



# Cures Program Research Strategy

## Executive Summary

### 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 (T1D) 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.

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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 Early Detection: Develop and execute a global universal early detection 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 can 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 toward a path to a successful therapeutic development that covers all stages and ages of T1D. The table on the following page provides an overview of the three roadmaps across the T1D stages.

## 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
Early Detection					
Disease-Modifying Therapies					
Cell Therapies					

## Early Detection

### Vision

A world where type 1 diabetes (T1D) risk is detected years before insulin dependence, where T1D early detection 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 early detection project is to establish T1D risk early detection in healthcare settings to improve near and long-term health benefits for those screened.

### 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) has increased to 40-60% percent.

T1D risk early detection is based on the presence or absence of islet autoantibodies (AAb). Individuals at risk for T1D that have been detected through early detection have significantly lower rates of DKA at diagnosis and a lower HbA1c several years after diagnosis, which correlates with negative health outcomes over time. While AAb detection can determine a person's T1D status, it

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does not inform well on the rate of progression to clinical disease. Additional biomarkers and monitoring guidelines are needed to increase predictability of onset of clinical diabetes, even in those who screen positive for AAb.

Despite the increase in the incidence and prevalence of T1D, the clinical development of therapies to delay, halt, or cure T1D is challenging. Randomized controlled trials to evaluate disease modifying therapies are slow to enroll, taking as long as 10 years to complete, which slows scientific discovery. 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.

In 2022, the U.S. Food and Drug Administration (FDA) approved the first therapy to delay the progression of T1D, Tzield™. Importantly, there is a pipeline of therapeutic candidates being evaluated for effectiveness as preventive therapies, but we anticipate that current early detection programs are insufficient to provide a platform for accelerated evaluation of these therapies – hence a strategy to expand early detection and follow up monitoring to a larger population is urgently required.

Considering the number of people in the U.S. living with T1D (1.4 million), the estimated number of first-degree relatives (FDR) with higher risk of T1D over the general population could be around 10 million. To date, T1D early detection programs have been restricted primarily to FDR of people with T1D and conducted only in the research setting, and data from the last 2 years reveals that only a small fraction of FDR have contributed to early detection programs.

Importantly, ADA Standards now endorse that first-degree relatives (FDR) participate in T1D early detection programs outside of the research setting, but there is not yet an established pathway for how this should be conducted. 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. It is estimated that this strategy only captures approximately 10-15 percent of the total at-risk population.

More recent but smaller, targeted studies have expanded to the general population with geographic and age restrictions. These FDR and pilot community early detection programs have unequivocally demonstrated that early detection and monitoring 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.

Familial and pilot general population early detection and monitoring research initiatives have been demonstrated to be feasible to deploy, efficient in mitigating the health and psychological impacts of T1D diagnoses, and 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. In addition, there is no consensus on monitoring

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protocols or guidelines which will be essential to successfully scale early detection to the population level.

This project area will prioritize improving upon and expanding general population early detection and monitoring programs globally, building evidence for their feasibility in the clinical setting, and developing evidence to accelerate and facilitate future adoption by health care providers, payers, and governments. Moving forward, early detection of T1D via early detection and follow up monitoring is critical to clinical trial participation for promising therapies under development that will prevent the onset of T1D.

Disease-modifying therapies will be dependent on T1D early detection to identify who may be eligible for these life-changing therapies. Breakthrough T1D envisions a future where the general population, both pediatric and adult, are screened for T1D as part of the routine care they receive in order to identify everyone at risk, not just those with a family history of T1D.

In addition to expanding our AAb early detection efforts in the general population, Breakthrough T1D will search for opportunities to leverage existing population early detection tools to identify individuals that would benefit from AAb early detection. So far, we have focused on these initiatives that fill a gap and overcome the barrier of predicting/identifying individuals at risk of developing T1D:

- Genetic Risk Score (GRS) is based on genetic markers that increase susceptibility to autoimmunity. The strongest genetic determinants of risk are the HLA genotypes, but other non-HLA susceptibility loci have also been identified. Almost 80 percent of individuals diagnosed with T1D have a predisposed genetic risk allele(s) in the familial populations, but little is known about the general population.
- "T1D Metabolic Profile" is based on an algorithm from Electronic Medical Records (EMR) to identify individuals with T1D that have been misdiagnosed with type 2 diabetes T2D: Nearly 40% of adults with T1D are initially misdiagnosed with T2D, leading to ineffective care (ex. high risk of DKA). Machine learning algorithms developed for the detection of undiagnosed or misdiagnosed patients have shown considerable potential to improve patient outcomes through accelerating time to correct diagnosis and treatment.
- Create an overall risk early detection roadmap that includes sequential risk assessment including genetic risk scores, metabolic risk assessment, C-peptide and or proinsulin levels, autoantibody status and other markers that collectively increase the prognostic value while providing an economy of scale to be rolled out in the general population.

Adding new conditions to early detection programs in Public Health practice follows specific criteria first formulated by Wilson and Jungner for the World Health Organization (WHO) over 50 years ago, and later revised. Some but not all the 12 early detection criteria for T1D, which are based on established evidence and arguments for general population early detection, are met but clearly capture the questions to be addressed before widespread adoption of population early detection.

