Immunotherapies

Vision

The JDRF Immunotherapies Program aims to halt the progression of and ultimately achieve a cure for type 1 diabetes (T1D) through the development of disease-modifying therapies that induce desirable and lasting changes to the immune system that result in the protection of pancreatic beta cells from the immune onslaught of T1D.

Mission

Disease modifying immune therapies will impact various stages of T1D by preventing insulin dependence in those at risk for developing T1D (Stages 1 and 2), maintaining or increasing insulin production in those recently diagnosed or living with established T1D (Stage 3) and ultimately restoring insulin independence in these populations (Stage 3). To achieve our goals, we are pursuing two broad categories of effort - development of a number of classes of immunotherapies for T1D as well as strategies to better enable more efficient, cost-effective clinical development of immune therapies for T1D.

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, Prevention, and Replacement Programs will be required to ultimately prevent and cure T1D.

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

1. **Establishment of effective immune therapies for T1D:** to halt disease progression. Halting the loss of insulin producing cells in those recently diagnosed or living with established T1D will result in improved glucose control and reduced risk of complications. Halting disease progression in stage 1 or 2 has the potential to slow or stop progression and prevent T1D onset and insulin dependence. The rich diversity of the immune system warrants a sophisticated approach to developing T1D relevant immune therapies and this program has prioritized efforts that target distinct immune compartments. The goal of this focus area is to facilitate progress along a bench to bedside paradigm, encompassing efforts aimed toward the discovery, development and repositioning of effective immune therapies for T1D.

2. **Enabling clinical path to approved immune therapies:** to improve, optimize and accelerate the delivery of T1D-specific immunotherapies. Addressing roadblocks in the development path of immune therapies will accelerate progress and inform nuanced strategies for delivering the right therapeutic to the right subject at the right time. This program is committed to driving efforts targeted in three high priority categories: immune-pathogenesis, to allow deeper understanding of the disease; biomarkers, to facilitate trial design and readouts; and lowering obstacles in clinical development that should add efficiencies to clinical evaluation of candidate immunotherapies

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Rationale

T1D is an autoimmune disease characterized by immune-mediated loss of pancreatic beta cell mass and function ultimately resulting in a state of insulin deficiency and life-long insulin dependence. This deviant activity of the immune system is associated with an early breach of tolerance, measured by the appearance of beta cell specific autoantibodies in the circulation of those in the earliest stages of T1D (Stage 1). Ultimately, the combination of a number of factors, along with immune abnormalities (such as beta cell specific defects, environmental triggers) are responsible for the manifestation of this disease.

There are currently no approved disease modifying therapies for T1D and this is a critical unmet medical need. This is in contrast to several other autoimmune diseases where the approval and availability of multiple immune therapies have transformed treatment. There have been several immunotherapy trials in T1D with positive impacts on T1D progression (teplizumab, rituximab, abatacept)), including positive outcomes in more tangible measures such as daily insulin needs and time in range (alefacept). These partial successes suggest that greater and more lasting efficacy could be achievable with more informed strategies.

T1D has been strongly implicated as a T cell mediated disease, with defects in multiple pathways across cell types of the adaptive immune system. Alterations in B cells and APCs contribute to the T cell pathology and therapies targeting these cells types have shown benefit in T1D. In addition, some features of an auto-inflammatory process are manifest in T1D, with imbalances in secreted mediators (such as cytokines and chemokines; e.g. IL-6, CXCL10, others) that are candidate therapeutic targets. Thus, a choice of therapeutic candidates that target different pathways of the immune system will be valuable to have as treatment strategies become more personalized in the future. Insulin replacement therapy has been the standard of care for T1D for nearly 100 years, however insulin use carries significant daily risks and requires significant daily burden and is unable to fully prevent long and short term complications of T1D. The difficulty in evaluating responses to immunotherapy in an expeditious fashion is another challenge in the field as local immune activity in the pancreas cannot be measured and beta cell loss is difficult to track. In recent years, the heterogeneity within T1D has been illuminated both by immune-pathogenesis studies and from trial outcomes. There is strong reason to believe that various subtypes may exist within the umbrella of T1D. The implications of this knowledge are 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). In addition, it is highly probable that immune therapies will need to be combined with beta cell regenerative therapies for reversal of disease after a set point of beta cell loss. The approval path for combination therapies is still under development in the field, as is the path towards pediatric trials and trials in earlier stages of disease (stages 1, 2).

