Cures

Vision

Cures therapies available to all affected by or at risk of type one diabetes (T1D).

Mission

Accelerate the development of therapies to prevent, slow, halt or reverse disease progression and provide insulin independence to all those at risk or affected by T1D.

Background and Overview

Type 1 diabetes is a chronic autoimmune disease that progresses through distinct stages. The ability to stage the progression of the disease, from the initial presence of beta cell autoimmunity with no signs of dysglycemia, to the occurrence of diabetic complications due to a long-standing symptomatic disease, provides the opportunity to develop diagnostic tools and multiple strategies for therapeutic interventions. Autoantibodies to beta cell antigens, proteins produced by the immune system in response to a person's own beta cells, can develop before any clinical symptoms of T1D. Individuals in stages one and two of disease progression have two or more autoantibodies and can have normal or slightly altered blood sugar levels. The therapeutic interventions at these stages are intentioned to delay or prevent the onset of disease symptoms once the autoimmunity has developed. Individuals at stage three of the disease have progressed to symptomatic disease and require variable levels of insulin therapy. Therapeutic approaches at this stage are directed at preserving beta cell function and restoring glycemic control. Individuals beyond stage three (long-standing T1D) show overt hyperglycemia, must closely monitor their blood glucose levels and rely on exogenous insulin to regulate changes in blood glucose levels. While new therapies and therapeutic concepts for cures that halt autoimmunity and restore beta-cells in stages one to three are being developed, replacing beta-cell function via cell therapy in the long-standing T1D stage remains the only approach with a clinical proof of concept that demonstrates full glucose control and insulin independence can be achieved.

Goals

The overall goal for the Cures Program is to deliver disease-modifying therapies (DMT) and cell replacement therapies that lead to prevention of disease onset at any age, restoration of pre-diabetes physiology in people that are insulin dependent or providing sustainable and safe insulin independence. The research strategy will prioritize projects with the highest likelihood of accelerating the delivery of therapies to cure and prevent T1D by supporting strategic gap-filling funding in research and resources in the following projects:

- **T1D screening:** Develop and execute a global universal screening strategy that reduces diabetes ketoacidosis (DKA) at diagnosis, identifies high-risk individuals for early detection and evaluation of disease-modifying therapies, and simultaneously develop data and analyses necessary for healthcare system adoption.

- **Disease modification:** Accelerate the development of disease modifying therapies that delay, stop or reverse the development and progression of T1D, and enable pivotal clinical testing of these therapies.
- **Insulin independence:** Accelerate the development of first-generation beta cell replacement products demonstrating at least six months of reduction in insulin requirements while continuing to support research that enables the development of safe, more efficacious, and longer-lasting cell therapies

Understanding the pathogenesis of T1D will contribute to future attempts to prevent and reverse the course of the disease. While new therapies and therapeutic concepts for cures strategies that halt autoimmunity and restore beta-cells in stages one to three, replacing beta-cell function via cell therapy remains the only approach with a clinical proof of concept that demonstrates insulin independence can be achieved in long-standing T1D. Accelerating life-changing breakthroughs and interventions mean prioritizing the opportunities with the greatest potential to lead us to cures, but also identifying the gaps and barriers that prevent advancing through the different phases of the roadmaps. The research strategies outlined in the Cures Program Research Strategy document will provide a rationale for each of the three roadmaps designed towards a path to a successful therapeutic development that covers all stages and ages of T1D. The table below provides an overview of the three roadmaps across the T1D stages.

		Stage One	Stage Two	Stage Three	Established
Multiple AAb	**-**	**+**	**+**	**+**	**+**
C-peptide	**+**	**+**	**+**	**+/-**	**-**
Glycemia	**Normoglycemia**	**Normoglycemia**	**Glucose intolerance**	**Insulin-Dependence**	**Insulin-Dependence**
Screening					
Disease Modifying Therapies					
Cell Therapies					

Screening

Vision

A world where type 1 diabetes (T1D) risk is detected years before insulin dependence, where T1D screening has been adopted by healthcare systems, and where a robust selection of preventive therapies is available to those at risk.

Mission

The mission of the screening project is to establish T1D risk assessment as a standard preventive service worldwide.

Rationale

According to data reported by the Search for Diabetes in Youth Study (SEARCH) from 2002 to 2015, the incidence of T1D has risen in all age, sex, and ethnicities with few exceptions. From the period between 2001 and 2014, the rates of T1D diagnosis in the pediatric age group in the context of the life-threatening complication diabetic ketoacidosis (DKA) increased from 22 percent to 30 percent. Similar trends have been reported in geographies outside the United States with incidence ranges of 15 percent to 80 percent. DKA at diagnosis strongly correlates with long term negative health outcomes. Despite the increase in the incidence and prevalence of T1D and rates of DKA at diagnosis, approved therapies to delay, halt, or cure T1D are not yet available. Pharmaceutical developers indicate the lack of availability of at-risk individuals for clinical drug development programs as a major hurdle slowing the path to approval of new therapies for T1D.

The U.S. Food and Drug Administration (FDA) is currently evaluating the safety and efficacy of the first preventive therapy towards approval for T1D – Tepluzimab (Provention Bio). There is a pipeline of therapeutic candidates being evaluated for effectiveness as preventive therapies, but we anticipate that current screening programs are insufficient to provide a platform for accelerated evaluation of these therapies – hence a larger population-based screening approach is urgently required.

To date, T1D screening programs have largely been restricted to first degree relatives (FDR) of people with T1D and are entirely restricted to the clinical research setting. It is estimated that this strategy only captures approximately 10-15 percent of the total at-risk population. These programs have focused almost entirely on pediatrics and adolescents, missing adults who are often misdiagnosed with type 2 diabetes (T2D) and who represent 50 percent of new T1D diagnoses. More recent but smaller, targeted studies have expanded to the general population with geographic and age restrictions. These FDR and pilot community screening programs have unequivocally demonstrated that they can reduce the incidence of DKA at diagnosis to less than five percent in children and adolescents. However, this still leaves a large segment of the population undiagnosed and unable to participate in and accelerate clinical research toward developing new curative therapies, unable to access curative interventions when they become available, and at risk for DKA at diagnosis.

In addition, better understanding of the prevalence and etiology of adult T1D diagnoses are needed as the body of literature describing the pathogenesis of T1D is largely based on findings from the pediatric populations. Findings based on pediatric data may not accurately inform on the risk and rates of disease progression or appropriate therapeutic intervention for adults. JDRF and others have begun efforts to better characterize this adult onset T1D population by including non-FDR adults in new screening programs and identifying the prevalence of T2D/T1D misdiagnoses.

Familial and pilot general population screening research initiatives have demonstrated to be feasible to deploy, efficient in mitigating the health and psychological impacts of T1D diagnoses and have been an integral part of successful drug development activities in this space. However, their reach is limited, and they are not currently adopted at the state or national level in any country nor are they consistently reimbursed. They are not efficient enough to accelerate T1D drug development activities nor identify all the individuals who will benefit from potential therapies. As such, this project area will prioritize improving upon and expanding general population screening programs globally, and the development of data packages to accelerate the development of new curative therapies and facilitate future adoption by health care providers, payers, and governments.

Strategy

Expansion of Screening for T1D Risk

Our near-term goal is to make T1D screening available to the general population. This will increase the number of people identified who could benefit from near- and long-term risks of diagnosis at DKA, participate in clinical research and benefit most from preventive therapies once approved. Near-term efforts will focus on generating data on the benefits of screening and monitoring in improving health outcomes while determining the optimal nature, timing and cadence of screening to most efficiently identify those at risk in the general population. The long-term goal is for T1D screening to be fully integrated into healthcare systems across the globe. The expansion of ongoing general population screening studies to larger geographies will generate important data to allow for future country-wide adoption of such programs.

Development of New Risk Assessment Tools

Currently, T1D risk screening is based on the presence or absence of islet autoantibodies (AAb). The presence of two or more AAb can predict, with high certainty, the progression to clinical diabetes. The assays for these autoantibodies have only recently been adapted for in-home use, but in the past have required a venous blood draw in a hospital or doctor's office. Recent work has prioritized the validation of next-generation AAb assays to replace classic radio-binding assays which are not compatible with modern drug development programs because of the use of radioactivity, large blood volumes required, being labor- and cost-intensive, and technically challenging. JDRF funded research has led to the availability of new multiplex-assay formats that are more amenable to current drug development programs by prioritizing sensitivity, reduced sample volume, disease specificity, and cost-effectiveness. Our near-term goals will be to drive the more advanced assays towards commercialization as point of care systems to create a competitive landscape that will drive cost down and foster innovation. In addition, we will continue to work with stakeholders to define the guidelines for AAb assay development (specificity, sensitivity, benchmarks).