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## Strategy

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.

### Expansion of Screening and Monitoring for T1D Risk

Our near-term goal is to increase adoption of T1D early detection and monitoring for first degree relatives in the clinical setting. Our intermediate goal is to expand adoption of T1D early detection and monitoring to those not covered by existing programs.

This will increase the number of people identified who would be protected from the near- and long-term consequences 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 early detection and monitoring in improving health outcomes while determining the optimal nature, timing, and cadence of these to most efficiently identify and track those at risk.

Consensus development and dissemination will be an integral part of this process. The long-term goal is for T1D early detection and monitoring to be fully integrated into healthcare systems across the globe. The expansion of ongoing general population early detection 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 early detection is based on the presence or absence of islet autoantibodies (AAb) in presymptomatic (Stage 1, Stage 2) T1D. The presence of two or more Aab can predict, with high certainty, the progression to Stage 3 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.

Breakthrough T1D-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 lower cost. Our near-term goals will be to determine the positive predictive value of the available assays and drive the more advanced assays towards commercialization, with a specific focus on point of care systems to drive lower cost and integration into clinical care. 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 risk status and stage, it does not predict well the timing of progression to stage 3 clinical disease. Additional biomarkers are needed to generate more precise time horizons. 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 non-HLA genes as well. 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 metrics derived from continuous glucose measurement devices (CGM), 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 biomarkers 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

In order to integrate early detection and monitoring into healthcare systems, data will be needed specifically for healthcare decision-makers to demonstrate the feasibility, benefits and value of early detection to a health system. The data needed will vary by geography and will most likely need to be generated within a specific geography or healthcare system. Our near-term goal is to generate data and analyses for the feasibility (implementation science), efficacy (ongoing monitoring and reduced DKA at diagnosis), acceptability (minimized psychosocial burden/distress), and health economics of ongoing and future general population early detection efforts to support adoption by healthcare providers, payers and other decision-makers within a health system. Our current early detection efforts are collecting valuable data in various geographies that will inform our future strategy, identify gaps to be addressed and move us closer to implementation.

Roadmap

First Generation	Second Generation	Third Generation	Fourth Generation	Aspirational
<b>Familial early detection</b>	<b>Targeted community early detection</b>	<b>Expanded community early detection</b>	<b>Targeted global early detection</b>	<b>Expanded global early detection</b>
Risk: AAb	Risk: AAb	Risk: Aab +/- genetics	Risk: Aab, genetic, metabolic	Risk: Aab, genetic, metabolic, other
Assay platform: research lab	Assay platform: point-of-care	Assay platform: point-of-care (AAb)	Assay platform: point-of-care	Assay platform: point-of-use
Public Health Benefits: Reduce DKA at diagnosis to < 15 percent	Public Health Benefits: Reduce DKA to < 10 percent	Public Health Benefits: Reduce DKA to < 5 percent	Public Health Benefits: Reduce DKA to < 3 percent	Public Health Benefits: Eliminate DKA
Reach: Familial Risk Groups	Reach: selected geographies	Reach: US health systems	Reach: Restricted global	Reach: Global

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## Current Status

### General Population Early Detection Initiatives

Recent community early detection and monitoring 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 early detection such as the need for health care provider education, the absence of appropriate risk monitoring protocols including psychological support, lack of penetrance into socioeconomically disadvantaged geographies, and early detection 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, our initiative, Breakthrough T1D Early Detection, adopts many of these findings with the goal of providing access to T1D risk assessment to first degree relatives in the near term and the general population in the long-term. Breakthrough T1D Early Detection is a early detection, monitoring, education, and awareness program that clarifies early detection pathways for T1D risk early detection and connects at risk individuals with research opportunities and creates linkages to clinical and virtual monitoring support. Breakthrough T1D research funding has aided the development of AAb assays, awareness and education programs, and post-early detection monitoring protocols that have been incorporated into the real-world evidence setting of our early detection program.

Additional research resources will be used to validate improvements that can be deployed by Breakthrough T1D Early Detection in the future. This initiative continues to be supported with strategic input from Research. In addition to providing access to identifying people who are at risk of developing T1D, this effort includes important aspects of patient and health care provider education to reduce some of the barriers to T1D early detection adoption.

In summary, general population pilot studies provide real world evidence of general population T1D early detection in the U.S. and other countries and provide a key platform for testing of new assay types, generation of cost-effectiveness data, development of T1D early detection 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 early detection. 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 utmost importance to evaluate the relative benefits of inclusion of each of these features on sensitivity and specificity of



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risk assessment protocols with an eye towards improved prognosis and feasibility of implementation.

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 early detection protocols. Diagnosis and effective care of adult-onset type 1 diabetes is challenging due to the complexity of risk factors involved. To reduce misdiagnosis and improve effective care, machine learning algorithms show potential for being translated into early detection guidelines or a clinical decision support tool embedded directly in an Electronic Medical Record (EMR) system. Other recent Breakthrough T1D-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 are 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 early detection and to assess the success of future mitigation strategies.

Breakthrough T1D 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 low cost for current drug development programs.

To address this gap, Breakthrough T1D, 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 commercialization of the current assay platforms and the expert opinion of this group is used to inform Breakthrough T1D priorities in this area.