There is a clear need and opportunity for development and clinical assessment of T1D immune therapies. With a concerted community wide effort, this is an achievable reality, building on the deep understanding of the immunology of T1D and the successes in bringing disease modifying, life changing immune therapies to other autoimmune disease.

4+ Immunotherapy trials reporting in 2019; 4+ trials launching by 2020; increasing industry interest and industry-academia partnerships

Tactics for Success

Generate *Guidelines for Preclinical and Clinical Studies*

Engage with Regulatory Agencies

Understand the market for t1D disease modifying therapies

Establish and bolster partnerships with industry and non-profit funders

Leverage existing partnerships with consortia and trial networks and facilitate engagement with pre-clinical groups early

Bolster early scientist training program: integrate industry, clinical and data-based training

Improve T1D education and outreach on the value proposition of immunotherapies

Leverage efforts with other disease communities and funders to achieve common goals

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Strategy

Establishment of effective immune therapies for T1D

Built on years of research that has contributed to our current understanding of the immuno-pathogenesis of T1D, this program proposes a rational approach towards developing and evaluating immune therapies, that involves the three major 'types' of therapies as mentioned earlier:

1. **Autoreactivity disabling therapies** to arrest the aggressive autoimmune attack on the beta cell by pathogenic cells (Teff, other) and create a permissive space for therapies targeting other immune components. To date, the most durable effects on disease modification in clinical trials have been shown with Teff disabling therapies (anti-thymocyte globulin, anti-CD3, and anti-LFA3).

2. **Regulation enhancing therapies** that can effectively restore mechanisms of normal immune regulation and tolerance by directly or indirectly enhancing T regulatory cell (Treg) function or numbers. Antigen-specific therapies that deliver tissue specific antigens to antigen presenting cells in a tolerogenic manner may be strong candidates for selective, effective tolerance induction.

3. **Immune deviation therapies** that preserve tolerance long term, preventing re-emergence of Teff cells and/or generate a permissive milieu that supports and maintains Treg function. This has been the area of the most clinical studies of the three categories to date and two phase 2 trials are on track for reporting for outcomes in 2019 (anti-TNF, anti-IL-6R).

