Beta Cell Regeneration

OVERALL VISION AND LONG-TERM OBJECTIVES
The JDRF Beta Cell Regeneration Program aims to alter the course of and ultimately achieve a cure for type 1 diabetes (T1D) through the development of disease-modifying therapies (small molecules and/or biologics) that promote the survival, function and regeneration of insulin-producing beta cells. These therapies will impact various stages of T1D by preventing progression in those at risk for developing T1D (Stages 1 and 2), improving control in those recently diagnosed or living with established T1D (Stage 3) and ultimately restoring insulin independence (Stage 3). As T1D pathogenesis involves multiple factors (beta cell, immune cell, genetic, environmental), a multi-pronged approach involving efforts from JDRF’s Beta Cell Regeneration, Immunotherapies and Prevention Programs will be required to ultimately prevent and cure T1D. To achieve our disease-modifying goals, we are pursuing development of two primary therapeutic classes as well strategies to better enable more efficient, cost-effective clinical development of beta cell-directed therapies for T1D.

1. Beta cell survival therapy to maintain beta cell health and function and prevent disease for those at risk of developing T1D, to preserve remaining beta cells in recent onset T1D and prolong the “honeymoon period”. These therapies may also prove to be of use in the islet transplant setting and support the goals of JDRF’s Beta Cell Replacement Program.

2. Beta cell regeneration therapy to restore beta cell function and reduce and ultimately eliminate insulin dependence in recent onset and established T1D without the need for transplantation.

3. Enable clinical development by driving innovative trial design paradigms and discovering and validating biomarkers to non-invasively detect beta cell stress, death, mass and function. These efforts may also yield a better understanding of fundamental disease mechanisms.

OVERVIEW
Beta cell survival and beta cell regeneration therapies address a critical unmet need for T1D. The only therapies currently approved for T1D address insulin replacement, blood glucose monitoring and insulin action. There are currently no therapies available that address the causes, drivers or underlying pathology of T1D. Beta cell survival and beta cell regeneration therapies, combined with appropriate immune therapies, will be necessary to alter the course of T1D to delay, prevent and ultimately cure T1D.

A top priority for JDRF’s Beta Cell Regeneration Program is a beta cell survival therapy for the prevention of loss of beta cell function for those at risk or at an early stage of T1D when significant beta cell function still remains. These therapies also have potential application to maintaining survival and health of regenerated or transplanted beta cells.

The development of a beta cell regenerating therapy is also a high priority since this will be needed to restore beta cell function and achieve insulin independence in people with established disease lacking...
significant functional beta cell mass. To protect newly formed beta cells, a combination of beta cell survival and beta cell regenerating therapies may be required.

In parallel with its therapeutic objectives, the JDRF Beta Cell Regeneration Program has also prioritized the need to enable clinical development of beta cell-directed therapies to allow for more efficient testing of these therapies. This includes efforts to test innovative clinical trial designs as well as the discovery and development of biomarkers of beta cell function and mass. Earlier detection of beta cell dysfunction and health will enable earlier diagnosis of T1D, improve disease staging and aid in the design and execution of more efficient and effective clinical studies by allowing selection of target subject groups as well as providing more specific endpoints. The JDRF Beta Cell Regeneration Program is initially focusing on: (1) the validation and development of biomarkers of early beta cell stress, death and dysfunction; (2) the discovery of markers of beta cell mass and function; and (3) the testing of novel clinical trial paradigms.

**BETA CELL SURVIVAL THERAPIES**

The goal of the beta cell survival therapy pipeline is to discover and develop a small molecule or biologic therapy to prevent disease for those at risk of developing T1D (Stage 1 and Stage 2) as well as to slow or stop the progression of recent onset T1D (Stage 3). Survival therapies are likely to be used in conjunction with beta cell regenerating therapies in the established disease setting to restore beta cell function and ultimately insulin independence. Survival therapies may also have the potential to improve transplant outcomes from islets/beta cells by extending function of islet/beta cells derived from human cadaveric, porcine, stem cells or other sources.

