Immunotherapies

OVERALL VISION AND LONG-TERM OBJECTIVES

Based on JDRF’s vision of a world without type 1 diabetes (T1D), the mission of the Immunotherapies Program is to deliver “disease-modifying therapies” that are intended to alter the course of disease so that pancreatic beta cells are protected from beta cell directed autoimmunity. To meet this goal from an immune standpoint, we wish to achieve the following outcomes:

1. Prevent autoimmunity/breach of immune tolerance: Prevent/reverse dysglycemia and delay or prevent the diagnosis of diabetes and insulin dependence in the at-risk population.
2. Halt or reverse existing autoimmunity/induce immune tolerance: Prolong honeymoon and delay disease progression, decrease insulin requirements, improve glycemic control and reduce hypoglycemic events after disease onset.
3. Achieve lasting immune tolerance: Restore insulin independence, remove risk of complications and ultimately cure disease.

In order to achieve these goals, the Immunotherapies Program’s efforts fall into two broad categories:

1. Immunotherapies: discover, develop and reposition effective immunotherapies for T1D.
2. Clinical path to approved immune therapies: improve, optimize and accelerate the delivery of T1D-specific immunotherapies.

OVERVIEW

T1D is an autoimmune disease characterized by immune-mediated destruction of insulin-producing beta cells that reside in pancreatic islets. This deviant activity of the immune system is associated with what is called “breach of tolerance” or an inability to recognize proteins or antigens made in certain tissues as “self”. Evidence for the autoimmune nature of T1D includes the strong association of genes of the immune system (e.g., HLA) with disease, presence of autoantibodies to proteins made in the pancreatic islet beta cell, and the presence of autoantigen-specific immune cells in the pancreas and peripheral blood. In preclinical models of T1D, transfer of immune cells from a diseased animal to a healthy animal precipitates disease.

There are currently no approved disease modifying therapies for T1D and this is a critical unmet medical need in the field. While research grade diagnostics are available to identify disease progression defined as Stage 1 (2+ autoantibodies; normoglycemia), Stage 2 (2+ antibodies; dysglycemia) or Stage 3 (overt symptoms; recent onset), there are no licensed therapies that delay, halt or reverse disease course of T1D. Of note, several other autoimmune conditions have multiple licensed immune therapies available to subjects (e.g., inflammatory arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis). Key elements that make T1D different for drug development include the existence of replacement therapy (insulin) that does have efficacy but comes with risk of side effects, significant daily burden of disease management and is unable to prevent long term complications. The difficulty in evaluating responses to immunotherapy in an expeditious fashion is another challenge in the field (e.g., in contrast to psoriasis...
where visual appearance is easily evaluated). Lastly, the complexity of T1D suggests that combination therapies targeting various aberrant components of T1D autoimmunity will likely be essential for altering the biological course of disease, in order to restore and maintain normal immune function (i.e., immune tolerance). The development and clinical assessment of diverse T1D targeted therapies is therefore a clear opportunity for stakeholders, including companies, to engage in and make a difference.

**IMMUNOTHERAPIES**

Built on years of research that has contributed to our current understanding of the immunopathogenesis of T1D, this program proposes a rational approach towards developing and evaluating immune therapies:

1. A logical first step is to therapeutically arrest the aggressive autoimmune attack on the beta cell.
2. This may be followed by delivery of a therapy that can effectively restore mechanisms of normal immune function and tolerance, such as enhancement of Treg function of numbers. Antigen-specific therapies that deliver tissue specific antigens to antigen presenting cells in a tolerogenic manner may be strong candidates for effective tolerance induction.
3. Lastly, in order to preserve tolerance long term, Teff must be prevented from re-emerging and a permissive milieu that supports Treg function should be maintained. This could be achievable with deviation therapies.

Each proposed therapeutic approach is described below.