Enabling clinical path to approved immune therapies

In parallel with the above mentioned objectives, this program has prioritized specific efforts that will further support the clinical path of T1D immunotherapies. These include a selection of activities in our three focus areas:
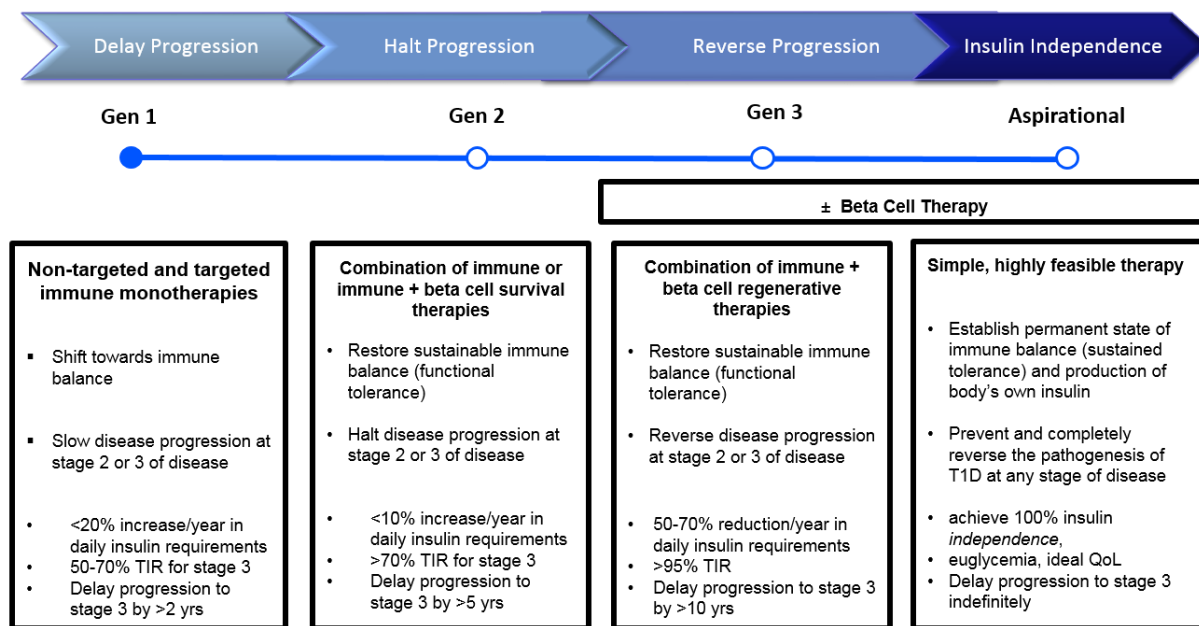
1. **Immuno-pathogenesis**: support of research to better understand the immune-pathogenesis of T1D in novel ways, leveraging knowledge from and partnerships with, other disease areas. Increased engagement with autoimmune fields and pharmaceutical partners, to better understand drug development strategies that have successfully yielded approved therapies in other indications, will be prioritized for informing T1D therapeutic development programs.

2. **Biomarkers:** This program will continue its strong commitment to immune biomarker-related efforts, and strive to further enhance its leadership role in the establishment of much needed validated immune biomarkers and fit-for-purpose assays to establish patient stratification tools and facilitate more efficient and harmonized clinical testing of candidate immune therapies in T1D.

3. **Lower obstacles for clinical testing:** A clear need for sophisticated and innovative trial designs has been illuminated by the composite of the immunotherapy trials conducted in T1D to date and by feedback from companies. There are clear hints that children may respond better than adults to certain immune therapies (and vice versa) in the stage3 setting. Moreover, the complexity of the immune processes governing a disease such as T1D will likely require combinations of therapies to achieve maximal therapeutic benefit in different subpopulations of people. Thus, a top priority of the Immunotherapies program is to champion the use of novel trial designs and mechanism guided clinical testing of rational combinations of drugs and/or biologics. 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**.**

Roadmap

This Roadmap provides a vision for achieving our goal of preventing and curing T1D through tangible, achievable steps and iterative improvements in the treatment of T1D.

As outlined below, a key feature of the progression from GEN1 to Aspirational Therapies, is a stepwise increment in the complexity of therapeutic choice, increasingly incorporating combination therapies in order to have greater and more durable impact on altering the biology of disease. In this conceptual roadmap, it is anticipated that the simplicity of the therapeutic regimen may follow a bell-shaped

curve from left to right, becoming more complex in approach before arriving the an 'un-vaccine' like format for complete disease eradication at the Aspirational stage.

Delay Progression	Halt Progression	Reverse Progression	Insulin Independence
Gen 1	**Gen 2**	**Gen 3**	**Aspirational**

± Beta Cell Therapy

Non-targeted and targeted immune monotherapies	**Combination of immune or immune + beta cell survival therapies**	**Combination of immune + beta cell regenerative therapies**	**Simple, highly feasible therapy**
▪ Shift towards immune balance ▪ Slow disease progression at stage 2 or 3 of disease • <20% increase/year in daily insulin requirements • 50-70% TIR for stage 3 • Delay progression to stage 3 by >2 yrs	• Restore sustainable immune balance (functional tolerance) • Halt disease progression at stage 2 or 3 of disease • <10% increase/year in daily insulin requirements • >70% TIR for stage 3 • Delay progression to stage 3 by >5 yrs	• Restore sustainable immune balance (functional tolerance) • Reverse disease progression at stage 2 or 3 of disease • 50-70% reduction/year in daily insulin requirements • >95% TIR • Delay progression to stage 3 by >10 yrs	• Establish permanent state of immune balance (sustained tolerance) and production of body's own insulin • Prevent and completely reverse the pathogenesis of T1D at any stage of disease • achieve 100% insulin *independence*, • euglycemia, ideal QoL • Delay progression to stage 3 indefinitely