While AAb detection can determine a person's T1D status, it does not inform well on the rate of progression to clinical disease. Additional biomarkers are needed to generate more precise predictions. In accordance with T1D being a highly genetically influenced disease, the measurement of certain genetic markers has been shown to improve the estimation of rates of progression. Variations in the HLA (human leukocyte antigen)

class II region have been found to strongly correlate with rates of progression to clinical T1D, but genetic risk has been found to stem from the contributions of upwards of 40 different genes. Currently, a handful of genetic risk scores exist for T1D, which focus on subsets of genes with the largest influence on risk, with varying levels of clinical validation and early data showing their benefit in defining risks and rates of progression when combined with AAb measurement. Other biomarkers, such as circulating C-peptide or degree of glucose intolerance, can also be used to improve estimations of rates and risks of progression. Our near-term goals will be to support further validation of these different scores and advancement of their specific assay platforms toward commercialization so that in the future they can be combined with AAb testing in the point of care setting.

Data to Enable Healthcare System Adoption

Type 1 diabetes risk screening is not yet fully integrated into healthcare systems, despite the known benefits of reducing DKA at diagnosis in the population. Data will be needed specifically for healthcare decision-makers to demonstrate the benefits and value of screening to a health system. One type of analysis will likely be cost-effectiveness studies. Recent analyses calculating the cost-benefit ratio of reducing DKA at diagnosis by general population screening initiatives have shown that the cost of testing is an important driver. As mentioned above, JDRF and others are working to drive the assay costs down to address this hurdle. Our near-term goals are to generate data and analyses, such as new cost-effectiveness data from ongoing and future general population screening efforts, to support adoption by health care providers and payers. These data will provide us with important value inflection points for cost of assay and economic benefit to guide our future screening efforts.

Deprioritized

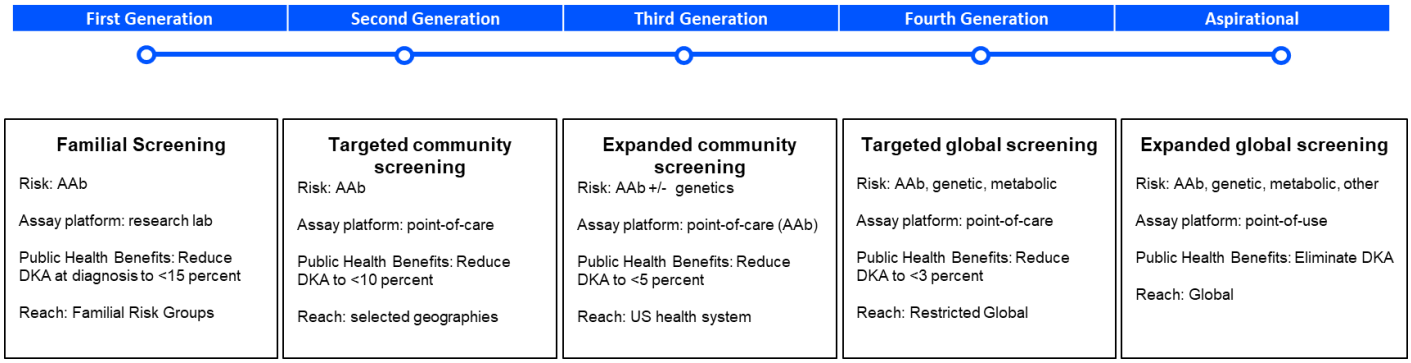
Pathogenesis: Significant progress has been made in elucidating some of the major driving factors in T1D pathogenesis allowing us to therapeutically intercept the disease: the major immune cell type contributing to disease progression, the prevalence and timing of beta cell dysfunction and key biological gatekeepers of this process, and the importance of the type 1 interferon cascade in disease initiation and progression. Many of these pivotal findings stem from the network for Pancreatic Organ Donors (nPOD), established by JDRF in 2007 to specifically drive research on human organ samples, and we will continue to support this program. Currently, deep phenotyping of the T1D diseased pancreas is being supported by the NIH and other funding organizations and is very likely to reveal new insights into the pathogenesis of the disease. While additional understanding of disease pathogenesis can support improved diagnosis and prognosis, the screening portfolio will temporarily deprioritize this area as we focus on applying recent findings in this space in the clinical setting.

Environmental Triggers: Many environmental factors have been implicated in the etiology and pathogenesis of T1D. JDRF has focused on changes in the microbiome and viral infections as two potentially important contributors. A greater understanding of the complex interactions between the intestinal microbiota or viruses associated with risk and several interacting systems in the body is needed before interventions based on these potential triggers can be developed. These will be deprioritized until more specific understanding allows for a broadly applicable therapeutic approach.

Biomarkers: Staging of T1D is dependent on well-established assays that measure the presence of AAb and dysglycemia as measured by C-peptide secretion in response to a meal or glucose challenge. Multiple researchers are currently studying ways to improve staging T1D by adding more extensive immune analyses or metabolic profiling using glucose monitoring systems. JDRF has prioritized the use of CGM devices for

glucose metrics to provide a real-time assessment of disease progression as estimated by progressive loss of glucose control through loss of functional beta cells. Similarly, genetic testing has been used to improve the determination of rates and risks of progression when added to classic AAb testing. Other additional biomarkers, such as neoepitopes or lipid profiles, have not yet revealed their ability to increase our ability to stage T1D or better predict rates and risks of progression. Other organizations continue to pursue the early discovery and validation efforts on these and other biomarker fronts. JDRF will deprioritize these early biomarker research activities to focus utilizing more highly validated novel biomarkers (like proinsulin) in future clinical efforts.

Roadmap



Current Status

General Population Screening Initiatives

Recent community screening initiatives (ASK, FR1DA, TEDDY) have demonstrated both feasibility and the ability to almost eliminate DKA at diagnosis, and potentially provide a major long-term health benefit to those screened. These pilot initiatives are providing important data on the barriers preventing wide scale adoption of general population screening such as the need for health care provider education, appropriate risk monitoring protocols including psychological support, lack of penetrance into socioeconomically disadvantaged geographies, and screening in the era of telemedicine. Findings from these and other such initiatives are crucial to inform the development of large-scale initiatives globally. For example, a newly launched JDRF-led community screening initiative, T1Detect, will adopt many of these findings with the goal of providing access to T1D risk assessment to the general population in the US and beyond. T1Detect is a universal screening, education and awareness program that, regardless of family history of disease, will allow anyone to get tested for autoantibody (AAb) and connect them with clinical trials and subsequent health care support for those identified to be at risk. JDRF research funding has aided the development of AAb assays, awareness and education programs, and post-screening monitoring protocols that will be incorporated into the real-world evidence setting of T1Detect. Additional research studies will be used to validate improvements that can be deployed by T1Detect in the future. This initiative will continue to be supported with strategic input from Research. In addition to providing access to screening, this effort will include important aspects of patient and health care provider education to reduce some of the barriers to screening adoption. This initiative will provide real world evidence of general population screening in the U.S. and provide a key platform for testing of new

assay types, generation of cost-effectiveness data, development of screening strategies, and acceleration of clinical research.

Improving on Existing Risk Assessment Tools

Important improvements in T1D risk assessment have been achieved in the last year. Genetic risk scores have been shown to dramatically improve the estimation of rates and risk of progression to clinical T1D. Work from The Environmental Determinants of Diabetes in the Young (TEDDY) Study Group has shown that using a combined risk score, including genetic, immunological, and clinical features, can double the estimated efficiency of population-based newborn screening. Comparable results were seen by the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) investigators who saw that birthweight and parental T1D status were important clinical features that could improve the efficiency of risk assessment. It will be of the utmost importance to evaluate the relative benefits of inclusion of each of these features on sensitivity and specificity of risk assessment protocols with an eye towards improved prognosis and cost-effectiveness.

Another important and related improvement in T1D risk assessment stems from the utilization of machine learning tools to identify novel features that could positively impact the specificity and sensitivity of screening protocols. Recent JDRF supported studies focused on T1D disease modeling have used machine learning tools to reproduce and corroborate findings on the timing of autoantibody occurrence and contribution of birthweight or parental T1D status on T1D risk, as mentioned above, and is identifying novel features, such as antibody titer and growth rates, that can improve on current antibody-based risk assessment protocols. Future studies will be performed to validate these in the clinical setting.

Lastly, significant progress has been made in the deployment of standardized survey tools to qualify and quantify the psychological impact of learning T1D risk status. The TEDDY study for example, used the State Anxiety Inventory (SAI) to quantify parent anxiety. As expected, parents experienced increased anxiety when faced with a positive AAb result. This and other similar studies reinforce the need to use standardized survey tools to quantify the psychological impact of screening and to assess the success of future mitigation strategies.

