Beta Cell Replacement

Vision

Deliver life-changing therapies consisting of a safe and renewable beta cell source capable of restoring glucose control and achieving long-term insulin independence without the need for chronic broad immunosuppression – a functional cure.

Mission

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 lifelong systemic immune suppression to keep the cells alive after transplantation. Importantly, islet transplantation can reverse severe hypoglycemic events and unawareness, a serious consequence of T1D in ~5-10% of those affected, as well as halt or stabilize other complications associated with T1D. Therefore, JDRF's Beta Cell Replacement program supports research and clinical trials toward development and commercialization of a cell-based product capable of restoring glucose control and achieving long-term insulin independence without the need for chronic broad immunosuppression therapy.

Rationale

44%

of islet cell transplant recipients remain insulin independent after 3 years

In the past two decades, there have been major advances in the field of islet transplantation 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 reversal of hypoglycemia unawareness after islet transplantation. 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 currently limited to patients with severe life-threatening hypoglycemia unawareness and increased incidence of hypoglycemic events. Several factors unrelated to the immune response and use of immunosuppressive drugs can contribute to long-term graft failure including poor islet quality, insufficient islet mass, poor vascularization, and hypoxia. The generation of renewable alternative beta cell sources, development of delivery systems and strategies to support and protect such cells, and optimization of implantation sites, may address the limitations that restrict the glycemic benefits of current human pancreas/islet transplantation to a small group of individuals with T1D. More importantly, 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 user effort, eliminating the excessive burden of managing T1D and decreasing the risks of many of the life-threatening complications of the disease.

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Strategy

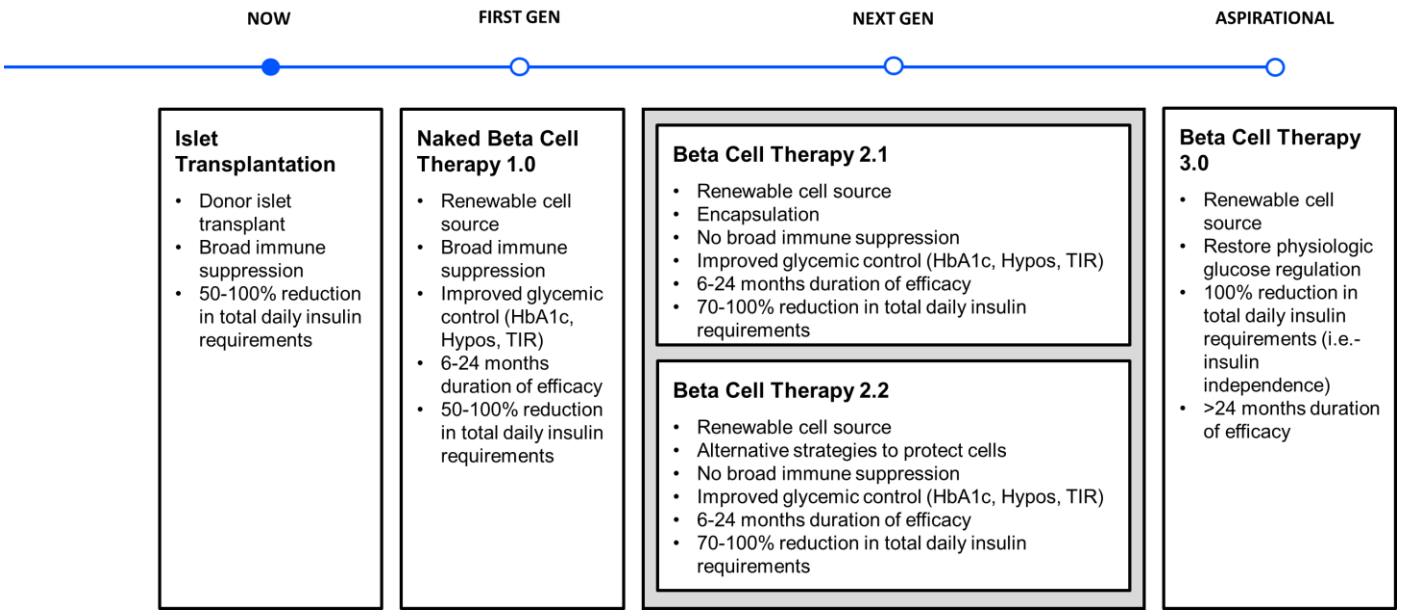
The Beta Cell Replacement program supports gap-filling research from basic discovery towards translational studies, and clinical studies to validate meaningful therapies. Today, while a commercially available beta cell replacement product is unavailable, there are a variety of promising approaches in preclinical validation and early clinical evaluation.