Current Status

Successes across multiple aspects of T1D Immunology, have now brought the field to a unique place that will greatly benefit from co-ordination, integration and harmonization of efforts both in the preclinical and clinical settings. This is essential if, with increased number of candidate therapies, the field is to bring compelling and consistent data packages to industry for uptake, and to regulators for approval of trial protocols, novel endpoints, and ultimate approval of drug.

It is noteworthy that the current challenges in the field of T1D Immunotherapies come at the heels of major accomplishments in recent years. To name a few:

1. Multiple T1D trials with immunotherapies are ongoing, of which several are positioned to report in 2019.
2. Extensive and ongoing mechanistic insights from previous immunotherapy trials in stage3 disease have shown that enhancement of Tregs and exhaustion of Teff correlate with positive outcomes.
3. Children and/or those with identifiable immune characteristics (such as higher inflammation index at baseline) might be better responders in several immune targeted therapies.
4. Key outcomes such as incidence of hypoglycemia, time-in-range, and daily insulin burden can be reduced by immune therapies, sometimes with durable effects.

The current status of the field in our strategic focus areas is relayed below.

Establishment of effective immune therapies for T1D

Autoreactivity Disabling Therapies
Several Teff-directed therapies have been clinically tested in T1D and have been shown to slow the loss of beta cell function. However, response to therapy is typically heterogeneous. While the source of this heterogeneity is not clear, some baseline clinical and immune characteristics appear to predict clinical response in some trials (e.g. HLA, age, insulin use, duration of disease, Teff exhaustion state, etc.). These observations suggest the possibility that certain Teff pathways are active in certain individuals or at

certain stages of disease and that no singular autoreactivity disabling therapy may achieve the efficacy endpoints around which these trials were designed.

There remains a clear need to either develop new therapies for T1D or reposition candidates that may be in clinical testing in other fields. This may occur either via new therapeutics specifically designed for T1D (e.g., antigen-specific agents) or line extension testing of autoimmune therapeutics/products approved or in clinical development for other autoimmune disorders). Suboptimal knowledge around dose, regimen, formulation and route of administration for autoreactivity disabling and regulation enhancing targeted therapies continues to be a key challenge facing the field that requires further investment of resources and innovative strategies for answers. This challenge opens up the opportunity to learn from other autoimmune diseases where approval of such therapies has been achieved.

Regulation enhancing therapies

Several Treg enhancer therapies have been tested in T1D and have been shown to be safe, but evidence of efficacy has been modest with both polyclonal therapies and therapies that have involved whole proteins or specific peptides from pro-insulin. One may argue that not all eligible peptides have been comprehensively tested in the human setting, either because they were not known at the time (e.g. modified or hybrid epitopes) or because they were not tested in the correct combination. There is general agreement, however, that improvement in regulation enhancing therapies may be possible through improved tissue targeting and/or and with antigen specific immunotherapies.

Significant technological advances have provided opportunities for the design and evaluation of novel tolerance delivery systems (TDS) for antigen specific therapies. TDS carry disease relevant antigens and other desired cargo such as anti-inflammatory substances, to actively induce tolerance. Several early TDSs are in early clinical testing in other autoimmune disease indications and in preclinical development in T1D. The challenges in the development of these moieties is non-trivial as often there are sophisticated manufacturing considerations, in addition to identifying the best preclinical model(s) that inform the right choice of antigen(s) and 'modulators' to include as cargo to go into humans. In fact, accurate determination of dose, route and frequency of administration remains a pivotal challenge in the field of antigen specific therapies; one that will benefit tremendously from the identification of reliable and representative blood biomarkers of desired changes in the antigen specific compartments of the immune system.