Beta cell therapies may represent disease-modifying therapies by directly targeting the defect or biologic dysfunction underlying T1D. Heterogeneity in beta cell mass and function as well as signs of inappropriate insulin processing have been described in both recent onset and longstanding T1D, signifying the presence of dysfunctional beta cells. In the healthy state, beta cells secrete sufficient insulin to match metabolic needs. In T1D, however, there is a progressive decline in beta cell function and mass. It is not known what triggers T1D; metabolic changes, local viral infection or other environmental factors combined with a person’s genetic or epigenetic background have all been implicated. In recent years, it has become appreciated that beta cells are not merely passive victims in the development of T1D, but that beta cell stress occurs very early in the course of T1D and likely plays a role in the loss of beta cell function and mass in T1D, conceivably triggering or potentiating the beta cell-specific autoimmune response. Beta cell survival therapies are envisioned to prevent loss of beta cell function and/or restore function of beta cells in the at-risk (Stage 1 and Stage 2) and new onset (Stage 3) stages of T1D and to preserve residual beta cell function in individuals with established T1D.

Insights into the pathways and mechanisms mediating beta cell loss in T1D are providing potential targets for discovery of beta cell survival therapies. Safety concerns are of paramount importance for T1D therapies and thus, drug discovery efforts are directed at upstream events in beta cell function (such as cytokine-induced endoplasmic reticulum stress) implicated in the pathophysiology of T1D rather than generic cell death pathways that are also involved in other biologic processes such as tumor
growth. Based on progress to date and biochemical insights into the disease process, JDRF is focusing survival therapies efforts on:

**Repositioning of Drugs from Other Indications**
JDRF-supported studies have been pivotal in demonstrating the role of the endoplasmic reticulum stress response and closely linked oxidative stress response as likely causes in the initiation and progression of T1D and have identified key regulators of the process. As a result of these efforts, a number of pathways have been identified where there are existing drugs, approved for different indications, that have beneficial effects on beta cell survival. This repositioning of drugs for T1D provides an accelerated path to the clinic for proof-of-concept testing and potential patient impact. The Beta Cell Regeneration Program will continue to prioritize preclinical and clinical testing of repositioning candidates for beta cell survival therapies and the progression of drug discovery projects towards preclinical and clinical development.

**Novel Targets**
The investigation of pathways mediating beta cell survival and health is leading to the identification of potential novel drug targets and enabling the development of novel drug screens. Similar to the stress and inflammatory pathways outlined above, future studies of beta cell survival should be focused on understanding of the pathological events and responses that drive beta cell loss in T1D.

**Dual Immune and Beta Cell Therapies**
Biologic factors, including cytokines, chemokines and other inflammatory mediators, produced by infiltrating immune cells or locally in the islet, contribute to the dysfunction and loss of the beta cell in T1D. Inhibition of the effect of these biologic factors may have a dual effect of slowing or stopping progression of T1D by dampening the immune response coupled with alleviating destructive signals, including stress pathways, triggered within the beta cell. Future efforts will focus on advancing potential therapeutic targets into drug discovery projects and towards preclinical and clinical development.

**BETA CELL REGENERATING THERAPIES**
The goal of the beta cell regenerating therapies pipeline is to discover and develop a small molecule or biologic therapy to restore beta cell function in T1D. This therapy may also have the potential to improve transplant outcomes from islets/beta cells by extending function of islets/beta cells derived from human cadaveric, porcine, stem cells or other sources. It is also likely to be used in conjunction with beta cell survival therapy to protect newly formed beta cells.

To achieve our objectives in developing regenerating therapies, the Beta Cell Regeneration Program supports two major approaches to expand functional beta cell mass as well as the development of technologies to allow the targeted and selective delivery of therapeutics to human beta cells.

**Targeted Delivery of Beta Cell Therapies**
Our efforts are focused on the discovery of beta cell selective “addresses” to enable targeting, adaptation of existing targeting technologies being developed in other fields for use in beta cell targeting and testing of candidate targeted molecules in appropriate preclinical models. Recent
advances have led to the discovery of several small, drug-like molecules that are capable of driving human beta cell replication. However, none of these molecules act on pathways that are sufficiently selective or specific for the beta cell. Achieving sufficient beta cell selectivity and an appropriate safety margin for beta cell regeneration therapies may require the use of targeted delivery approaches. Cell-selective targeted drug delivery has advanced considerably in recent years, particularly in the oncology setting, raising the possibility of adapting such technology for use in T1D.

**Beta Cell Expansion Therapies**
Current efforts are focused on identification and validation of drug targets from physiologic pathways of beta cell growth that have the potential to drive safe and regulated human beta cell expansion. Normal, functional beta cell mass is not fixed after birth, but rather increases in response to increased metabolic demand such as in the growing child and in response to obesity/insulin resistance and pregnancy in the adult. Increasing knowledge of the mechanisms regulating the physiologic expansion of beta cells is providing insight into potential pathways and targets for therapies to restore functional beta cell mass. By targeting physiologically relevant biochemical pathways to promote beta cell expansion, the potential to discover safe strategies to expand beta cell mass while preserving function.