To support development across our pipeline, the program also supports commercial commitment and regulatory activities to define and accelerate development plans that lead to product approvals. While considering patient access and clinician adoption issues, the program helps define target product profiles and commercial products that may presently be advanced for a subset of people living with T1D, but would also benefit the development of beta cell replacement products for the broader T1D population. JDRF brings significant resources to both academic and industry partners. For companies aligned with the Beta Cell Replacement program's goals and looking to attract investment, JDRF's Industry Discovery and Development Partnerships (IDDP) program provides an opportunity to advance their discoveries and early pipeline through preclinical development and clinical validation. When considering commercial opportunities, it's important to emphasize that JDRF works the entire pipeline, providing health policy, advocacy, education and awareness for all promising T1D therapies to realize their full potential. The IDDP program has enabled several beta cell replacement companies to advance their discovery and development efforts in T1D, and importantly, JDRF is uniquely positioned to help companies advance towards commercialization, attracting significant investment in T1D as a result.

While current lines of investigation and commercialization focus on developing a product consisting of a renewable beta cell or islet source in an immune protective device, in the long run there may be alternative strategies in the design of future generation products. 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 Another potential strategy involves genetically modifying cells to (1) evade immune recognition and promote tolerance so that less or no immunosuppression would be required, and/or (2) make them resistant to metabolic stress and hypoxia to enhance engraftment and cell survival.

Roadmap

While the concept of beta cell replacement has been evaluated for decades, there are realistic near- and long-term projections as many technical challenges remain. Lessons from past studies and future advancement in stem cell biology, immunology, and biomaterial engineering may contribute to scientific advances and further improve the strategies and product prototypes required for making cell therapies a reality. It is expected that beta cell replacement products will evolve over a multi-stage development pathway. Each iterative product using cadaveric islets, stem cell--derived sources or porcine islet cells is anticipated to demonstrate the optimal risk:benefit ratio for a specific population, and deliver the potential commercial opportunities for a cell replacement therapy within this population. Evolution of these products will result in progressively improved glycemic outcomes and better immune protection over previous versions to increase function and durability, as they further reduce and eventually eliminate the burden of broad immunosuppression. As a result, the population beffiting useof these products will progressively broaden accordingly. The first generation therapeutic product will likely consist of a renewable cell dose in an open scaffold protected by standard , broad immune suppression. The development of next generation and aspirational products will focus on strategies to deliver insulin producing cells from a renewable source without broad immune suppression. While encapsulated cell therapies are a promising pathway towards providing insulin independence, alternative approaches under development include the generation of genetically modified cells that can evade immune detection and/or resist metabolic stress, as well as the use of targeted immune modulation strategies to induce graft tolerance. The research is early, and advancing multiple next generation strategies provides additional potential opportunities to succeed in the generation of a cell therapy product to restore glucose control and deliver insulin independence without the need for broad immune suppression.



Current Status

At the present time, there is no commercially available beta cell replacement product. The priority effort is supporting research and early clinical development. Recent advances in cell therapy have positioned cells derived from human embryonic stem cells (hESC) and human induced pluripotent stem cells (iPSC), as well as porcine islets as the most promising renewable alternative sources of beta cells. Advances in genome editing, biomaterial research, 3D medical printing, immunomodulation and drug delivery strategies, as well as preclinical models to assess fibrosis and allogeneic responses have allowed development of both device and device-less approaches to protect beta cells after implantation. As such, developing effective strategies for providing immune protection of these cell sources is currently a major priority. The ultimate goal is to provide clinical proof for the development of a renewable insulin-producing cell source that can accurately provide glucose control in people living withT1D.