JDRF has prioritized research that has led to the availability of novel testing platforms that are high throughput, low cost, and amenable to at-home testing using minimal blood volumes. However, there yet remains a dearth of commercially available AAb testing systems that achieve the requirements for specificity, sensitivity, low sample volume, and cost effectiveness for current drug development programs. To address this gap, JDRF and the Critical Path Institute (C-PATH) served as founding partners in the creation of the Islet AAb Assay Collaborative whose goal is to convene experts and define the requirements for the next generation assays to replace radio-binding assays for the AAbs. The Islet AAb Assay Collaborative continues to identify the gaps preventing productization of the current assay platforms and the expert opinion of this group is used to inform JDRF priorities in this area.

Health Economic Assessments

Screening for T1D risk, using autoantibodies or other measures such as genetics, is not widely available outside of research programs. It is not routinely prescribed by health care providers, robustly covered by payers, and is not included in any government sponsored health program. In order to ensure equal access to testing for all patients, the costs associated with these tests should be reimbursed by their respective national healthcare systems. Understanding the economic implications of T1D risk screening is critical to advance screening for T1D into routine healthcare Therefore, a goal of this project area is to collaborate with the JDRF

Health Policy team to identify and generate the data requisite for future healthcare changes. Importantly, JDRF supported health economic assessments have been performed on ongoing pilot screening programs in certain geographies and have begun to generate data to bolster the case for coverage of general population screening even in the absence of an approved therapy. These economic assessments will continue to be generated and refined by forthcoming screening initiatives.

Goals and Barriers

Goal: Expand general population screening initiatives and move towards adoption by health care systems.

- Clinical development of therapies in the at-risk population is slowed by reduced access to appropriate numbers of participants of all ages in trials.
- Robust cost-effectiveness data for screening is not yet available to support future inclusion into preventive care guidelines and healthcare systems.
- Screening for T1D may create a psychological burden on the person and their family. Standardized mitigation strategies to assess and address these burdens remain underdeveloped and underutilized.
- The efficiency of diagnosis is currently limited to AAb and needs refinement with other markers that are material to staging diabetes progression

Policy and Reimbursement Considerations

There are a few paths to coverage for T1D risk screening by insurers in the U.S. In the short-term, and before robust clinical recommendations are established, payers may consider coverage for screening. Private health insurers, who insure most Americans, generally focus on health outcomes in a timeframe of five to seven years. However, interventions that improve longer-term health outcomes of children are often covered with less stringent coverage policies. Since screening should lead to both long-term and short-term health outcome improvements, coverage could become standard, especially if costs related to screening are well below the potential costs of complications. To show that costs are less than the potential savings, the screening protocol will need to show how the intervention works to improve health outcomes. Showing a significant reduction in DKA at diagnosis will be important for payer coverage. Longer term improvements to HbA1c or complication risk will be important, but likely less so than DKA risk mitigation. Acceptance as standard of medical care will also improve coverage policies but are not a guarantee to coverage.

In the medium to long term, there are two important pathways to wide-spread coverage of screening and integration into the healthcare system. The first is through the American Academy of Pediatrics (AAP). Through their Bright Futures guidelines, AAP makes detailed recommendations for pediatric preventive care. A committee of experts reviews and recommends changes to these guidelines every few years, with small changes implemented as required. Most insures offer no cost coverage for preventive care recommended by these guidelines. Additionally, many states require their Medicaid program to pay for this care as well which is important because nationally, 40 percent of children under 18 are covered by Medicaid, while in a handful of states, more than 50 percent of children are covered by Medicaid. The second pathway is through a recommendation by the United States Preventive Services Task Force (USPSTF). Under federal law, most insurers must cover at no cost any service recommended with an A or B grade by the USPSTF. They weigh costs and benefits for preventive services across all life stages and give a ranking based on effectiveness, potential health costs and benefits. However, the process is lengthy, taking years to go from draft research plan to final recommendation.

Disease Modifying Therapies

Vision

A world where type 1 diabetes (T1D) is prevented in people at-risk and cured in people already affected by T1D.

Mission

The mission of DMT project is to accelerate the development of therapeutic products that can slow, halt, or reverse the course of T1D at any age or stage of disease.

Rationale

Type 1 diabetes is an autoimmune disease characterized by immune-mediated loss of pancreatic beta cell number, mass, and function, ultimately resulting in a state of insulin deficiency and life-long insulin dependence. This deviant activity is associated with an early breach of immune tolerance, measured by the appearance of beta cell specific autoantibodies in the circulation of those in the earliest stages of T1D (stage one). A strong association with genetic factors (such as HLA, and other immune related genetic variants) has been shown to exist in T1D, in addition, the combination of a number of factors, including non-immune abnormalities (such as beta cell inherent defects, environmental triggers) induce a state of stress in the beta cell that result in loss of beta cell function and cell death, all of which lead to insulin deficiency and a life-long dependence on insulin replacement therapy. It should be noted that beta cells are not merely passive targets of the T1D immune system; beta cell stress occurs very early in the course of T1D and plays a role in the loss of beta cell function and mass, conceivably by triggering or potentiating the beta cell-specific autoimmune response for this disease.

Type 1 diabetes 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 antigen presenting cells (APCs) contribute to the T cell pathology and therapies targeting these cells types have shown benefits in T1D. In addition, some features of an auto-inflammatory process are manifest in this disease, with observed imbalances in secreted mediators (cytokines and chemokines; e.g. IL-6, TNF, CXCL10, others), rendering such molecules as candidate therapeutic targets. Thus, a choice of therapeutic candidates that target different pathways of the T1D immune system will be needed for effective modification of this disease.

Aside from a deviant immune system, dysfunctional beta cells are found in many people with T1D. Inappropriate hormone processing, cellular senescence, and other indicators of diminished beta cell function have all been recently described to occur in the T1D prodrome. Strategies to improve beta cell function will need to be incorporated into approaches tailored towards increasing beta cell mass. Functional and dysfunctional beta cells can be detected prior to clinical diagnosis and for decades after the initial T1D diagnosis, indicating a need for therapies directed at increasing residual mass and function at all stages of

disease. Multiple lines of evidence have revealed means to preserve and increase beta cell mass- either through proliferation, differentiation from another cell type, or new growth.

Beta cell regenerative therapies provide a curative option for people living with T1D with therapies that increase the number and function of beta cells. Regenerative therapies would allow stage three individuals to achieve improved glucose control and eventually insulin independence. They could also replenish beta cell mass and/or improve residual cell function even in stage two or stage one T1D individuals preventing onset of insulin dependence.

In contrast to several other autoimmune disease areas where the approval and availability of multiple therapies have transformed treatment options and quality of life, there are currently no approved disease modifying therapies for T1D and this is a critical unmet medical need. There have been several DMT trials in T1D with positive impacts on progression (teplizumab, rituximab, abatacept, golimumab, verapamil, gleevec), including positive changes in clinically relevant measures such as daily insulin needs, C-peptide preservation and time in range (alefacept, IL-21+Liraglutide). In addition, early clinical testing for safety and mechanistic insights of therapeutic candidates for T1D have been reported in 2020 (AG-19 Lactococcus, DF-IL-2-child, DiagNode GAD-Alum).

These various findings and successes suggest that greater and more lasting efficacy could be achieved with more informed strategies either for the development of superior therapies than those that have been tested, or with improved generations of available therapies, such as with tissue or cell specific targeting, to deliver durable and lasting impactful alterations to the T1D disease process.

Strategy

Establish effective DMTs for T1D

Built on research that contributed to our current understanding of pathogenesis of T1D, this program proposes a rational approach towards developing and evaluating DMTs:

Therapies to disable the immune attack on beta cells (Disable Autoreactivity): These therapies are intended to arrest the aggressive autoimmune attack on the beta cell by pathogenic cells (Teff, others) and create a permissive space for therapies targeting of other immune components or the beta cell. To date, the most durable effects on disease modification in clinical trials have been shown with Teff disabling therapies (anti-thymocyte globulin, anti-CD3, anti-LFA3, abatacept, rituximab). There is an opportunity to support preclinical development of the next generation of therapies in this category and to test the first generation of these therapies in combination with others.

Therapies to enhance regulatory immune features that protect beta cells (Enhance Regulation): These therapies can effectively restore mechanisms of normal immune regulation and tolerance by directly or indirectly enhancing T regulatory cell (Treg) function or numbers. Early and limited clinical successes in this space have been seen with low dose IL-2 therapy, or insulin derived peptides in stage three disease and oral insulin at earlier stages, Antigen-specific therapies that deliver tissue specific antigens to T cells or antigen presenting cells (APC) in a tolerogenic manner may be strong candidates for selective and effective tolerance induction. In addition, efforts to enhance Tregs in an antigen non-specific fashion may show efficacy in T1D, and several candidates are in late stage preclinical and clinical testing stages in 2020. These efforts will benefit from JDRF involvement to move select promising candidates into and through early stages of clinical testing in the next few years.