**Reprogramming Therapies**
In individuals at late stages of T1D, where few or non-functional beta cells remain, efforts to promote beta cell survival or to promote replication of the few remaining beta cells might be ineffective or insufficient to restore measurable beta cell function. In these individuals, it will be necessary to generate new beta cells from non-beta cells. Recent studies have highlighted the plasticity of islet cell identity and suggested the potential of conversion of alpha or delta cells to beta cells. In addition, cells in the exocrine pancreas and in other organs might be induced to adopt a beta cell fate in vivo by modulating a small number of master transcription factors. Our current efforts in the area are focused on defining these mechanisms, identifying drug targets to mimic these effects therapeutically and validating their effect on human islets.

**ENABLING CLINICAL DEVELOPMENT**
As a means to enable more efficient, cost-effective clinical testing of beta cell-directed therapies, the biomarkers projects are focused on discovering, validating and developing biomarkers of beta cell function and mass. To this end, we have focused on two classes of potential biomarkers:

**Biomarkers of Beta Cell Stress, Death and Dysfunction**
Mounting evidence suggests that beta cell stress, dysfunction and loss occur at the earliest stages of T1D development. Sensitive markers of these would enable improved understanding of pathogenic mechanisms, improved staging of T1D, identification of patients likely to benefit from beta cell survival therapies and could serve as endpoints in clinical proof-of-mechanism studies. A number of candidate markers of beta cell stress and death have been proposed in recent years. Current efforts are focused on clinical validation of candidate markers and assay development.
Circulating Biomarkers and Imaging of Beta Cell Mass and Function

Non-invasive biomarkers that accurately and sensitively measure beta cell mass and function would provide the ultimate measure of T1D progression and effectiveness of disease-modifying therapies. To this end, we have pursued the discovery and validation of circulating biomarker as well as imaging approaches to measure beta cell mass. Imaging approaches have long been pursued as the ultimate direct measure of beta cell mass. However, anatomic challenges relating to the depth of the pancreas and relatively low number and wide distribution of beta cells within the pancreas as well as a lack of beta cell-selective imaging probes have stymied the field. Current efforts are focused on clinical testing of select beta cell imaging agents to determine the feasibility of beta cell imaging for T1D. Proteins or other molecules shed by beta cells have the potential to serve as circulating biomarkers of beta cell mass, and while these markers might not give as direct a reflection of the beta cell mass as imaging approaches, they do offer several potential advantages including ease of measurement and avoiding the anatomic challenges associated with imaging. Our efforts for the development of beta cell mass biomarkers are focused on discovery and validation of molecules detectable in circulation that accurately reflect beta cell mass.

Improving Clinical Trial Design

Despite the ability to rapidly advance some candidates to the clinic, current clinical testing approaches, due to patient heterogeneity, current surrogate endpoints and duration of trials, do not allow efficient mechanism-driven testing of beta cell-directed therapies.

To address this gap, JDRF has begun supporting efforts to develop novel clinical proof-of-mechanism testing paradigms, utilizing specialized patient populations, novel biomarkers and/or innovative study designs. Continuing to define and refine the clinical development path for beta cell survival and regenerative therapies will be critical for the long-term success of the program.

SHORT-TERM OBJECTIVES AND PRIORITIES

To achieve the goals outlined above, the JDRF Beta Cell Regeneration Program has prioritized the following areas for funding in FY2018–2020.

1. Repositioning of existing drugs or biologics with safety profiles acceptable for T1D to promote beta cell survival and function in clinical proof-of-concept studies.
2. Discovery of optimal drug targets, lead compounds and biologics to reduce beta cell stress and promote beta cell survival in T1D.
3. Discovery of optimal drug targets, lead compounds and biologics to safely promote human beta cell replication while maintaining beta cell health and function.
4. Discovery and validation of targets and approaches to drive formation of new human beta cells through conversion of other islet cells to become functional beta cells.
5. Development and testing of technologies to perform site-targeted delivery of therapeutics to pancreatic islet endocrine cells.
6. Discovery and validation of candidate biomarkers and imaging approaches to measure beta cell stress, death, function and mass or other processes that can provide insight into disease development and progression.

7. Development and testing of innovative strategies and processes for clinical proof-of-mechanism studies using agents to promote beta cell survival and/or regeneration.