Allogeneic Human Stem Cells (hSC) and Induced Pluripotent Stem Cells (iPSC)

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. The jury is still out 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 challenges. Current cell preparations still contain populations that are polyhormonal and not fully functional for insulin production, and it remains to be determined whether additional non-beta endocrine cells from the pancreatic islet will need to be produced to constitute a complete cell replacement 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 much higher quality control compared to 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

Pig and human insulin are almost identical in sequence (1 amino acid difference) and pig insulin was safely used to treat type 1 diabetes before recombinant DNA technology and manufacturing capabilities enabled the large-scale production of human insulin. 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 transmission of porcine endogenous retroviruses (PERVs) from the pig genome, and lastly the hyperacute rejection related to the immunogenicity of xenoantigens.

Advances in both assay development to assess potential pathogens and the ability to eradicate PERV sequences and/or xenoantigens using genome editing make xenotransplantation a promising option.

Encapsulation Technologies (Physical Barriers)

A current priority is developing effective encapsulation approaches for immune protection of cell sources to circumvent the use of systemic immunosuppression. 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 the need for 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 select nutrients in and out of the device *via* diffusion, while blocking immune cells and larger molecules such as antibodies. Cell devices under investigation differ by biomaterials, shape configuration and methods used in fabrication. Several synthetic polymers and natural materials including alginate, agarose, polysulphone and polyethylene glycol (PEG) are or have been used to encapsulate islet cells. 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). Additionally, more recent 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 shortcomings. Due to the reliance on passive transport for nutrient, glucose and insulin exchange, the distance between the graft tissue, its blood supply and the availability of a nutrient- and oxygen-rich environment poses a limitation on cell survival and proper glucose regulation. While this parameter is usually larger for macro-encapsulation devices, this approach enables retrievability of the entire graft, which may be a desirable feature for products using hESC/iPSC-derived cells. Micro-capsules pose more challenges for product developers that desire 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 “open” scaffolding technologies with the aim of developing devices that are more porous and permeable to enable better integration, resulting in improved vascularization and better exchange of oxygen and nutrients between the implanted cells and the recipient’s body. Scaffolds are sometimes referred to as “open devices” as they do not rely on 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.

Critical Gaps

Launching the First and Next Gen Therapy

To accelerate progress towards an available first generation product, we are focusing efforts on the most critical gaps.

1. Cell Source

Differences between beta cells from adult islets and beta cells derived *in vitro* from human stem cells still persist (function, kinetics, structure, access to vascularization, matrix composition and contact with other cell types). Porcine cells can induce hyperacute rejection and could result in zoonosis.

- Explore the human islet microenvironment as an approach to improve *in vitro* function of an "islet cluster":
- Reprograming of somatic cells *in vitro* into functional insulin-producing cells.
- Improve differentiation/maturation protocols (efficiency and reproducibility)
- 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.

2. Strategies to protect implanted cells

a. Delivery Device

Design, create, and validate bioengineered delivery devices.

- Identify agents, membranes, hydrogel formulations and novel biomaterials that prevent or mitigate host response to implanted material (foreign body response). Current approaches are testing the efficacy of several methods in reducing fibrosis, providing efficient vascularization and improving graft function.
- Validate methods for increasing oxygenation and measuring oxygen levels *in vivo*; bring in experts in oxygen delivery into tissues from the regenerative medicine field
- Demonstrate long-term cell survival with improved glucose control and adequate insulin kinetics.

b. Alternative Approaches for Cell Survival

Leverage advances in immuno-engineering and genome modification to identify novel approaches to deliver cells in an open scaffold or device-less approach without the requirement for chronic, systemic immune suppression.