Anti-inflammatory or immune deviation therapies to promote beta cell health (Deviate inflammatory processes): These are 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 with the greatest number of clinical studies of the three categories to date, with a mixture of successes and failures; two phase II trials have indeed reported positive outcomes in 2020 (anti-TNFalpha, anti-IL21 + Liraglutide combination), while a phase II trial with tocilizumab (anti-IL6) was not successful. Cumulative learning from this area of clinical testing has highlighted that lasting efficacy with these agents will require nuanced combination strategies as next steps.

Therapies to stimulate growth and derepress function of beta cells (Regenerate beta cells): Discovery work in regeneration of beta cell mass and function has yielded several novel targets in the areas of proliferation, neogenesis, and trans-differentiation. This project area will continue to support discovery work to provide additional drug targets in this area. In addition, we will continue to evaluate appropriate model systems (such as stem cell derived beta cells) that will enable more efficient preclinical screening and testing of candidate regenerative agents. An important consideration within this area of therapeutic pursuit is that therapies designed to increase beta cell mass may impact other organ systems in the body which may present certain deleterious side effects. To mitigate this potential safety concern, we have and will continue to support the development and validation of strategies for targeted delivery of such drugs to the islet or beta cell. Alongside, this project will track clinical testing efforts that are ongoing with therapies that impact beta cell survival.

Establish Efficiencies in Preclinical and Clinical Development for DMT

In parallel with the objective to create, develop and establish DMT for T1D, this program has prioritized additional efforts that are intended to further accelerate the clinical path of T1D DMT by focusing on three key activities:

Preclinical Development: Preclinical programs for candidate disease modifying therapies for T1D often face challenges in generating compelling preclinical (non-clinical) data packages to enable entry into clinical trials. There is need to put into place effective mechanisms to guide the appropriate utilization of complementary in vivo and ex vivo models for novel DMT development for T1D. JDRF will remain committed to facilitating such efforts, including early partnering of academic and industry groups to accelerate preclinical drug development and integration of core academic or private laboratories to efficiently generate partner ready preclinical data packages.

Clinical Development: A clear need for sophisticated and innovative trial designs has been reinforced by the collective of disease modifying therapy trials conducted in T1D to date and by consistent feedback from clinical trial sponsors and investigators. For example, there are clear hints that children may respond better than adults to certain immune therapies (and vice versa; such as with teplizumab, alefacept, abatacept, etc.) in the stage two and stage three setting, and emerging data suggest that there are certain immune and beta cell derived early signatures that may be required early during intervention. It is expected that the complexity of the biological processes governing a disease such as T1D will require combinations of therapies with different mechanisms of action to achieve maximal therapeutic benefit in different subpopulations of people. Thus, a priority of the DMT project is to champion the use of novel trial designs and mechanism-guided clinical testing of rational combinations of therapies that will provide the POC for pivotal testing of DMT to alter disease course. In this approach, combination therapies would include both immune- and beta cell-directed therapies, whenever potential synergies in therapeutic effects are plausible.

Industry engagement: A priority of the DMT project and the CUREs program area is to bolster partnerships with industry to achieve therapeutic goals. Many years of JDRF funded research has generated substantial knowledge around cell types, targets and early preclinical data within the academic sector that may be pursued further within industry into drug development programs. Similarly, success with therapies in non-T1D indications provides the rationale for exploring repositioning and combination options with different classes of therapies. JDRF thus recognizes the unprecedented opportunities within the realm of disease modifying therapies that the field faces to engage industry partners and this program will be reinforcing efforts to extend our reach within the private sector to bring disease modifying therapies to market. Similarly, efforts in academia may benefit from early guidance on how to successfully generate compelling non-clinical data to attract industry uptake.

Deprioritized

Vaccines: Anti-viral vaccines: Epidemiologic data demonstrating that a limited number of enteroviral serotypes are associated with T1D. Viral infections have long been considered as candidates for environmental triggers but, given the lack of evidence for an acute, widespread, cytopathic effect in the pancreas in T1D or for a closely related temporal association of diabetes onset with such infections, a role for viruses in T1D remains unproven. Studies into the effects of vaccinations and/or antiviral drugs is the next step to understanding the role of viruses in T1D, and there is a commercial entity developing an antiviral vaccine. For these reasons, JDRF has deprioritized research in this area.

Beta cell survival therapies: Recent clinical findings have shown for the first time that therapies aimed at prolonging survival of beta cells are capable of slowing the loss of insulin production that occurs after diagnosis. Repurposed agents are moving towards confirmation studies, while we await the first trials with novel survival therapies. Trials using Gleevec or Verapamil have reported positive results- delaying the loss of insulin production in stage three adults. Recent activities have been devoted to ensuring these findings are replicated and expanded into additional ages and stages of T1D, and in combination with appropriate immune therapies to induce a durable impact on disease modification. Two other clinical studies (TUDCA, DFMO) are ongoing and will report by 2022, at which time their eligibility for combination therapy trials will be determined. While JDRF will provide strategic support in moving therapies currently at a clinical stage closer to approval for T1D, the DMT project will deprioritize support of discovery or preclinical development efforts for novel survival therapies.

Biomarkers: The DMT project will discontinue its prior commitment to the discovery and validation of T1D biomarker-related efforts. Over the past few years, via efforts strongly steered by JDRF, multiple candidates have become lead candidates to track treatment effect of T1D DMTs and will be further validated in ongoing clinical studies. These include signatures of immune perturbation and the presence of pro-hormones in the blood, and ‘outcomes beyond A1C’ as described later in this document. JDRF will continue its leadership role in highly select efforts that accelerate biomarker studies within clinical initiatives, as appropriate. Lead immune based perturbation signatures have recently been shown to associate with therapeutic and treatment effect, which will be supported towards further validation within clinical testing programs and supported within drug development efforts as appropriate.

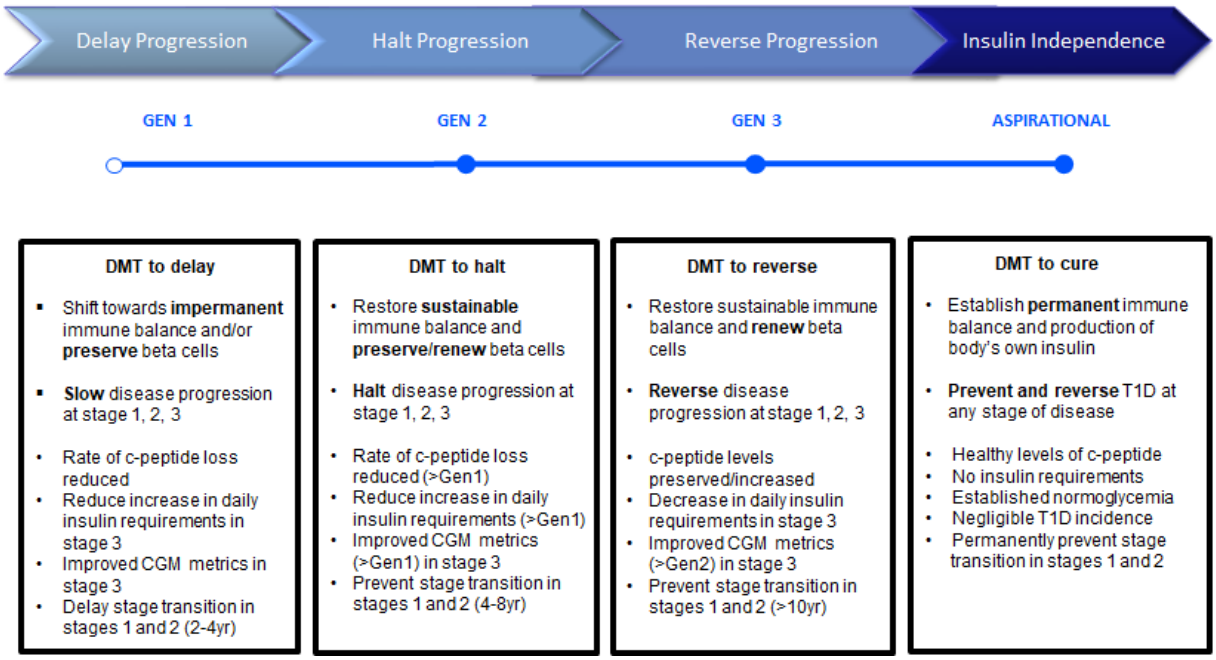
Roadmap

Our goals are based upon the clinical characteristics of those at risk of developing or currently living with T1D with the purpose of delaying, halting and ultimately reversing T1D progression. This will restore insulin

independence and non-diabetes like physiology. The roadmap below describes a therapeutic development path towards the goal of preventing and curing T1D. A key feature of the advancement from first generation to aspirational therapies is a stepwise progression in the complexity of therapeutic choice, increasingly incorporating combination therapies to achieve more potent and durable impact in altering the biology of disease until complete disease reversal is achieved.