If effective, TDS may be administered across the T1D disease spectrum, although a high safety bar will need to be met for stages earlier than stage 3 of disease or in pediatric populations. The attractive potential of TDS in Stages 1 and 2 of disease is that they may be sufficient as a monotherapies to have an enduring effect in these settings.

Immune Deviation Therapies

Many, if not all, autoimmune diseases involve over secretion and function of secreted immune mediators, which perpetuate the autoimmune process. It is therefore desirable to silence or neutralize factors that may enhance inflammation and auto-reactivity, i.e. "deviate" the immune system towards a tolerogenic or regulatory state. Deviation therapies have been successfully used to alter the course of multiple autoimmune diseases, including the slowing of progression and prevention of further deterioration of symptoms. These approved agents are attractive candidates for testing in T1D. Finding way to rapidly assess the treatment/therapeutic effects of such drugs in T1D would greatly facilitate evaluation of their candidacy alone or in combinations.

Enabling 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 (Stage3), from those in Stages 1 or 2 of disease. This introduces safety and feasibility challenges for testing therapies in these populations, particularly in adults. 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 at each stage. In light of the challenges of translating learnings 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 offer another timely setting in which to explore the convergence and divergence of immune networks and pathways that govern autoimmunity and manifest in those diseases or

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subsets of diseases. The emergence of unprecedented technologies, including machine learning capabilities, may allow key insights to be garnered from such projects and compelling opportunities will be prioritized, as will projects that allow recreating therapeutic strategies from the immune-oncology field.

Biomarkers

Biomarkers are closely linked to features of disease pathogenesis in that they may serve as peripheral surrogates for changes that occur in the pancreas. There is an important unmet need in the field both for validated immune biomarkers that track with disease, 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 and outcomes. The identification of immune biomarkers that track with therapeutic response may render them early surrogates of efficacy. Such biomarkers have the potential to greatly expedite go/no-go decision making in clinical trials. Recent studies have suggested the association of baseline T cell clonal diversity with therapeutic responses and Treg signatures as prognostic markers of C-peptide decline; results that await further confirmation.

JDRF will continue to take a leading role through collaborative funding mechanisms, in replicate and reproducibility testing of candidate immune biomarkers and associated assays (including composites, which may include non-immune markers) so that they may be utilized across the community in standardized ways to address biological questions and eventually be validated on a large scale. Novel approaches such as imaging of immune activity of the pancreas remain attractive in this setting and this program will track the ongoing emergence of cutting edge imaging technologies for testing in T1D.

Lowering obstacles in clinical development

With the expectation that increasing numbers of immune therapies will become available for human testing, the T1D Immunotherapy field will need to design and implement innovative and improved strategies to allow rapid and effective evaluation of therapeutic candidates that are optimized for cost, design, and power. To increase clinical trial activity and minimize enrollment issues, the development or extension of trial networks that capture large numbers of subjects willing to enter into clinical trials is important, as well as harmonized trial designs (including master protocols) and potential pooling of placebo data to allow timely and integrated analysis of data from across trials. It will be paramount for this program to leverage other funders, consortia and trial network partnerships whenever possible to effectively address these issues.

Critical Gaps

As JDRF participates in advancing the field of T1D immunotherapies, the following new and high priority gaps must be addressed to make the next generation therapies become a viable reality. These gaps, in no particular order, are:

- Lack of a systematic guidelines for preclinical studies involving candidate therapies.
- Need for pharmacodynamic biomarkers to guide dosing studies.
- Lack of novel clinical trial designs for rapid proof-of-mechanism and proof-of-concept testing.
- Lack of widely implementable guidelines for moving therapeutic candidates from the preclinical to clinical realm.
- Lack of available therapies that target different components of the T1D autoimmune system for human testing.
- Lack of a well-articulated and comprehensive Health Economics tool to communicate and influence industry to commit to T1D programs, and for payers to reimburse for such therapies.
- Underutilized PRO tools in therapeutic development and testing.
- Gap in complete knowledge of disease pathogenesis.
- Need for scale in clinical validation of existing and novel biomarkers in an expeditious fashion.
- Absence of well-defined pathways for industry to access existing trial networks and patient cohorts to conduct trials with new drugs in development.

