison of strategies and technologies, and facilitate sharing of data and reagents through the JDRF Encapsulation Consortium. Support innovative concepts and technologies.