The availability and ongoing clinical testing of repurposed therapies represent a set of candidate therapies (first generation) 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 first generation therapy testing in T1D, especially with the backing of substantial amounts of safety data. In addition, based on recent success in proof-of-concept studies using repurposed beta cell survival therapies (Gleevec; Verapamil), first generation beta cell targeted therapies may be ready for testing as part of second-generation combination therapies. In addition to repurposed agents first generation therapies are monotherapies and may include non-targeted and targeted immune or beta cell directed therapies that are currently in late preclinical development. As targeted DMTs become available and demonstrate superiority, novel and more efficacious therapies may replace repurposed systemic agents. This remains to be clinically proven, although a handful of clinical trials involving second generation regulation enhancing therapies are projected to launch soon while others are in various stages of clinical development.

Second- and third-generation therapies reflect incremental complexity in treatment plans, and are expected to be combination therapies, involving immune and beta cell targeted agents, that can provide additive effects to increase efficiency. Later generations of beta cell therapies rely on the discovery and development of novel regenerative therapies with safe and effective targeting features. 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 disease modifying therapies for T1D is the risk/benefit ratio of candidate immune and beta cell regenerative therapies. This complex ratio will directly draw from the ratio of

burden-of-disease/burden-of-therapy (including risk). This topic falls within the DMT project's priority area of adding efficiencies within the clinical development space. This project will facilitate efforts with key stakeholders such as industry and regulatory agencies. It is the DMT project area'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" and enable beta cell health and regeneration in a well-tolerated manner.

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

Current Status

Successes across multiple aspects of T1D disease modifying therapies, have brought the field to a unique place that will benefit from coordination, integration, and harmonization of efforts both in the preclinical and clinical settings for drug development. This is essential if, with increasing options 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.

Over many years, JDRF supported extensive research projects to better understand the immune pathogenesis of T1D. Results from this vast body of data has been foundational in informing current therapeutic strategies in DMTs and has enabled JDRF to move further into supporting preclinical and clinical development initiatives for various classes of therapies. As next steps to inform clinical path, the DMT project area will strategically engage with other disease areas and pharmaceutical partners, to better understand the knowledge base drug development strategies that have successfully yielded approved therapies in other indications, such as other autoimmune diseases.

It is noteworthy that the next opportunities and challenges facing development efforts for T1D disease modifying therapies come on the heels of major accomplishments in recent years. To name a few:

- Multiple recent JDRF grant commitments and investments in companies developing DMTs (Immunocore, TetraGenetics, ImmusanT, SQZ Biotech, Sonoma Biotherapeutics, Repertoire Immune Medicines, Pandion Therapeutics, Provention Bio, SAB Biotherapeutics, IM Therapeutics, AnTolRx, Kriya Therapeutics, DiogenX, Inversago Pharma, Veralox Therapeutics, Enthera Pharmaceuticals).
- Multiple T1D trials with DMTs have launched, enrolled, or reported in 2019-2020.

Trials reporting successful outcomes:

- Provention's Teplizumab in stage two disease, Sanofi's ATG in stage three disease Janssen's golimumab in stage three disease
- A combination of Novo Nordisk's anti-IL21 and liraglutide in stage three disease
- Diamyd's GAD-Alum in a subset of subjects with specific HLA (DR3/DQ2) in stage three disease
- Verapamil and Gleevec in small clinical studies in stage three disease (beta cell therapy)

Trials ongoing:

- Provention's teplizumab in pivotal trial in stage three disease
- Low dose IL-2 in stage three disease (multiple trials)
- DFMO, TUDCA small phase II trials in stage three disease
- Abatacept and hydroxychloroquine in stage one disease

- Novartis' anti-CD40L in stage three disease
- Sanofi's low dose ATG in stage three disease
- Imcyse, Tolerion and Intrexon's antigen specific therapies in stage three disease
- Verapamil in stage three disease (beta cell therapy)
- Oral insulin in pre-stage one disease

- Extensive and ongoing mechanistic insights from previous DMT trials in stage three disease have shown that enhancement of Tregs and exhaustion of Teff correlate with positive outcomes (immune therapy trials) as well as positive changes in proinsulin to C-peptide ratio appear that associate with positive outcomes.
- Children and/or those with identifiable immune characteristics (such as higher inflammation index at baseline and/or certain B cell signatures) might be better responders to some classes of DMTs.
- Key outcomes such as incidence of hypoglycemia, time-in-range, and daily insulin burden can be reduced by DMTs, sometimes with durable effects.
- Integrated project launch by cross-disease communities to tackle mutually relevant therapeutic challenges to help accelerate and refine therapeutic development strategies in novel ways.

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, there remains a clear opportunity to develop autoreactivity disabling therapies for outcomes superior to what have been achieved thus far. This may occur either via development of new therapeutics specifically for T1D as the primary indication (e.g., an alefacept biosimilar, humanized ATG, etc.) or line extension testing of approved therapeutics or ones in clinical development for other autoimmune disorders, such as anti-CD40L amongst others. In parallel, supporting the development of tissue targeted therapies and bi- or tri-functional next generation therapies to disable autoimmunity may provide greater efficacy than first generation of therapies in development such as teplizumab.

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. Improvement in regulation enhancing therapies may be possible through improved tissue targeting and/or with therapeutic cocktails inclusive of antigen specific immune therapies or with more refined polyclonal approaches, such as with IL-2 muteins.

Significant technological advances have provided opportunities for the design and evaluation of platform tolerance delivery systems (TDS) for antigen specific therapies. TDS carry disease relevant antigens and other desired cargo such as anti-inflammatory substances and even tissue targeting, to actively induce tolerance. Several early TDSs are in early clinical testing in other autoimmune disease indications and in preclinical development for T1D. The challenges in the development of these moieties is non-trivial as often there are sophisticated manufacturing considerations, in addition to the need to identify the best preclinical model(s) to inform the choice of cargo for best outcome.

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 three of disease or in pediatric populations. The attractive potential of TDS in stages one and two of disease is that they may be sufficient as a monotherapy to have an enduring effect in these settings. It is expected that the potential efficacy of this therapeutic class in stage three disease may be maximally achieved in a combination therapy setting, where autoreactivity is disabled first.

Anti-Inflammatory Therapies

Many, if not all, autoimmune diseases involve over secretion and function of secreted inflammatory immune mediators, which perpetuate the autoimmune process. It is therefore desirable to silence or neutralize factors that may enhance inflammation and auto-reactivity. Such 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 in rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), and other diseases. These approved agents are attractive candidates for testing in T1D. Finding a way to rapidly assess the treatment/therapeutic effects of such drugs in T1D would greatly facilitate evaluation of their candidacy alone or in combinations.

Suboptimal knowledge around dose, regimen, formulation and route of administration for various types of immune therapies continues to be a key challenge facing the field that requires further investment of resources and innovative strategies for getting to the best selection of approvable DMT candidates. These needs will be addressed and facilitated by the introduction of efficiencies within preclinical and clinical development programs, such as provisions of guidelines/recommendations for development and effective partnering between academia and industry.

Beta Cell Regenerative Therapies

Beta cell regenerative agents, specifically those targeting proliferation, are in the preclinical development. Beta cell mass is not fixed at birth, but rather increases in response to increased metabolic demand such as in the growing child, in response to obesity or insulin resistance, and pregnancy in the adult. Increasing knowledge of the mechanisms regulating the physiologic expansion of beta cells is providing insights into potential pathways and targets for therapies to restore beta cell mass and function. Newer technologies like single cell sequencing have greatly accelerated discovery in this field. The beta cell population in the pancreas has been shown to be highly heterogeneous – dynamic in its functional capabilities, phenotype, and identity. However, how these characteristics change during and contribute to diseases like T1D remains unknown. Factors such as proliferation, trans-differentiation, plasticity, and neogenesis may all contribute to this heterogeneity. Current discovery and validation efforts based on these recent works aim to generate novel targets for increasing beta cell mass and function.

Targeted Delivery of Beta Cell Regenerative Therapies

Recent advances have led to the discovery of several small, drug-like molecules that can drive human beta cell replication. However, none of these molecules act on pathways that are sufficiently selective 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 drug delivery has advanced considerably in recent years, particularly in the oncology setting, raising the possibility of adapting such technology for use in T1D. In the past couple of years, multiple groups have published on novel strategies to deliver drugs selectively to the beta cell such as zinc-based prodrugs and GLP1R mediated targeting of antisense oligonucleotides. While validation of these findings is ongoing there exists a need to develop additional strategies to feed this pipeline of therapies. Importantly, pursuing targeted delivery strategies has the potential to improve the safety profile of multiple classes of disease modifying therapies for T1D.