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Launching the First Gen Therapy

1. Establishment of effective immune therapies for T1D

- **Autoreactivity disabling therapies**
  - Support late stage development of and/or early clinical trials for therapeutic candidates.
  - Find new ways to target Teff effectively.
  - Identify dosing schemes to achieve desired effect and to best position these therapies for combinations.
- **Regulation enhancing therapies**
  - 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
  - Support pre-clinical efficacy and mechanistic studies of promising candidates for successful translation into humans.
  - Develop or reposition promising therapeutic platforms in an antigen specific or non-specific manner, or target other players in tolerance (Breg, APCs).
  - **Support late stage development of and/or early clinical trials for therapeutic candidates.**

- **Immune Deviation Therapies**
  - If needed, provide support for additional data collection/analysis in studies initiated by independent groups.
  - Support the evaluation of repositioned deviation therapies in the context of combinations.
  - Influence industry to commit to and extend license of such therapies to internal T1D programs.

2. Enabling Clinical Path

- **Immuno-pathogensis of disease**
  - Identify novel and innovative ways of gaining insights into the pathogenesis of human T1D to better inform choice of therapies and unravel novel therapeutic targets.
  - Common mechanisms: Partner with funders from other disease areas, technology experts and gatekeepers of cohorts, samples and data to support innovative projects that may offer new insights for immune therapeutic strategies for T1D.

- **Biomarkers**
  In order to facilitate progress along all aspects of our portfolio, The Immunotherapies Program continues to prioritize biomarker efforts in the following areas:
  - Explore cutting edge technologies for biomarker discovery
  - Triage and validate existing immune biomarkers and assays.
  - Address cohort and sample needs for validation studies.
  - Apply novel bio-informatics and machine learning approaches to interrogate available immune biomarker data.
  The generation of a T1D Biomarker Atlas is a goal of the immunotherapies program. The purpose of this project is to generate a living document that captures ongoing biomarker related priorities and activities across all active groups and consortia in this space, including resources that house samples, data and living bio banks. It is expected that this will evolve to become a tool with which studies can be synergistic, non-duplicative and generate opportunity for validation studies between groups.

- **Lowering obstacles in clinical development**
  - Engage with academia and industry to champion harmonized collection and subsequent sharing of samples and data for independent interrogation.
  - Facilitate community discussions around platform trials early to enable comparability of future data sets amongst groups.
  - Support inclusion of parameters such as CGM and pancreatic imaging in immunotherapy trials.
  - Play a central role in the T1D therapeutic community:
    - Facilitate the harmonization of preclinical and clinical studies across groups and put into place mechanisms that connect the preclinical and clinical communities effectively and early.
    - Champion the inclusion of CGM in immunotherapy trials to explore the utility of glycemic excursions as an early indicator of beta cell health; help generate a central database for the collection and analysis of such data.
    - Explore the utility of PROs as drug development tools for T1D as part of a cross functional team.
    - Establish the Health Economics of T1D to engage industry and payers.
    - Bring industry and academia together to achieve mutual goals.

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Towards Aspirational Therapy

In order prevent insulin dependence or to achieve true and durable insulin independence, it is likely that a combination of immune plus beta cell targeted therapies will be needed. This therapy would need to be highly feasible and simple to administer.

Regulatory + Reimbursement Pathway

Regulatory

Regulatory authorities, namely the Food and Drug Administration (FDA) in the U.S., make decisions about which medical products can be made available to the public. FDA bases its decisions on an assessment of whether the benefits of the product outweigh the risks, as demonstrated in clinical trials. For a novel drug or biologic product, FDA requires a development program that culminates in at least two adequate and well-controlled phase 3 clinical trials with the expectation of hundreds to thousands of people enrolled in those trials. For the Sponsor to expand the indications of an already approved drug or biologic to a new patient population or disease, in general, FDA will also require two adequate and well-controlled phase 3 clinical trials. Some earlier stage clinical and preclinical work from the previous approval can sometimes be relied upon for approval of the new indication, but it will depend on the specific situation. For a generic drug, the same will be expected but who can do that will be dependent on the specific situation.