#### Health System Adoption

Screening for T1D risk, using AAb or other measures such as genetics, is not widely available outside of research programs. It is not routinely prescribed by healthcare providers, systematically covered by payers, or included in any government public health program.

In the U.S., there are two broad policy pathways for adoption of T1D risk early detection and monitoring for the general population.

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One pathway is through direct engagement with the disparate parts of the U.S. delivery system that have influence and the power to implement/support T1D risk early detection and monitoring. Given the fragmented nature of health authority across the U.S. delivery system this pathway will require, among other things, endorsement by entities that establish relevant clinical guidelines (like the American Diabetes Association), public and healthcare provider education, adoption by healthcare providers, and systematic payer coverage.

The second pathway is via public health programs which endorse preventive early detection therapies that are either required by law to be covered by public and private insurance programs or carry such significant clinical authority that they are routinely covered by public and private insurance programs. It is important to note the second public-health pathway is, if appropriate data can be generated, a more direct way to ensure broad public early detection for T1D. However, this pathway is much longer and will likely take many years to complete.

The first pathway highlighted above has a shorter timeframe for impact and can be pursued largely with the datasets currently available. Breakthrough T1D is pursuing both pathways to ensure our short-term goal of expanded early detection is met while we secure our ultimate goal of general population early detection for T1D.

In other countries, health system adoption of T1D risk early detection will be based on the nature and particular policies of the country. This means that the data, strategies, and tactics deployed to achieve coverage and reimbursement for T1D risk early detection in the U.S. may not be viable in other countries.

For example, cost effectiveness data is not required to achieve coverage via public health programs in the U.S. However, it is vital and even required in many countries for access to a new therapy or clinical service. Breakthrough T1D will prioritize research and evidence that can be applicable in more than one country and will pursue health system adoption globally as evidence is available, partnering with other organizations as appropriate.

## Goals and Barriers

Goal: Expand general population T1D early detection 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.
- Full data for T1D early detection focused on the needs of healthcare system adoption is not yet available.
- Participating in T1D early detection may create a psychological burden on the person and their family. Standardized mitigation strategies to assess and address these burdens remain underdeveloped and underutilized.

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The efficiency of diagnosis is currently limited to AAb and needs refinement with other markers that are material to staging diabetes progression.

## 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 our disease-modifying therapies (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 cells that result in loss of beta cell function and cell death, all of which lead to insulin deficiency.

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 cell 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). 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

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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 preservation, proliferation, differentiation from another cell type, or new growth.

Beta cell regenerative therapies that increase the number and function of beta cells provide a curative option for people living with T1D. Regenerative therapies would allow stage three individuals to achieve improved glucose control and eventual 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 and treatment options have transformed quality of life, teplizumab (Tzielid™) remains the sole approved disease modifying therapy for delaying progression to Stage 3 T1D (clinical diagnosis), highlighting a critical unmet medical need. There have been several DMT trials in T1D with positive impacts on disease progression (teplizumab, rituximab, abatacept, golimumab, anti-thymocyte globulin, verapamil, and Gleevec), as well as trials reporting 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 gathering safety and mechanistic data of a variety of therapeutic candidates for T1D has been conducted (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 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 develop antigen, cell, and tissue specific therapies for enhanced safety and efficacy.

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- 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, 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 early clinical testing stages. These efforts will benefit from Breakthrough T1D 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 T<sub>H</sub>17 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 to date, with a mixture of successes and failures; two phase II trials have indeed reported positive outcomes (anti-TNF $\alpha$ , 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 early detection 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.
  - Therapies to improve beta cell survival (Protect beta cells): 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 confirmatory 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 and sustained

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impact on disease. Two other clinical studies (TUDCA, DFMO) are ongoing, and a key determinant of success of all beta cell survival therapies will be the preservation or improvement of C-peptide levels. Breakthrough T1D will provide strategic support in moving therapies currently at a clinical stage closer to approval for T1D, facilitating enhancements to clinical care guidelines, and supporting the continued discovery and preclinical and clinical development of novel survival therapies.

- Combining approaches to increase safety and efficacy (Combination Therapies): Breakthrough T1D has an opportunity to provide leadership and drive the development of therapies able to halt and/or reverse disease by facilitating the advancement of combination therapies. Combinatorial approaches aimed at multiple immune targets or beta cell pathways have the possibility of providing sustained immune rebalancing and/or beta cell protection to halt disease. The pairing of agents aimed at alleviating mechanisms of autoimmunity with those for renewing or regenerating beta cell health and function have the possibility of reversing disease and move the field closure to a cure. With the FDA approval of teplizumab for stage 2 T1D in the US, and potential for approval for stage 3, the assessment of companion therapies to test in combination is of high priority. Breakthrough T1D continues robust discovery, preclinical, and clinical investigation into monotherapies with the appropriate safety and efficacy profiles for consideration as part of a combination. A major component of this work will be to promote the selection of individual agents based upon solid preclinical and clinical data, and the design of effective adaptive trials to test the combined safety and efficacy (similar to the INNODIA master protocol). Furthermore, Breakthrough T1D will lead an effort to develop clinical trial guidelines aimed at promoting the safe and efficacious testing of rational combinations at various stages of T1D with stakeholders.