**Treg Enhancer Therapies**

One of the Immunotherapies Program’s top priorities is to establish effective Treg enhancer therapies for T1D. This need is underscored by the limited but tangible success of antigen-based therapies in T1D, including a dearth of insightful correlation of immune mechanistic readouts with clinical outcomes. Dose, formulation or route of administration are likely key factors responsible for the outcomes from previous antigen-specific immunotherapies, but there is also general consensus that tolerance in T1D would benefit from being established in a more potent and directed manner. The key goal of the Treg enhancer therapy pipeline is to develop tolerance delivery systems (TDS) that allow targeted delivery of candidate antigens to the pancreas, pancreatic lymph node or key components of the immune system in order to increase the number and function of pancreatic beta cell-specific Tregs and induce tolerance. Significant technological advances have provided opportunities for the design and evaluation of such different delivery modalities, some with platform potential, in preclinical models or clinical settings for diseases where key autoantigens are known. Several tolerance delivery systems are already in clinical testing in other autoimmune disease indications (multiple sclerosis, Crohn’s disease). These TDS carry disease relevant antigens and other desired cargo such as anti-inflammatory substances, to actively induce tolerance. Key efforts supported in the Treg enhancer pipeline involve preclinical proof-of-concept studies with an eye to developing promising candidates for clinical testing preferably with commercial partners. These therapies should be relevant across the T1D disease spectrum, although a high safety bar will need to be met for them to be applicable earlier than Stage 3 of disease. The
attractive potential of TDS in Stages 1 and 2 of disease is that they may be sufficient as a monotherapies in this setting.

In parallel, the development or repositioning of promising therapies that enhance Tregs in an antigen non-specific manner, or target other players in tolerance (e.g., Breg, antigen presenting cells (APC)), are in priority and may be supported by this program, especially if they have compelling safety and efficacy profiles.

Teff Disabling Therapies
As explained earlier, for Treg enhancer therapies to be effective, Teff disabling therapies will be needed to effectively ablate, disable or otherwise inhibit the Teff population. This is especially relevant in Stage 3 of disease where an autoimmune attack is underway, involving T cells that recognize multiple self-proteins generated in the pancreas. Several Teff-directed therapies have been clinically tested in T1D in the past, including anti-CD3, LFA-3Ig and CTLA4Ig. While utility of these agents became compromised by issues related to toxicity, drug availability or transient effects, it is important to note that most trials had a responder population with some interesting baseline clinical characteristics (e.g., age, insulin use, duration of disease, in the case of anti-CD3) and, more interestingly, possibly baseline immune features as well (e.g., Teff “exhaustion”). These observations suggest the possibility that certain Teff pathways are active in certain people and that perhaps no singular Teff therapy can achieve the efficacy endpoints around which these trials were designed. Important to consider with this class of therapeutics is safety, as this cell subset is key in anti-viral, anti-tumor and anti-bacterial immunity. According to the Immunotherapies Program’s proposed therapeutic paradigm, it is hoped that the utility of effective Teff therapies will lie in their limited and infrequent administration, a regimen that will be sufficient to keep the autoreactive Teff at bay without compromising resistance to infections. The current status of Teff disabling therapeutic candidates is that none have a clear commercialization path for T1D. Therefore, there is a clear unmet need to either develop new therapies for T1D or reposition candidates that may be in clinical testing in other fields. This program will support compelling and selective efforts around the early development of therapies against new and known targets in the Teff population.