There is increasing rationale to move into clinical testing of combination therapies to effectively and durably modify disease course in T1D, as outlined in this project's roadmap. The utility of targeting distinct immune pathways with safe combinations of drugs is increasingly manifest in the immuno-oncology field, To that end, JDRF will support efforts to clinically test rational combinations of available agents in T1D. JDRF strongly

appreciates that this space must engender multi-stakeholder engagement to be successful, including strong involvement from drug developers to not only provide their therapies for early clinical assessments but also to consider co-development programs for promising combinations as opportunities arise. JDRF will commit strategic efforts to facilitate such movement, including the support of novel and nimble approaches for clinical testing of combination DMTs.

Goals and Barriers

As JDRF participates in advancing the field of T1D DMTs, the following high priority barriers must be addressed to make the next generation therapies become a viable reality.

Therapeutic Development

- Need for larger pipeline of differentiated and next-GEN/targeted DMTs in late preclinical development and in FIH studies.
- Targeted drug delivery systems are mostly not yet ready to enable movement of GEN 2 therapies into the clinic.
- Safety remains a consideration for DMTs - both for immune and beta cell targeted therapies.
- Identify which therapeutic targets and drug combinations will be most efficient.
- Lack of validated early surrogate endpoints of efficacy (within three to six months of treatment) to enable rapid testing of disease modifying therapies in stage two or stage three of disease

Inefficiencies Within Preclinical and Clinical Therapeutic Development

- Lack of widely utilized guidelines for IND enabling studies involving candidate therapies. These include choice of orthogonal models, including ex-vivo assays, to identify appropriate pharmacodynamic (PD) and/or efficacy markers and demonstrate potential impact on human disease.
- Lack of accessible mechanisms for moving therapeutic candidates from the preclinical studies into drug development programs, this includes early academia-industry partnerships, out-licensing opportunities, and opportunities to introduce industry level rigor into early drug discovery programs.
- Lack of efficiencies within clinical trial designs for rapid proof-of-mechanism and proof-of-concept testing to facilitate combination treatments. This includes slower progress towards utilization of adaptive trial designs such as those that have been successful in oncology.

Policy and Reimbursement Considerations

JDRF is focused on how research can advance product development with regulatory and reimbursement considerations in mind so that JDRF's work accelerates products through the pipeline and into the hands of people with T1D.

Regulators

Regulators generally base their decisions on an assessment of whether the benefits of the product outweigh the risks, as demonstrated in clinical trials. For traditional development of a novel drug or biologic product, the Food and Drug Administration (FDA) in the US and other regulators around the world generally require a development program that culminates in at least two adequate and well-controlled phase III clinical trials with the expectation of a sufficient number of people exposed to assess benefits and risks . For the Sponsor to expand the indications of an already approved drug or biologic to a new patient population or disease, in general, FDA and other regulators will also require two adequate and well-controlled phase III 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 pharmacodynamic 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 one year as the primary efficacy endpoint for phase III clinical trials intended to preserve endogenous beta-cell function. 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. Importantly, FDA and the European Medicines Agency (EMA) are working with the community on the outcomes for these trials. In early 2020, JDRF organized a small group of key opinion leaders to present to FDA on the use of C-peptide in new onset T1D clinical trials. Subsequently, a public meeting is being planned with the broader community around this topic, and JDRF is serving on the planning committee. Community consensus around the use of C-peptide dates back to 2004 and to support drug development in this area, JDRF is leading a multi-stakeholder effort to update the consensus around C-peptide. Doing so will help to ensure regulators have the most up-to-date information as they provide guidance to developers in this space and make risk benefit decisions on disease modifying therapies in T1D.

To support development of therapies to target the earliest stages of T1D and delay or halt progression to insulin dependence, JDRF has been working with the FDA and the European Medicines Agency (EMA) to qualify a set of biomarkers used to define the earliest stages of T1D. A consortium of patient organizations, academic investigators, and industry, under the leadership of the Critical Path Institute, has proposed qualification of these biomarkers to FDA and EMA and is actively working with both regulatory agencies. Qualification of these biomarkers is a critical step to encourage development of therapies in this area.

In conjunction with the disease modifying therapies community, JDRF has also developed and is pursuing publication on a white paper underscoring the need and providing justification for the research of disease modifying therapies in pediatric populations where disease progression and responses to interventions has differed from those of adults

Reimbursement

Considerations for payer coverage of DMT in the U.S. 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 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.

For drugs and biologics, the manufacturer sets the price and then regularly reports to CMS on the various discounts, rebates, or fees they contract to make in association with that product. This allows CMS to calculate an “average sales price,” (ASP). Under the Medicare program, for physician administered products, providers typically purchase them from a specialty pharmacy and are paid an administration fee to provide them to the patient, plus 106 percent of the “average sales price” (ASP) of the product itself. Many private payers use an ASP-based reimbursement methodology as well, though they typically pay more than 106 percent and ASP-based reimbursement is more common for physicians than for hospital outpatient departments. If the product is considered a hospital service or physician service, rather than a drug or biologic, 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.

Therapeutic Concepts

First Generation

Properties	First Generation: DMT to delay disease progression
Primary Product Indication	Slow disease progression from stage two to stage three and from stage three onwards. Increase time to insulin dependence, Reduce the rate of C-peptide decline.
Target Population	Stage two and three adults and pediatrics; possible extension to stage one if exceptionally safe and efficacious
Features	Single agent
Efficacy	Reduce rate of progression to stage three from stage one or two 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

Second Generation

Properties	Second Generation: DMT to halt disease progression
Primary Product Indication	Stop disease progression from time of therapy. *Stop* C-peptide decline in stage three. Stop progression to insulin dependence from stage two.
Patient Population	Stage three then stage two adults with step-down development into pediatrics; possible extension to stage one if exceptionally safe and efficacious
Features	Multiple agent
Efficacy	Prevent increase in insulin needs and with less rise and greater durability than monotherapies; maintain stage two or stage one of disease indefinitely, improve quality of life > first generation
Risk/Side Effect	No significant short-term morbidity and minimal risk of increased infection.
Therapeutic modality	Drug, biologic, or cell therapy

Third Generation

Properties	Third Generation: DMT to reverse disease progression
Primary Product Indication	Reverse disease progression at all stages of disease. Increase c-peptide levels with sustained therapy.
Patient Population	Stage three then stage two adults with step-down development into pediatrics; possible extension to stage one or earlier if exceptionally safe and efficacious
Features	Multiple agent
Efficacy	Lower insulin needs in stage three with durability greater than or equal to second generation, reverse stage two to stage one or earlier, improve quality of life > second generation, prevent progression to or from stage one
Risk/Side Effect	No short-term morbidity and minimal risk of increased infection
Therapeutic modality	Drug, biologic, or cell therapy

Aspirational

Properties	Aspirational: DMT to cure T1D
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 quality of life
Risk/Side Effect	Negligible
Therapeutic modality	Drug or biologic

Cell Therapy

Vision

A world where everyone living with insulin-dependent diabetes (type 1 diabetes, type 2 diabetes, pancreatic, or monogenic diabetes) can easily access curative therapies consisting of a safe and effective beta cell replacement product capable of restoring glucose control and achieving long-term insulin independence without the need for chronic broad immunosuppression.

Mission

To accelerate the development of breakthrough beta (or islet) cell replacement therapy products which replicate non-diabetes like physiology and result in insulin independence in all ages and stages of type 1 diabetes (T1D) and other forms of insulin-requiring diabetes.

Rationale

Replacing beta cell function via islet transplantation, a cell-based therapy, remains the only approach with clinical proof of concept demonstrating that insulin independence can be achieved in people with long-standing T1D. In the past two decades, major advances such as improvements in surgical techniques and immunosuppressive strategies have resulted in the introduction of donor islet transplantation with minimally invasive procedures. Phase III clinical data, including the recent report from the Clinical Islet Transplantation (CIT) Consortium have demonstrated durable near-normal glycemic control and insulin independence in up to 44 percent of recipients after three years, as reported by the Collaborative Islet Transplant Registry (CITR). Importantly, islet transplantation can reverse severe hypoglycemic events and unawareness, a serious consequence of T1D in about five to ten percent of those affected, as well as halt or stabilize other complications associated with T1D. However, due to the limited supply of donor islets and the risks and side effects associated with immunosuppression, the availability of these treatments is currently limited to patients with severe life-threatening hypoglycemia unawareness and increased incidence of severe 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 validation of beta cells derived from alternative renewable sources, development of delivery systems and strategies to support and protect the cells, and optimization of alternative 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. Moreover, these therapies would also benefit people who suffer from other forms of diabetes and are dependent on insulin therapy such as type 2 diabetes (T2D), approximately seven million of which live in the United States and millions more across the globe, pancreatic diabetes, and monogenic diabetes. These groups also suffer from poor clinical outcomes

and complications that result from poor glycemic control and comprise broader group of people that represent a significantly larger market.