#### 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 a 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. Breakthrough T1D 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

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three setting, and emerging data suggest that there are certain immune and beta cell derived early signatures that may be required 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/adaptive 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 addition, Breakthrough T1D will promote the use of clinically relevant endpoints such as C-peptide for measuring efficacy with regulators and researchers and the identification of markers of immune modulation as indicators of response to support trial design. Finally, the combination of multiple disease modifying therapies will be explored whenever potential synergies in therapeutic effects are plausible.

## Roadmap

The disease-modifying therapies strategy is 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 based upon the stepwise progression of therapeutic response. It was developed with an understanding of current regulatory and access expectations and also helps to frame and inform how these pathways may need to be optimized to accelerate development and availability of DMTs to benefit people with and at risk for T1D.

The availability and ongoing clinical testing of repurposed agents 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 or early clinical 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.

<b>Delay Progression</b>	<b>Halt Progression</b>	<b>Reverse Progression</b>	<b>Insulin Independence</b>
<b>First Generation</b>	<b>Second Generation</b>	<b>Third Generation</b>	<b>Aspirational</b>
<b>DMT to delay</b>	<b>DMT to halt</b>	<b>DMT to reverse</b>	<b>DMT to cure</b>
Shift toward impermanent immune balance and/or preserve beta cells	Restore sustainable immune balance and preserve/renew beta cells	Restore sustainable immune balance and renew beta cells	Establish permanent immune balance and production of body's own insulin
Slow disease progression at stage 1, 2, 3	Halt disease progression at stage 1, 2, 3	Reverse disease progression at stage 1, 2, 3	Prevent and reverse T1D at any stage of disease
Rate of c-peptide loss reduced	Rate of c-peptide loss reduced (>Gen1)	c-peptide levels preserved/increased	Healthy levels of c-peptide levels preserved/increased
Reduce increase in daily insulin requirements in stage 3	Reduce increase in daily insulin requirements (>Gen1)	Decrease in daily insulin requirements in stage 3	No insulin requirements; Established normoglycemia
Improved CGM metrics in stage 3	Improved CGM metrics (>Gen1) in stage 3	Improved CGM metrics (>Gen2) in stage 3	Negligible T1D incidence
Delay stage transition in stages 1 and 2 (2-4 yr)	Prevent stage transition in stages 1 and 2 (4-8 yr)	Prevent stage transition in stages 1 and 2 (>10 yr)	Permanently prevent stage transition in stages 1 and 2

Central to defining therapeutic concepts of disease modifying therapies for T1D is the risk/benefit ratio of candidate immune and beta cell survival and 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. For example, to further inform risk benefit assessments by the regulators, Breakthrough T1D is launching a patient preference study to provide well designed, quantitative, and qualitative data, on patient preferences for cures therapies in T1D. 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 BREAKTHROUGH T1D'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.



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## 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 ultimately product approval.

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

To this end, the continuation of coordinated efforts with others in the autoimmune disease community to accelerate research and discovery of common mechanisms of disease and the generation of new insights for novel therapeutic approaches remains a priority. The identification of targets for disease modification and the development of subsequent therapies requires continued exploration of the immunological, histological, viral, and metabolic factors contributing to disease development and progression.

The Network for Pancreatic Organ Donors with Diabetes (nPOD), a flagship BREAKTHROUGH T1D program to procure, characterize, and disseminate samples from cadaveric organ donors has been a cornerstone for the study of T1D biology and endotyping disease heterogeneity. Investigators working with nPOD samples continue to advance the field and challenge longstanding dogmas of how type 1 diabetes develops, making this program an important part of the disease modifying therapy strategy.

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, most notably the approval of the first DMT in the U.S., Tzield for stage 2 disease.

In addition, positive clinical trial outcomes for stage 3 patients have been reported for anti-thymocyte globulin (ATG), Anti-IL21 combined with liraglutide, GAD-Alum (for patients expressing HLA DR3-DQ2), Verapamil, and Gleevec. 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.

## Autoreactivity Disabling Therapies

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Several T<sub>H</sub>17-directed therapies have been clinically tested in T1D and shown to slow the loss of beta cell function, and teplizumab has been approved for delaying the onset of T1D in stage 2 individuals. Importantly, there remains a need to develop autoreactivity-disabling therapies with increased safety and efficacy. This may occur via development of new therapeutics specifically for T1D as the primary indication (e.g., an alefacept biosimilar, humanized ATG, etc.) or through realignment of approved therapeutics or ones in clinical development for other autoimmune disorders, such as anti-CD40L. In parallel, supporting the development of tissue-targeted therapies and next generation therapies to disable autoimmunity will increase upon the safety and efficacy of first-generation therapies.

#### Regulation Enhancing Therapies

Several Treg enhancer therapies have been tested in T1D with positive safety profiles, but with modest efficacy. These include polyclonal Treg therapies and therapies that have involved tolerizing with whole proteins or specific peptides from pro-insulin. Improvement in regulation enhancing therapies will likely require improved tissue targeting, antigen and receptor specificity, and/or more refined approaches, such as the use of 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 carrying disease relevant antigens and other desired cargo such as anti-inflammatory substances to actively induce tolerance. Several early TDSs are in early clinical testing in other autoimmune disease indications and in preclinical development for T1D. The challenges in the development of these moieties include complex manufacturing considerations and a need to identify the best preclinical model(s) to inform the choice of cargo for best outcome.