In general, clinical trials aiming to preserve beta-cell function should be randomized, placebo- controlled studies that investigate early pharmacodynamics markers of effect as well as the safety of the medical product. In addition, FDA will accept a measurement of C-peptide compared to control at 1 year as the primary efficacy endpoint for phase 3 clinical trials intended to preserve endogenous beta-cell function. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm. Specifics about the development program including the duration of study, number of subjects enrolled, and efficacy/safety endpoints depend on the exact product, the patient population and the indication for use being sought. FDA and EMA (EU regulatory authority) have each developed a guidance document to provide their current thinking on the development of diabetes therapies and each document provides guidance related to products for preservation of beta-cell function in patients with T1D. As specific products are being researched and pursued, JDRF explores the possible development pathway with the developer to identify challenges for that specific product as needed. JDRF is also involved in and a founding member for an important effort that will have an impact on the regulatory use of islet autoantibodies as a risk marker in T1D disease progression. JDRF is also working with the immunotherapies community on an effort to further facilitate the enrollment of pediatric subjects in T1D studies.

Reimbursement

Before any new therapy can be regularly covered by public or commercial payers, certain standard steps must be taken. A code identifying the product or service must be obtained, either from the American Medical Association, or from the Centers for Medicare & Medicaid Services (CMS). In the case of a product that is approved by the FDA as a biologic, which immunotherapies are highly likely to be, the code would be obtained from CMS. In addition to an identifying code, diagnostic codes that describe the condition being treated by the product or service must also be in place. If the product is a biologic, the manufacturer sets their price and then engages in price reporting to CMS to regularly report the various discounts, rebates or fees they contract to make in association with that product. These data are used to determine reimbursement and are largely in control of the manufacturer. If the product is considered a hospital service or physician service, CMS will go through a complex process to establish a reimbursement rate and most, if not all, private payers will use the Medicare allowed amounts as the basis for their own reimbursement.

Things to consider when approaching a payer to request coverage would include the efficacy of the product in terms of its ability to modify the target disease, the cost of the present standard of care for the disease and how the new product or service may change that picture, the safety profile of the new product or service, and the size of the population that will potentially be treated using the new product or service.

Payers will give most credence to peer reviewed literature from an independent source. They will generally want to see randomized controlled trials as opposed to observational studies and of course multiple studies, studies with larger numbers of participants, and those that include a range of participants, such as children or older adults will be helpful.

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Patient preference is not necessarily something that insurers find exceptionally compelling. For example, they may not respond to products whose chief virtue is convenience, comfort or appearance as opposed to an impact on clinical aspects of the target condition. Thus, if patient preference data is presented to payers, it should have a tie to measurable changes in the kinds of things that plans care about.

It may appear that plans wouldn't care, for example, about a product that aids in sleep. However, if an economic case can be made that improvements in sleep lead to lower absenteeism from work, or fewer comorbidities, which lowers costs to employers customers or to the plan itself, a stronger case can be made for coverage and adequate reimbursement. Non-direct but real economic ties to characteristics of a product that impact patient preference could be very helpful in motivating plans to extend coverage.

JDRF could foster the creation of a patient preference hierarchy, noting which sorts of patient centered factors attract the most attention and approbation by the T1D community. New immunotherapy products could be evaluated in light of such factors and plans could then be informed about the correlation between the performance of the new product and JDRF's measurement of applicable patient preferences.

Therapeutic Concepts

The availability and ongoing clinical testing of repurposed therapies, represent a set of candidate therapies (GEN1) that have shown efficacy in either disabling, enhancing, or deviating relevant arms of the immune system in other autoimmune disease settings. These products therefore present a faster path to GEN1 therapy testing in T1D, especially with the backing of large amounts of safety data. GEN1 therapies are monotherapies and may also include non-targeted and targeted therapies that are currently in development. As targeted immunotherapies become available and demonstrate superiority, novel and more efficacious therapies may replace repurposed systemic agents. This remains to be clinically proven, although multiple clinical trials are projected to launch soon using Tolerance Delivery Systems (TDS), while others are in various stages of clinical development.