Strategy

The Cell Therapy project supports gap-filling research that advances new technologies from basic discovery towards translational studies and clinical studies to validate effective therapies and accelerate the development of a cell-based product capable of restoring glucose control and achieving long-term insulin independence without the need for chronic broad immunosuppression therapy. This is one of JDRF's strategies to find cures for T1D. 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.

While current lines of investigation and commercialization focus on developing a product consisting of beta cells or islets derived from a renewable source in an immune protective device, there may be alternative strategies in the design of future generation products. For example, induction of immune tolerance toward implanted 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 evade immune recognition and promote tolerance so that less or no immunosuppression would be required, and/or make them resistant to metabolic stress and hypoxia to enhance engraftment and cell survival. The cell therapy program also covers unique opportunities in specific areas of research such as induction of immune tolerance by mixed chimerism, and the generation of in vitro models of T1D to better understand autoimmunity.

JDRF's Cell Therapy project will continue to support the late preclinical development and clinical translation of first-generation beta cell therapy (BCT) products that rely on a renewable source of insulin-producing cells to improve glycemic control in adults living with T1D who suffer from hypoglycemia unawareness. In parallel, we will continue to support the preclinical and early clinical development of second-generation products that aim to deliver further improvements in glycemic control and Diabetes Quality of Life (DQoL) measures in an expanded population of people with poorly controlled T1D or established T1D by reducing the requirements for broad immune suppression. Finally, we will continue supporting the discovery and early preclinical development of third generation products capable of delivering even further improvements in glycemic control and DQoL measures in people with established T1D while obviating the need for immune suppression. Further details of these successive generations of BCT products, anticipated outcomes, and expected target populations are described in the "Roadmap" and "Therapeutic Concepts" sections below.

Prioritized

In order to deliver on these products, JDRF's Cell Therapy project is prioritizing the following areas of research:

- Late preclinical and early clinical research on validation of alternative sites of implantation such as the skin, muscle, or abdominal space.
- Preclinical and clinical testing of technologies to enhance cell survival, integration, and function after implantation.
- Late preclinical and early clinical testing of encapsulated combination products consisting of insulin secreting cells derived from renewable sources delivered in an immune protective encapsulation device.
- Discovery, preclinical, and clinical testing on alternative strategies to protect the cells that do not involve encapsulation and obviate the need for immune suppression.

Deprioritized

Given progress made thus far in this space and current funding landscape, JDRF's Cell Therapy project is deprioritizing the following areas of research:

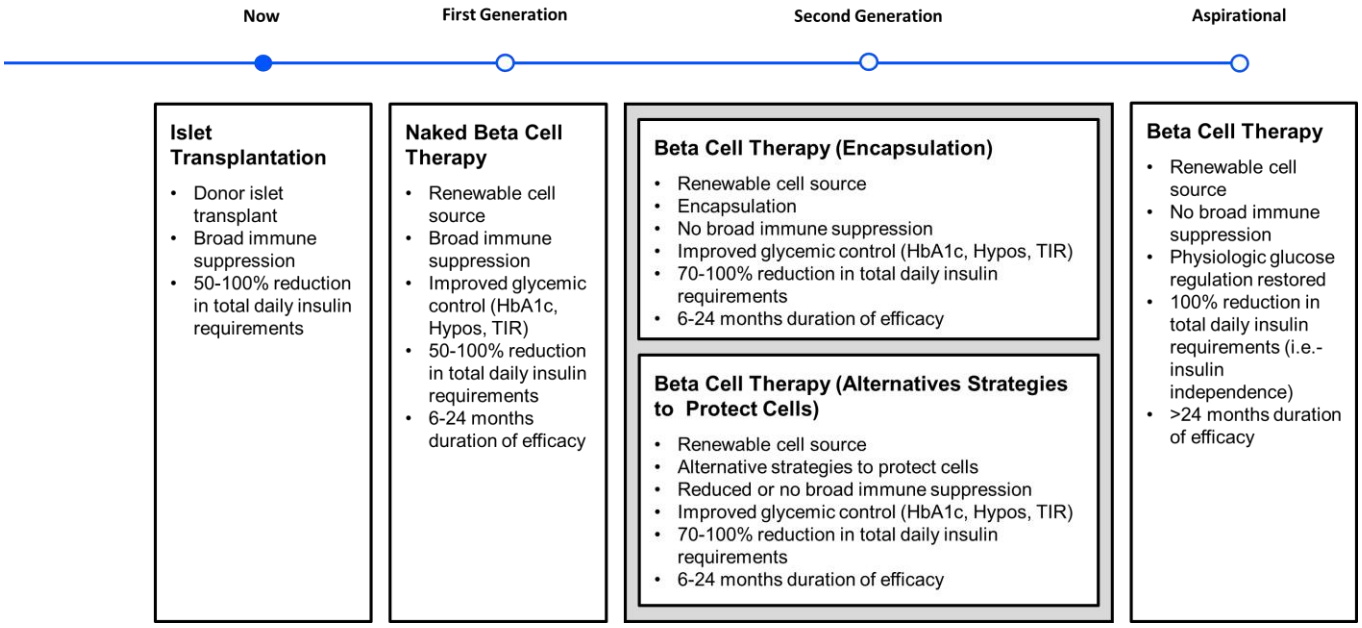
- Development of renewable sources of insulin-secreting cells, study of pancreatic development, and optimization of protocols for differentiation of stem cells into beta cells.
- Early preclinical testing and development of immune protective encapsulation technologies.
- Early stage discovery of approaches to improve engraftment.

The development of beta cell replacement therapies entails overcoming a variety of challenges is multiple scientific areas including, but not limited to, stem cell and beta cell biology, wound healing and immunology, bioengineering, and translational research. As such, one major aspect of the Cell Therapy project's strategy to deliver curative therapies is fostering collaborations between researchers across several different disciplines. Through the support of the Beta Cell Replacement Consortium, the Cell Therapy project promotes the sharing of experimental data, exchange of ideas, and establishment of multidisciplinary collaborations with the goal of accelerating research progress and product development. This consortium consists of a select number of investigators from both industry and academia who are global leaders in their respective fields focused on overcoming the challenges encountered in the development of beta cell replacement therapies. Through JDRF support, this group meets twice a year to discuss the latest scientific developments and identify various challenges and opportunities in the development of beta cell replacement products.

Roadmap

While the concept of beta cell replacement has been evaluated for decades and many technical challenges remain, realistic near- and long-term projections for the development of beta cell replacement products can be made. Findings from past studies and future advancements in stem cell biology, immunology, and biomedical engineering will 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 beta cells, or porcine islet cells is anticipated to demonstrate the optimal benefit-to-risk 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 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 befitting use of these products will progressively broaden accordingly. The first-generation therapeutic product will likely consist of insulin-secreting cells from a renewable source delivered in an open scaffold or device which will be protected by standard, broad immune suppression. The development of next generation and aspirational products will focus on strategies to deliver insulin-secreting cells from a renewable source with reduced or no 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 development of a cell therapy product that restores glucose control and delivers insulin independence without the need for broad immune suppression.



Current Status

At the present time, there is no commercially available beta cell replacement product. However, there are several cell therapy approaches moving into proof-of-concept studies in humans. The main priority is to support 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, biomaterials 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 near-term goal is to provide clinical proof (measurable clinical outcomes) of the development of a renewable source of insulin-producing cells 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 research has resulted in protocols for deriving human pancreatic endocrine cell progenitors and surrogate beta cells from hESC and iPSC. We do not yet know whether the optimal commercial cell therapy product will incorporate a pancreatic progenitor cell population or a fully mature beta cell population. Both cell sources have advantages and challenges. Current cell preparations still contain populations that are polyhormonal and not fully functional in terms of insulin secretion, and it remains to be determined whether additional non-beta endocrine cells from the pancreatic islet will need to be incorporated to generate a complete and functional cell replacement product. Development of stem cell therapies will also require long-term safety assessment for the risk of uncontrolled growth and formation of teratomas. Overall, beta cells manufactured from renewable sources should have much higher degree of quality control compared to cadaveric islet isolations such that safety and

beta cell survival and functional durability after implantation 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. Additionally, JDRF is supporting research exploring avenues to scale up production of stem cell-derived beta cells and establish a source of high-quality cells for distribution for research purposes to accelerate development of other technologies.

Xenogeneic Islets

Pig and human insulin are almost identical in sequence (one amino acid difference) and pig insulin was safely used to treat T1D for decades before recombinant DNA technology and manufacturing capabilities enabled the large-scale production of human insulin. Xenotransplantation using porcine islets has also advanced and these cells are gaining acceptance as a potential readily available cell source for human application. 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 islet cells to circumvent the use of broad immunosuppression. Immune protection 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, broad 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 natural materials and synthetic polymers 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 onto the islet surface via layer-by-layer assembly at the nanometer scale; and other technologies. 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 limitation is more significant for macro-encapsulation devices, this approach facilitates 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 the present time, JDRF is supporting both approaches to better understand the potential benefits and liabilities of each approach.