The attractive potential of TDS for stages one and two of disease is their potential sufficiency as a monotherapy with an enduring effect in delaying disease progression. It is expected that the efficacy of this therapeutic class in stage three disease may be maximized in a combination therapy setting, where autoreactivity is disabled first.

#### Anti-Inflammatory Therapies

Many, if not all, autoimmune diseases involve elevated levels of inflammatory immune mediators, which target cell stress and destruction. 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 disease by slowing progression and preventing further deterioration of symptoms in rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), and other autoimmune diseases. These approved agents are attractive candidates for testing in T1D.

Identifying ways to rapidly evaluate the treatment/therapeutic effects of such drugs would accelerate the evaluation of their candidacy alone or in combination. 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. Further investment of resources and innovative strategies is required for identifying DMT candidates.

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### Beta Cell Regenerative Therapies

Beta cell regenerative agents, specifically those targeting proliferation, are in 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, neogenesis and apoptosis/necrosis 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.

### Beta Cell Survival Therapies

Agents designed to prolong beta cell survival and enhance beta cell protection in the face of autoimmune attack are in pre-clinical and clinical development. Prolonging beta cell survival and function, as measured by extended maintenance of C-peptide levels, have the potential to provide significant benefits towards individuals in the early stages of T1D.

Examples of this positive benefit are by extending the honeymoon period, decreasing or eliminating the need for exogenous insulin, and by complementing therapies aimed at inducing immune tolerance. Recent clinical results have shown a positive impact on delaying the loss of insulin production in stage three disease. Additional efforts are ongoing to expand these findings into broader groups and stages of T1D, along with being evaluated in combination with immune therapies. BREAKTHROUGH T1D will continue to provide strategic support for these therapies at the clinical stage and support preclinical and clinical development efforts for novel survival therapies.

### 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.

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## Clinical Development

Several ongoing activities are focused on optimizing the clinical development pathway for DMTs. There are inconsistencies in how C-peptide can currently be used in drug development programs for DMT. To facilitate its critical use as an efficacy outcome and accelerate development, Breakthrough T1D is working with the community, including regulators, through scientific workshops, leading a multi-stakeholder effort to update the consensus around C-peptide and funding a recent analysis of the TOMI dataset, with Diabetes UK, that supports and validates the clinical meaningfulness of C-peptide preservation.

Additionally, Breakthrough T1D has also been working to qualify a set of biomarkers, islet autoantibodies, used to define the earliest stages of T1D with a consortium of patient organizations, academic investigators, and industry, under the leadership of the Critical Path Institute. They received qualification as enrichment markers from the EMA in 2022 and FDA published their viewpoint on their utility as enrichment markers in *Diabetologia* in 2023.

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 immunology field. To that end, Breakthrough T1D will support efforts to clinically test rational combinations of available agents in T1D. Breakthrough T1D 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. This also requires a thoughtful approach to ensure a smooth regulatory pathway. Breakthrough T1D will commit strategic efforts to facilitate such movement, including the support of novel and nimble approaches for clinical testing of combination DMTs.

## Access Considerations

Based on the response to the launch of Tziel and what we are seeing for these types of therapies to treat other diseases, we expect that DMTs for T1D will be covered by commercial insurers and government programs like Medicare and Medicaid.

Elements that are often required and will help accelerate coverage in the U.S. include FDA approval, available clinical guidelines that are in accordance with the FDA approved label, and published data on efficacy and safety.

We are actively monitoring the broad landscape of DMT coverage to understand what will be optimal for T1D therapies. To help ensure timely and affordable access for T1D therapies, we are working with clinical partners, payers, and policymakers who establish rules governing Medicare and Medicaid, to provide education and raise awareness about the innovative research in T1D DMTs.

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The goal of these efforts is to reduce the knowledge gap among these key decisionmakers and shorten the time from FDA approval to coverage. We recognize that access in non-U.S. countries may require additional data to be provided, such as cost-effectiveness. We will continue to work with our global network of affiliates, clinical partners, industry, and non-U.S. policymakers to develop and evolve our strategy as DMTs near the market to ensure that everyone who could benefit from these therapies has timely and affordable access.

## Goals and Barriers

Breakthrough T1D aims to support development of single or combinatorial therapies that alter disease course in all stages and ages of T1D alongside the creation of clinical trial guidelines for testing and regulatory considerations. As BREAKTHROUGH T1D leads 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

- A need for a larger pipeline of differentiated and next-GEN/targeted DMTs in late preclinical development and in first-in-human (FIH) studies.
- Targeted drug delivery systems are not yet ready to enable movement of GEN 2 therapies into the clinic.
- Safety remains a consideration for DMTs - both for immune as well as beta cell targeted therapies.
- A strategy must be developed and implemented to identify which therapeutic targets and drug combinations will be most efficient.
- A lack of validated early surrogate endpoints of efficacy (within three to six months of treatment), including markers of response to immune-based therapies, to enable rapid testing of disease modifying therapies in stage two or stage three of disease.
- A lack of understanding of disease progression, and hence DMT strategies, in adult-onset T1D that accounts for ~50 percent incidence.
- Significant disease heterogeneity underscores a need to endotype disease toward development of personalized medicines.
- A need to reduce barrier-to-entry for drug developers for commitment toward DMT therapy development.