Deviation Therapies
Many, if not all, autoimmune diseases involve over secretion and functions of secreted immune mediators, which perpetuate the autoimmune process. It is therefore desirable to silence/neutralize factors that may enhance inflammation and auto-reactivity (i.e., “deviate” the immune system towards regulation). In the area of deviation therapies, JDRF is best positioned to leverage its partnerships with trial networks and autoimmune disease consortia for evaluating therapies repositioned from other autoimmune diseases. Because a number of therapies in this category are already approved or in late-stage clinical evaluation for other disease indications (e.g., some anti-cytokine therapies), the Immunotherapies Program has prioritized efforts in the clinical setting and aims to champion and support rigorous mechanistic analysis of trial samples to identify which deviation therapies, if any, are applicable to T1D. This program proposes that deviation therapies, analogous to Teff disabling therapies, may facilitate the induction or maintenance of tolerance by impacting the activity of soluble mediators and therefore only need be administered infrequently when used in conjunction with other therapies.
Generally, these therapies are well tolerated. Deviation therapies, as a class of readily testable immunotherapies, also present an opportunity to conduct novel trials across diseases and compare mechanistic data to gather insights into common mechanisms of autoimmunity. The Immunotherapies Program will be keen to support approaches such as these, with an emphasis of understanding mechanisms across multiple autoimmune diseases, which can directly inform the greater goal of identifying effective combination therapies for T1D.

**CLINICAL PATH TO APPROVED IMMUNE THERAPIES**

**Immuno-pathogenesis of Disease**

In recent years, natural history studies and clinical trials have increasingly suggested the existence of disease heterogeneity or distinct disease sub-types within the T1D population. For example, there is significant uncertainty around who will progress to overt T1D (Stage 3), from those in Stages 1 or 2 of disease. This introduces safety and feasibility challenges for testing therapies in these populations. Also, the rate of progression through disease varies greatly across the disease spectrum and responses to immune therapies occur in subsets of people and only for defined periods of time. A plausible explanation for these observations is that the immune-specific drivers of disease are different in different people and at different stages of the disease, thereby warranting sophisticated combinations of therapies to effectively combat them. In light of the challenges of translating learnings regarding disease processes from the NOD mouse model to humans, this program is keen to identify novel and innovative ways of gaining insights into the pathogenesis of human T1D. Such efforts are intended to better inform choice of therapies and unravel novel therapeutic targets. Common mechanisms across multiple autoimmune diseases may provide key insights and relevant projects will be prioritized.

**Biomarkers**

Biomarkers are closely linked to features of disease pathogenesis in so far as being surrogates for them. There is an important unmet need in the field both for validated immune biomarkers that track with disease (i.e., predict disease course or identify distinct subgroups of subjects) or represent immune perturbations in the face of therapeutic interventions. Both of these needs, if met, should vastly improve clinical trial design strategies and outcomes. Importantly, immune biomarkers that track with therapeutic response may be candidates for early surrogates of efficacy and greatly expedite go/no-go decision making in clinical trials. In order to meet these needs of the field, the Immunotherapies Program has prioritized the discovery and validation of immune biomarkers and the approval of assays that measure them. Also prioritized are cohort and sample needs for validation studies, bioinformatics approaches and harmonization efforts to generate and evaluate comparable data sets across prospective trials and natural history studies. Comprehensive bio-informatic approaches to query available datasets to identify and validate novel markers are now possible and should be encouraged.

In parallel, the development of metabolic markers and imaging approaches to evaluate beta cell health, mass and death may prove complementary as surrogate markers of efficacy beyond standard c-peptide preservation (a focus of the beta cell survival and regeneration program) and opportunities to combine immune biomarkers with beta cell (and other) markers for greater predictive power will be prioritized.
Combination Therapies
As explained in the pathogenesis section above, the complexity of the immune processes governing a disease such as T1D will likely require combinations of therapies to achieve maximal therapeutic benefit. For this reason, a top priority of the Immunotherapies Program is to support clinical proof-of-concept or proof-of-mechanism studies involving rational combinations of drugs and/or biologics that target different arms of the immune system as outlined in the proposed therapeutic paradigm. High in priority are opportunities where novel and innovative trial designs are tested to allow timely and informed decisions about the choice of therapies in combinations. Importantly, in this approach, combination therapies tested need not be limited to immune agents only and may include both immune and beta cell-directed therapies, when potential synergies in therapeutic effect are plausible. To increase clinical trial activity and minimize enrollment issues, the development or extension of trial networks that capture large numbers of subjects at Stages 1, 2 and 3 willing to enter into clinical trials is important, as are agreed trial designs (e.g., master protocols) and pooling of placebo data to allow timely and integrated analysis of trial data across the community. It will be paramount for this program to leverage other funders, consortia and trial network partnerships whenever possible to effectively address these issues and such partnerships are also prioritized.