GEN2 and 3 therapies reflect anticipated levels of increasing complexity in treatment plans, as features of precision medicine come to the fore. It is envisaged that once efficacy is shown, the therapeutic concepts of effective combination therapies will continue to improve in order to meet greater demands of feasibility.

Central to defining therapeutic concepts of immunotherapies for T1D, is the risk/benefit ratio of candidate immunotherapies. This complex ratio will directly draw from the ratio of *burden-of-disease/burden-of-therapy (including risk)*. Patient reported outcome (PRO) studies in the context of T1D immune therapy development may be helpful in better understanding this ratio as drug candidates move into the commercial space. Exploration of PRO measures as drug development tools has been used successfully in other disease indications.

Scientifically, it is this program's ultimate expectation that the therapeutic concept of an effective and complete disease modifying therapy will include a composite of therapies (co-formulated, co-administered, or in simple sequential combination) that will induce and maintain durable "immune tolerance" to facilitate beta cell health and regeneration in a least disruptive, well tolerated manner.

All therapeutic concepts are projected, present JDRF's opinion on ***minimally acceptable criteria*** for each property, may be non-linear in progression, and will ultimately be guided by how effectively human biology responds to any intervention.

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First Gen – Product 1.0

Properties	Non-targeted or targeted mono therapies
Primary Product Indication	Slow disease progression from stage 2 to stage 3 and from stage 3 onwards. Increase time to insulin dependence, *Reduce the rate* of C-peptide decline.
Target Population	Stage 2 and stage 3 adults and pediatrics
Features	Single agent
Efficacy	Reduce rate of progression to stage3 or rate of increase in insulin needs with defined durability, improve Quality of Life
Risk/Side Effect	No increased risk of mortality compared to standard of care, no increased risk of accelerated disease. Manageable short-term morbidity (e.g., in-patient administration acceptable) or mechanistically related increased infection risk is acceptable.
Therapeutic modality	Biologics, cell therapy, small molecules

Next Gen – Product 2.0

Properties	GEN 2: Combination of immune therapies
Primary Product Indication	Stop disease progression from time of therapy. *Stop* C-peptide decline in stage3. Stop progression to insulin dependence from stage2.
Patient Population	Stage 3 then stage 2 adults with step-down development into pediatrics
Features	Multiple agent
Efficacy	Prevent increase in insulin needs and with greater durability than monotherapies; maintain stage2 of disease indefinitely, improve QoL>Gen1
Risk/Side Effect	No significant short-term morbidity and minimal risk of increased infection.
Therapeutic modality	Drug, biologic, or cell therapy

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Next Gen – Product 3.0

Properties	GEN 3: Combination of immune and beta cell therapies
Primary Product Indication	Reverse disease progression to and from stage 3. Increase C-peptide levels with sustained therapy.
Patient Population	Stage 3 then stage 2 adults with step-down development into pediatrics
Features	Multiple agent
Efficacy	Lower insulin needs in stage 3 with durability greater than or equal to Gen2, reverse stage 2 to stage1 or earlier, improve QoL >Gen2
Risk/Side Effect	No short-term morbidity and minimal risk of increased infection
Therapeutic modality	Drug, biologic, or cell therapy

Aspirational – Product 4.0

Properties	ASPIRATIONAL
Primary Product Indication	Subjects at all stages of disease: - Completely prevent or reverse the autoimmune disease process; restore endogenous insulin secretory capabilities - Remove insulin dependence and prevent progression to insulin dependency
Patient Population	All stages of disease
Features	Simple, least invasive, highly feasible therapy
Efficacy	Achieve/maintain complete insulin independence, maintain euglycemia, ideal QoL
Risk/Side Effect	Negligible
Therapeutic modality	Drug or biologic

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For more information:
Please contact the program lead, Simi Ahmed, Ph.D.
sahmed@jdrf.org; Tel: (212) 479-7679