### Inefficiencies Within Preclinical and Clinical Therapeutic Development

- A need to recognize the specific value and limitations of preclinical models and implement research approaches with physiological relevancy to human islet and immune biology whenever possible/appropriate.
- A 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.
- A lack of efficiencies within clinical trial designs for rapid proof-of-mechanism and proof-of-concept testing to facilitate single and combination agent(s) treatments. This includes

slower progress towards utilization of adaptive trial designs such as those that have been successful in oncology.

- A lack of full acceptance of C-peptide as an efficacy outcome by regulators
- A need for clinical consensus on the clinical trial pathway to allow for facile drug development and regulatory advisement/approval.

## First Generation

Properties	First Generation: DMT to delay disease progression
<b>Primary Product Indication</b>	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.
<b>Target Population</b>	Stage two and three adults and pediatrics; possible extension to stage one if exceptionally safe and efficacious
<b>Features</b>	Single agent
<b>Efficacy</b>	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
<b>Risk/Side Effect</b>	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.
<b>Therapeutic Modality</b>	Biologics, cell therapy, small molecules

## Second Generation

Properties	Second Generation: DMT to halt disease progression
<b>Primary Product Indication</b>	Stop disease progression from time of therapy. <i>Stop</i> C-peptide decline in stage three. Stop progression to insulin dependence from stage two.
<b>Patient Population</b>	Stage three then stage two adults with step-down development into pediatrics; possible extension to stage one if exceptionally safe and efficacious
<b>Features</b>	Multiple agent
<b>Efficacy</b>	Prevent increase in insulin needs and with less rise and greater durability than monotherapies; maintain stage two or stage one of disease indefinitely, improve QoL>Gen 1
<b>Risk/Side Effect</b>	No significant short-term morbidity and minimal risk of increased infection.
<b>Therapeutic modality</b>	Drug, biologic, or cell therapy

## Third Generation

Properties	Third Generation: DMT to reverse disease progression
<b>Primary Product Indication</b>	Reverse disease progression at all stages of disease. Increase c-peptide levels with sustained therapy.
<b>Patient Population</b>	Stage three then stage two adults with step-down development into pediatrics; possible extension to stage one or earlier if exceptionally safe and efficacious
<b>Features</b>	Multiple agent
<b>Efficacy</b>	Lower insulin needs in stage three with durability greater than or equal to Gen2, reverse stage two to stage one or earlier, improve QoL >Gen2, prevent progression to or from stage one
<b>Risk/Side Effect</b>	No short-term morbidity and minimal risk of increased infection
<b>Therapeutic modality</b>	Drug, biologic, or cell therapy

## Aspirational

Properties	Aspirational: DMT to cure T1D
<b>Primary Product Indication</b>	Subjects at all stages of disease: <ul style="list-style-type: none"> <li>• Completely prevent or reverse the autoimmune disease process; restore</li> <li>• endogenous insulin secretory capabilities</li> </ul> Remove insulin dependence and prevent progression to insulin dependency
<b>Patient Population</b>	All stages of disease
<b>Features</b>	Simple, least invasive, highly feasible therapy
<b>Efficacy</b>	Achieve/maintain complete insulin independence, maintain euglycemia, ideal QoL
<b>Risk/Side Effect</b>	Negligible
<b>Therapeutic modality</b>	Drug or biologic

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# Cell Therapies

## 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 or pancreas transplantation, a cell/organ-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 chronic systemic 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



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implantation sites, may address the limitations that restrict the 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 many 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 a 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 Breakthrough T1D's strategies to find cures for T1D. Today, while a beta cell replacement product is not commercially available, there are a variety of promising approaches in preclinical validation and early clinical evaluation.

While lines of investigation have historically focused 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 that coaxes the host immune system to accept grafts and eliminates the need for 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.

Breakthrough T1D'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 or burden associated with broad immune suppression. Additionally, we will continue supporting the discovery

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and 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.

To help achieve the mission of the Cell Therapy project to accelerate the development of cell replacement therapies for T1D, the goals, strategy, and roadmaps are developed taking into consideration what will be needed to commercialize these types of products. This involves an understanding of the current regulatory expectations, what may need to change to optimize the regulatory pathway and what payers will require to cover these types of products.

#### Priorities

In order to deliver on these products, Breakthrough T1D’s Cell Therapy project is prioritizing the following areas of research:

- Late preclinical and early clinical research on cell dose optimization and 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.
- Development and validation of tools for non-invasive monitoring of biological factors and processes that play a key role in the success of beta cell replacement therapy.
- Increasing access to clinical grade iPSC cell lines compatible with beta cell differentiation to bolster the ecosystem and enable clinical development of other components of combination products.

Establishment of research- and clinical-grade stem cell resources to aid in the development and execution of late preclinical and early clinical studies.

The development of beta cell replacement therapies entails overcoming a variety of challenges in 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 our 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.