3. Clinical Path and Commercialization

Accelerate product development. Define the pathway towards late-stage clinical trials and regulatory approval.

- Development of a complete cell replacement system consisting of a renewable beta cell source with supportive scaffolds, delivery devices or other components/strategies that protect cells after implantation.
- Leverage early clinical data to improve next-gen products.
- Establish implantation site.
- Establish industry partnerships with particular assets/expertise

4. Standardization + Sharing

Implement standardization, encouraging head-to-head comparison of strategies and technologies, and facilitate sharing of data and reagents through the JDRF Beta Cell Replacement Consortium. Support innovative concepts and technologies.

Towards the Aspirational Therapy

The first available cell therapy may not be the ultimate solution for people with type one diabetes. Development of future generation - products and ultimate aspirational therapy will require additional refinement of the renewable cell source (differentiation protocols, biologic function, and manufacturing process) as well as enhanced cell protection strategies and long-term functionality. The broader indications of these products will also require further investment in commercial infrastructure, but the aspirational therapy will represent a functional cure for people living with T1D.

Regulatory + Reimbursement Pathway

The state of the science and product development for a beta cell replacement therapy for T1D has made significant advances over the years. The maturation of the science and understanding in this area will be the ultimate driver for regulatory requirements. There is a regulatory path for development of a beta cell replacement product, however, requirements will evolve based on specific products and may vary as more knowledge and experience with this kind of therapy occurs.

A beta cell replacement product would likely be considered a combination product by the FDA (as well as some other regulatory agencies), because it involves a biologic (cells) as well as a "device" component (macro-, micro-scaffold, etc.), and will be considered a "first in class" product. Combination products are assigned to a lead review division within the FDA based on the Primary Mode of Action (PMOA) of the combination product. PMOA is defined as "the single mode of action of a combination product that provides the most important therapeutic action. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…" (21 CFR 3.2(m)).

The Office of Tissues and Advanced Therapies (OTAT) within FDA's Center for Biologics Evaluation and Research (CBER) regulates gene therapies, cellular therapies, therapeutic vaccines, xenotransplantation products and tissue products. The combination of cellular therapies with medical devices (e.g., encapsulation, scaffolds) will be reviewed by OTAT in conjunction with FDA's Center for Devices and Radiological Health (CDRH) with OTAT, in most cases, being the lead review division since the PMOA is coming from the insulin producing cells (Au, P. "Developing Stem Cell-Based Therapies: FDA Preclinical Regulatory Considerations." HSCI Translational Research Workshop. 30 March 2012). Requirements related to preclinical/clinical safety testing, product characterization and measures of potency related to both xenogenic and hESC/iPSC cell sources will be product specific since combinations of different cell sources as well as "encapsulation" devices made from various materials is likely.

In Europe, regulation of most encapsulated products would fall under the Advanced Therapy Medicinal Products (ATMPs) regulation (Regulation (EC) No 1394/2007). The ATMP Regulation and the Directive 2001/83/EC (Annex I Part IV) provide precise legal definitions for ATMPs. As a prerequisite to ATMP classification, the product under development first has to be qualified as a biological medicinal product for human use (according to the definitions in the Directive 2001/83/EC). The ATMP regulation give sponsors access to a non-mandatory, free of charge, legally non-binding procedure (called Committee for Advanced Therapies, CAT) that helps developers clarify the applicable regulatory framework and provides scientific recommendations for the classification of ATMPs. This procedure can be used in order to clarify the status of a product which may fall under different legislation (e.g. medical devices, transplants and cosmetics, etc…). FDA will provide parallel advice with EMA on ATMP products for sponsors who request such.

Therapeutic Concepts

Based on the landscape of current therapies for T1D, and what is currently known about the benefits of islet and pancreas transplantation, there are several proposed therapeutic concepts for existing and future beta cell replacement products. These profiles attempt to capture the anticipated outcomes and expected product features in the potential succession of next generation cell replacement therapies. As the cell sources, immune protection strategies, and optimization of implantation sites progress, the next generation products are expected to deliver better glycemic endpoints, longer durability, and ultimately provide a functional cure that improves outcomes and eliminates the burden of current approaches for delivering insulin.