Regulatory Path
Central to obtaining approval for any new or repositioned therapeutic is the effective and early engagement of regulators. Given the advancement of immunotherapies across autoimmune diseases, it is not unreasonable to predict that the first approved drug or biologic therapy for modifying the biology of T1D may be an immunotherapy. To that end, this program and the JDRF regulatory affairs team will work with the community and regulators as needed to ensure a reasonable development pathway for an immune therapy to be approved within a reasonable time frame. Not unrelated and equally timely is the need for novel and early endpoints in T1D-specific clinical trials, amongst which immunotherapy trials are in the lead. The definition of clinical relevant and patient facing outcomes that are acceptable to regulators (e.g., reduced glycemic variability, reduced hypoglycemia, quality of life markers) may facilitate early approval of new agents and increase likelihood of widespread payer engagement. The Immunotherapies Program is committed to gathering the necessary data to support defining a clear and reasonable path towards securing approvals for the first and subsequent immunotherapies in a timely fashion. Such efforts should facilitate retention and expansion of investment and commercial portfolio development in this area.

SHORT-TERM OBJECTIVES AND PRIORITIES
To achieve the goals outlined above, the JDRF Immunotherapies program has prioritized the following areas of funding in FY2018–2020.

1. Discovery, development, clinical testing and commercialization of disease-modifying immunotherapies for T1D (in conjunction with effective partnerships where applicable). These include:
   a. Establishment of tolerance delivery systems (drugs and biologics that may include autoantigens) to enhance T1D-specific Treg cells.
b. Evaluation, development and clinical testing of lead compounds and biologics to purge or disable Teff cells.

c. Clinical evaluation of novel or repositioned deviation therapies as potential partners in future combination therapies.

2. More T1D clinical research focused on development of proof-of-mechanism and proof-of-concept clinical protocols and appropriate endpoints to more rapidly evaluate candidate T1D immunotherapies.

3. Confirmation and validation of immune biomarkers and assays, including necessary resources to define T1D subgroups and evaluate responses to therapies.

4. More research to better understand of T1D immuno-pathogenesis, including study of disease mechanisms across relevant diseases (e.g., other autoimmunity, cancer), T1D heterogeneity and the differences between pediatric-onset T1D and adult-onset T1D.

5. Leverage efforts with multiple autoimmune disease communities to achieve common goals.

Other prioritized and ongoing areas of activity include:

1. Development of improved metabolic outcome assessments that are more rapidly responsive, clinically relevant and may be associated with immune measures.

2. Catalyzing more companies into the T1D immunotherapies space, bringing companies together for mutual learning and progress whenever possible and development of more T1D immunotherapies product candidates.

3. Improved education and outreach, creating better understanding of potential benefits of immunotherapy/beta cell preservation vs. insulin therapy amongst potential payers and the healthcare field.

**Note:** This program operates in close coordination with other therapeutic programs, such as JDRF’s Beta Cell Regeneration Program, which is dedicated to understanding beta cell biology during disease course and the development of related therapies. In order to achieve maximal improvement of clinical outcomes in T1D, it is quite likely that immunotherapies will be combined with beta cell-directed therapies that improve beta cell survival, function and/or regeneration. The mission of this program also closely interfaces with that of the JDRF Prevention Program, where prevention of autoimmunity with immunotherapies is directly relevant. A better understanding of immune processes governing T1D (immune-pathogenesis), is central to the Immunotherapies program’s efforts and integrated into the Prevention program’s plans. Such efforts will contribute towards understanding disease etiology and inform both disease prevention and treatment strategies.