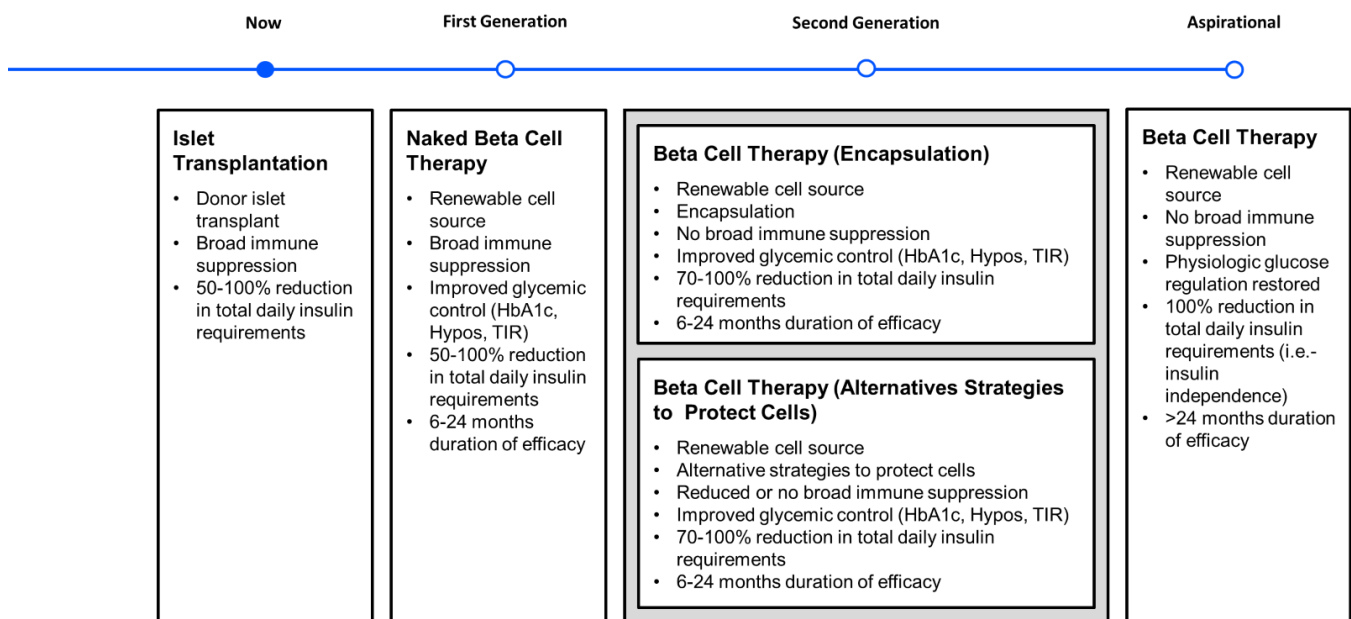
## Roadmap

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 and beta cell biology, immunology, gene editing, regenerative medicine 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 will need 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 intraportally like in CIT, or in an open scaffold or device which will be protected by standard, broad immune suppression. The development of second generation and aspirational products will focus on strategies to deliver insulin-secreting cells from a renewable source with reduced or no broad immune suppression, respectively.

While encapsulated cell therapies are a promising pathway towards providing insulin independence, alternative approaches under development include the use of targeted immune modulation strategies to induce graft tolerance as well as the generation of genetically modified cells that can evade immune detection and/or resist metabolic stress. The research is early and advancing multiple next generation strategies in parallel provides increased potential for success in the development of a cell therapy product that restores glucose control and delivers insulin independence without the need for broad immune suppression.



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## 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 while also optimizing the regulatory and access pathways. Recent advances in cell therapy have positioned cells derived from human embryonic stem cells (hESC) and human adult 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 with T1D. In the long term, the goal is to provide immune protection to these cells without the use of broad immunosuppression.

### 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 or other non-endocrine cells will need to be incorporated to generate a complete and functional cell replacement product. Development of stem cell-based 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 primary cadaveric islets such that safety, 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- and iPSC-derived pancreatic progenitors and functional surrogate beta cells as potential commercial beta cell replacement products. Nevertheless, limited access to clinical grade iPSC lines that are amenable to differentiation into beta cells hinders further development of beta cell replacement products and must be addressed to invigorate the field. Additionally, BREAKTHROUGH T1D 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. While much work remains, it is encouraging to see some of these cell preparations already being tested in early clinical trials with promising results.

### Xenogeneic Islets

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Pig and human insulin are almost identical in sequence (one amino acid difference) and pig insulin was safely used to treat T1D for decades globally before recombinant DNA technology and manufacturing capabilities enabled the large-scale production of human insulin and is still being used in some countries (OUS) for individuals intolerant to recombinant 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, overcoming the concerns over transmission of porcine endogenous retroviruses (PERVs) from the pig genome, and 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. While BREAKTHROUGH T1D will continue to prioritize research on development of beta cell replacement products that use porcine islets as a renewable source of cells, an opportunistic approach will be pursued where investments will focus on supporting mature research in late preclinical or clinical stages of development.

#### 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,

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maximizing diffusion of oxygen and nutrients. At the present time, BREAKTHROUGH T1D is supporting both approaches to better understand the potential benefits and liabilities of each approach.

#### Scaffolds (Open Devices)

Breakthrough T1D 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).