First Gen – Naked Beta Cell Therapy

Parameter	Target
Primary Indication	▪ Reverse life-threatening hypoglycemic unawareness ▪ Restore glucose control in insulin-dependent diabetes
Target Population	▪ Adult T1D patients who suffer from hypoglycemic unawareness
Features	▪ hSC-derived beta cell source or porcine islets ▪ Minimally invasive surgery ▪ Retrievable scaffold for stem cell-based preparations preferred ▪ Duration: 6-24 months
Efficacy	▪ Primary – reduced HYPO frequency, severity, and related hospitalization ▪ HbA1c improved ▪ Improved metabolic control (decreased insulin usage or insulin independence) ▪ Improved Diabetes Quality of Life (DQoL) scores
Risk/Side Effect	▪ Side effects from chronic immunosuppression ▪ Surgical risks in diabetics and immunosuppression ▪ Risks of teratoma from stem cell based product ▪ Risks of sensitization from allo- and xeno-cells. Zoonosis from porcine cells

Next Gen – Beta Cell Therapy 1.1 (Encapsulation)

Parameter	Target
Primary Indication	▪ Reverse life-threatening hypoglycemic unawareness ▪ Optimally restore physiological glucose regulation
Target Population	▪ Poorly controlled T1D ▪ Established T1D ▪ Insulin-dependent Diabetes
Features	▪ hSC-derived beta cell source or porcine islets ▪ Minimally invasive surgery ▪ Retrievable scaffold for stem cell-based preparations preferred ▪ Duration: 6-24 months
Efficacy	▪ Primary – HbA1c improved and insulin usage decreased ▪ HYPO and Clarke scores improved ▪ Improved Diabetes Quality of Life (DQoL) scores ▪ Duration of the effectiveness on primary endpoint should be at least 1 year
Risk/Side Effect	▪ Surgical risks ▪ Risks of teratoma from stem cell based product ▪ Risks of sensitization from allo- and xeno-cells. Zoonosis from porcine cells

Next Gen – Beta Cell Therapy 1.2 (Alternative Strategies to Protect the Cells)

Parameter	Target
Primary Indication	▪ Reverse life-threatening hypoglycemic unawareness ▪ Optimally restore physiological glucose regulation
Target Population	▪ Established T1D ▪ Insulin-dependent T2D
Features	▪ hSC-derived beta cell source or porcine islets ▪ Surgery is minimally invasive. ▪ Retrievable scaffold for stem cell-based preparations preferred ▪ Genome modification/tolerance/local immune suppression ▪ Dosing regimen: 6-24 months
Efficacy	▪ Primary – HbA1c improved and insulin usage decreased ▪ HYPO and Clarke scores improved ▪ Improved Diabetes Quality of Life (DQoL) scores ▪ Duration of the effectiveness on primary endpoint should be at least 1 year
Risk/Side Effect	▪ Surgical risks ▪ Risks of teratoma formation ▪ Risks of sensitization from allo and xeno cells.

Aspirational–Beta Cell Therapy

Parameter	Target
Primary Indication	▪ To fully restore physiological glucose regulation
Target Population	▪ Established T1D ▪ Insulin-dependent T2D
Features	▪ hSC-derived beta cell source or porcine islets ▪ Surgery is minimally invasive. ▪ Retrievable scaffold for stem cell-based preparations preferred ▪ Strategy that provides full protection to insulin-producing cell source ▪ Dosing regimen: Minimum 24 months
Efficacy	▪ Primary – HbA1c improved and insulin independence ▪ HYPO and Clarke scores significantly improved ▪ Significantly improved Diabetes Quality of Life (DQoL) scores ▪ Duration of the effectiveness on primary endpoint should be at least 2 years
Risk/Side Effect	▪ Minimal Surgical risks ▪ Minimal Risks of teratoma formation for stem-cell products ▪ Minumal Risks of allo-sensitization

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