Scaffolds (Open Devices)

JDRF has previously supported research to explore "open" scaffolding technologies with the aim of developing devices for cell delivery 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 implanted cells from the immune response. 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, broad immunosuppressive therapy is to employ strategies for localized delivery of immunosuppressive drugs or immunoregulatory molecules to protect the implanted cells or promote tolerance. One might envision engineering scaffolds to present or release such molecules as prodrugs, or as an alternative approach, one could leverage recent progress in gene-editing techniques, enabling cells to evade immune 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.

Alternative Sites of Implantation

Currently, CIT consists of a minimally invasive procedure entailing infusion of cadaveric islets into the portal vein of the liver where they are lodged in the vasculature. However, this method of delivery is not ideal as it does not allow for retrieval of the graft and results in a significant loss of the implanted beta cell mass due to direct contact with blood leading to increased immunogenicity. Moreover, the liver is responsible for performing various metabolic functions and can potentially result in a highly toxic environment that can be detrimental for islet cells. Finally, occlusion of the liver vasculature can induce inflammation at the site. Consequently, there is a need to explore and validate alternative implantation sites that can accommodate therapeutically relevant doses of cells and provide enough blood vessels and nourishment for the cells to survive and perform their function. In addition, a site that allows for monitoring and retrieval of the cells if necessary, would be highly advantageous. Alternative sites being explored include the skin (subcutaneous space), muscle, and the abdominal cavity (peritoneal cavity, omentum).

Goals and Barriers

The Cell Therapy project's strategy is driven by specific goals related to the development of products for people with insulin-requiring T1D and the key barriers that stand in the way of achieving them. JDRF's role is to help lower these barriers to enable academics and the private sector to move products forward. Critical goals and associated barriers in the area of developing beta cell replacement therapies consist of the following:

Goal: Demonstrate glycemic benefit from stem cell-derived beta cells implanted in an alternative site in humans

Barriers:

- Safety concerns over stem cell-derived beta cells.
- Optimal stage of differentiation and dose remain to be determined.
- Poor cell survival, engraftment and function due to poor vascularization and lack of oxygen immediately following implantation.

Goal: Achieve immune protection of the cells without broad immune suppression

Barriers:

- Adverse inflammation and humoral immunity.
- Adaptive immunity mediated by indirect antigen presentation pathway(s).
- Adaptive immunity mediated by direct antigen presentation.
- Fibrosis of implanted biomaterials and mass exchange limitations (encapsulation approaches).
- Slow preclinical development by lack of standardized high-quality SC-derived beta cells for distribution for research.

Additional barriers related to the development and commercialization of beta cell replacement products also include the following:

- The need for multidisciplinary collaborative teams that can address, develop and integrate and solve remaining solutions to complex challenges in various scientific and technical areas simultaneously in order to deliver effective products.
- The lack of tools and methods for non-invasive longitudinal in vivo monitoring of vascularization, cell engraftment, and the local immune response.
- Limited investment from industry and large pharma in high-risk innovative and potentially paradigm changing technologies necessary for success leading to stagnation or slow progress.
- The need to define and establish processes for scaled-up manufacturing under cGMP conditions, quality management systems, and supply chain management for the commercialization of effective products.

Policy and Reimbursement Considerations

JDRF is focused on how research can advance product development with regulatory and reimbursement considerations in mind so that JDRF's work accelerates products through the pipeline and into the hands of people with T1D.

Regulators

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 Food and Drug Administration (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 are 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 must first 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.

Over the last few years and in response to the surge of research and development activities in cellular and gene therapies, FDA has issued guidance documents that provide their general thinking in areas of preclinical, early clinical considerations and manufacturing. While these guidances are not disease specific, they do provide context to the flexible regulatory approach taken by CBER in reviewing novel cell and gene therapy products. Cadaveric islet cell transplantation has demonstrated clinical proof of concept for cell replacement therapy as a viable therapy in T1D. The CIT consortium, funded by NIH, completed a successful Phase III safety and efficacy study for islet transplantation. FDA provides its thinking on this topic in a September 2009 Guidance document entitled “Considerations for Allogenic Pancreatic Islet Cell Products.” Of note, CBER includes in this guidance recommendations for other key clinical outcomes that include discussion of measures of glucose and metabolic control such as fasting plasma glucose, 2-hour post prandial, mean amplitude of glucose excursion and glucose variability as measured by CGM.

Activities we are undertaking to optimize the regulatory pathway for these therapies include:

- Partnering with OTAT (since 2007) to hold seminars on the latest scientific and technological developments in beta (or islet) cell replacement for T1D by bringing researchers from the Beta Cell Replacement Consortium to present their work to agency staff.
- Regulatory support to JDRF Beta Cell Consortium members (investigators/researchers, industry).
- Review and comment on guidances from FDA in the area of cell therapies to guide our researchers as they approach interactions with regulatory agencies.

Reimbursement

Beta cell replacement is likely to be covered as either a hospital inpatient or outpatient service, depending on whether the patient must be admitted overnight for the procedure. Inpatient service reimbursement does not result in a separate payment being made for biologics or devices used in the service. When a biologic or device used in an inpatient service is very expensive, it can be a disincentive to the hospital because the Medicare reimbursement methodology may not adequately account for the cost of the biologic or device. Manufacturers who believe that their product will be provided through an inpatient service should carefully study the system to understand how it might motivate behavior by hospitals.

Biologic products that are implanted or delivered in the hospital outpatient department are paid for based on the "Average Sales Price" (ASP) of the biologic, which is a sales-weighted average, post-rebate, post-discount price, received by a range of commercial purchasers. Hospital outpatient departments are paid at the rate of 106 percent of ASP by Medicare. Commercial insurers will sometimes use the ASP as the basis for their reimbursement to outpatient departments, but more often they use a percentage of billed charges or even list price for the drug.

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 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.

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 therapy.

First Generation

Properties	First Generation: Naked Beta Cell Therapy
Primary Product Indication	Reverse life-threatening hypoglycemic unawareness Restore glucose control in insulin-dependent diabetes
Target Population	Adult T1D patients who suffer from hypoglycemia unawareness (HU) or hypoglycemia associated autonomic failure (HAAF), with unstable diabetes
Features	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Duration: 6-24 month

Efficacy	Primary – reduced hypoglycemia frequency, severity, and related hospitalization HbA1c improved Improved glucose control (decreased insulin usage or insulin independence) Improved Diabetes Quality of Life (DQoL) scores
Risk/Side Effect	Reverse life-threatening hypoglycemic unawareness Restore glucose control in insulin-dependent diabetes

Next Generation: Beta Cell Therapy (Encapsulation)

Properties	Next Generation: Beta Cell Therapy (Encapsulation)
Primary Product Indication	Reverse life-threatening hypoglycemic unawareness Optimally restore physiological glucose regulation
Patient Population	Poorly controlled T1D Established T1D Insulin-dependent T2D
Features	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Duration: 6-24 months
Efficacy	Primary – HbA1c improved and insulin usage decreased Improved HYPO and Clarke scores Improved Diabetes Quality of Life (DQoL) scores Duration of the effectiveness on primary endpoint ≥ 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 Generation: Beta Cell Therapy (Alternative Strategies to Protect the Cells)

Properties	Next Generation: Beta Cell Therapy (Alternative Strategies to Protect the Cells)
Primary Product Indication	Reverse life-threatening hypoglycemic unawareness Optimally restore physiological glucose regulation
Patient Population	Established T1D Insulin-dependent T2D
Features	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Genome modification/local immune suppression/ tolerance induction Duration: 6-24 months
Efficacy	Primary – HbA1c improved and insulin usage decreased

	Improved HYPO and Clarke scores Improved Diabetes Quality of Life (DQoL) scores Duration of the effectiveness on primary endpoint ≥ one 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

Aspirational

Properties	Aspirational: Beta Cell Therapy
Primary Product Indication	To fully restore physiological glucose regulation
Patient Population	Established T1D Insulin-dependent T2D
Features	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Strategy that provides full immune protection to insulin-producing cell source Duration ≥ 24 months
Efficacy	Primary – HbA1c improved and insulin independence Significantly improved HYPO and Clarke scores Significantly improved Diabetes Quality of Life (DQoL) scores Duration of the effectiveness on primary endpoint ≥ two years
Risk/Side Effect	Minimal surgical risks Minimal risks of teratoma formation for stem-cell products Minimal risks of sensitization from allo- and xeno-cells or zoonosis from porcine cells