#### Commercialization Drivers

While there are many considerations to ensure commercialization readiness of a novel type of therapy, two of the main drivers are the pathway to regulatory approval and prospects for healthcare access. Therefore, BREAKTHROUGH T1D seeks to optimize both of these areas to accelerate the development and availability of cell replacement therapies for T1D.

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The current regulatory pathway for T1D cell replacement products has largely been defined through the experience of CIT and will need to evolve as more knowledge and experience with this kind of therapy is gained. To guide those conducting research and developing products, FDA has issued guidance documents that provide their general thinking in areas of preclinical, early clinical considerations and manufacturing for cell and gene therapies. They have also provided their thinking on CIT in a September 2009 guidance document entitled “Considerations for Allogenic Pancreatic Islet Cell Products.” To keep regulators up to date on this evolving area of research, BREAKTHROUGH T1D has hosted a seminar series with researchers presenting to FDA staff on scientific and technological developments in cell therapies for T1D since 2007. To further add to this foundation, BREAKTHROUGH T1D is conducting a patient preference study to provide well designed, quantitative, and qualitative data on patient preferences for cures therapies in T1D to help inform the benefit-risk decisions that regulators make. We are also continuing to work with regulators to incorporate newer outcomes, like CGM metrics and specifically time in range, into development programs and performing an assessment of patient reported outcome (PRO) measures used in drug development to understand the gaps and build a strategy to support their routine use in drug development programs.

As novel cell and gene therapies become available, coverage and reimbursement pathways and mechanisms are being adapted and developed to accommodate them. Based on what we are seeing for these types of therapies to treat other diseases, we expect that cell replacement therapies for T1D will be covered by commercial insurers and government programs like Medicare and Medicaid. Elements that are often required and will help accelerate coverage in the U.S. include: FDA approval, available clinical guidelines that are in accordance with the FDA approved label, and published data on efficacy and safety. We are actively monitoring the broad landscape of cell and gene therapy coverage to understand what will be optimal for T1D therapies. To help ensure timely and affordable access for T1D therapies, we are working with clinical partners, payers, and policymakers who establish rules governing Medicare and Medicaid, to provide education and raise awareness about the innovative research in T1D cell replacement therapy. The goal of these efforts is to reduce the knowledge gap among these key decisionmakers and shorten the time from FDA approval to coverage. We recognize that access in non-U.S. countries may require additional data to be provided, such as cost-effectiveness. We will continue to work with our global network of affiliates, clinical partners, industry, and non-U.S. policymakers to ensure that everyone who could benefit from these therapies has timely and affordable access.

## 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. BREAKTHROUGH T1D’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 of cells remain to be determined.
- Durability of glycemic and other benefits remains unknown.
- Poor cell survival, engraftment and function due to poor vascularization and lack of oxygen immediately following implantation.
- Lack of full acceptance of CGM metrics, including time in range, within the regulatory process

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 immune responses towards implanted cells.
- 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.
- Limited access to clinical grade iPSC lines that are amenable to differentiation into beta cells
- Lack of clinical consensus on the clinical trial pathway for development of products
- Novel types of products that may require new types of coverage and reimbursement mechanisms
- Expansion into T1D populations beyond the initial limited cohort of individuals with hypoglycemia unawareness or autonomic failure to accelerate development and incentivize commercial investment.

## Therapeutic Concepts

Based on the landscape of current therapies for T1D, what is currently known about the benefits of islet and pancreas transplantation, and an understanding of current regulatory expectations, 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. These therapeutic concepts also help to frame and inform how the



regulatory and access pathways may need to be optimized to accelerate development and availability of products to benefit people with T1D.

## First Generation

Properties	First Generation: Naked Beta Cell Therapy
<b>Primary Product Indication</b>	Reverse life-threatening hypoglycemic unawareness Restore glucose control in insulin-dependent diabetes
<b>Target Population</b>	Adult T1D patients who suffer from hypoglycemia unawareness (HU) or hypoglycemia associated autonomic failure (HAAF), with unstable diabetes
<b>Features</b>	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Duration: 6-24 month
<b>Efficacy</b>	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
<b>Risk/Side Effect</b>	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)
<b>Primary Product Indication</b>	Reverse life-threatening hypoglycemic unawareness Optimally restore physiological glucose regulation
<b>Patient Population</b>	Poorly controlled T1D Established T1D Insulin-dependent T2D
<b>Features</b>	hSC-derived beta cell source or porcine islets Minimally invasive surgery Retrievability for stem cell-based preparations preferred Duration: 6-24 months
<b>Efficacy</b>	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 $\geq 1$ year
<b>Risk/Side Effect</b>	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)
<b>Primary Product Indication</b>	Reverse life-threatening hypoglycemic unawareness Optimally restore physiological glucose regulation
<b>Patient Population</b>	Established T1D Insulin-dependent T2D
<b>Features</b>	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
<b>Efficacy</b>	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 $\geq$ one year
<b>Risk/Side Effect</b>	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
<b>Primary Product Indication</b>	To fully restore physiological glucose regulation
<b>Patient Population</b>	Established T1D Insulin-dependent T2D
<b>Features</b>	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 $\geq$ 24 months
<b>Efficacy</b>	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 $\geq$ two years

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<b>Risk/Side Effect</b>	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
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