

Beta Cell Regeneration

Vision

The JDRF Beta Cell Regeneration Program aims to halt the progression of type 1 diabetes and ultimately achieve a cure for type 1 diabetes (T1D) through the development of disease-modifying therapies (small molecules and/or biologics) that promote the survival, function, and regeneration of endogenous insulin-producing beta cells.

Mission

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

1. **Beta cell survival therapy** to halt disease progression. Halting the loss of insulin producing cells in those recently diagnosed or living with established T1D will result in improved glucose control and reduced risk of complications. Halting disease progression in stage 1 or 2 has the potential slow or stop progression and prevent T1D onset and insulin dependence either alone or with concomitant immune therapies. Improving beta cell survival in stage 3 disease will enable the protection of residual beta cell mass and any newly regenerated or implanted beta cells, improving glycemic control and long-term outcomes.
2. **Beta cell regeneration therapy** to restore the numbers and function of beta cells lost during the progression of T1D. Human beta cells do not readily renew after injury and deficient beta cell function is a feature observed very early in the disease process that persists throughout disease. In order to reverse the loss of beta cell mass and function, beta cell regenerating therapies will be needed. Even modest gains in beta cell mass and function will improve glucose control and reduce complications in those living with T1D. Regeneration therapies have the potential, likely in combination with immune and/or survival therapies, to restore insulin independence and cure T1D.
3. **Enable clinical development** by driving innovative trial design paradigms and discovering and validating biomarkers to non-invasively detect beta cell stress, death, mass, and function. These efforts may also yield a better understanding of fundamental disease mechanisms that can inform on appropriate treatment regimens.

As T1D pathogenesis involves multiple factors (beta cell, immune cell, genetic, environmental), a multi-pronged approach involving efforts from JDRF's Beta Cell Regeneration, Immunotherapies, Prevention, and Replacement Programs will be required to ultimately prevent and cure T1D.

Rationale

There are currently no therapies available that address the causes, drivers, or underlying pathology of T1D. The only therapies currently approved for T1D address insulin replacement, blood glucose monitoring, insulin action, and organ transplant. Type 1 diabetes is characterized as the progression towards and state of insulin deficiency caused by an immune mediated loss of functional insulin producing beta cells. During this process various factors (genetic, environmental, immune), either alone or in combination, induce a state of stress in the beta cell that result in loss of beta cell function and cell death, both leading to insulin deficiency and a life-long dependence on insulin replacement therapy.

2 recent POC clinical trials show that beta cell survival therapies can halt or delay T1D progression

Therapies that directly modify beta cell biology can stop the loss of function and number of insulin producing cells that occurs in T1D and increase their number when they have been lost. Recent studies suggest that impairment of beta cell function is an early feature of disease pathogenesis while a decrease in beta cell mass occurs more closely to clinical manifestation. Beta cells are not merely passive victims in the development of T1D, but pathological beta cell stress occurs very early in the course of T1D and plays a role in the loss of beta cell function and mass in T1D, conceivably by triggering or potentiating the beta cell-specific autoimmune response. The dynamic nature of the beta cell population continues to be revealed. In the healthy pancreas, this population is heterogeneous in both function and phenotype- exhibiting fluctuations in levels of insulin secretion and endoplasmic reticulum stress, for example. This program has and continues to support research to discover and intervene in these beta cell intrinsic pathways.

Beta cell survival therapies will **delay** and **halt** the progression of T1D in all stages of the disease – preserving insulin independence for individuals with no beta cell loss (stage 1), preventing insulin dependence in those with asymptomatic loss of beta cell mass (stage 2), and maintaining residual beta cell mass in those already insulin dependent (stage 3). Survival therapies will also have utility in protecting regenerated or replaced beta cell mass as part of these strategies to achieve insulin independence. Beta cell survival therapies are intended to nurture and protect the cells' number and function as they experience the stressors unique to T1D. Success of these therapies will depend on population screening efforts driven by the Prevention program and complementary therapeutic strategies being developed in the JDRF Immune Therapies and Replacement programs. Recent clinical findings have bolstered the validity of approaches to enhance beta cell survival. Separately, both Gleevec and Verapamil were shown to delay or slow the loss of insulin production in stage 3 adults, improve their glucose control, and reducing the incidence of diabetic ketoacidosis. Whether beta cell survival therapies will provide an added benefit when combined with immune or replacement therapies is yet to be determined.

Loss of beta cell function occurs early in the T1D disease process and precedes the loss of beta cell mass. In addition, dysfunctional beta cells can be found in many people with longstanding T1D. Inappropriate hormone processing, cellular senescence, and other indicators of diminished beta cell function have all been recently described to occur in the T1D prodrome. Strategies to improve beta cell function will need to be incorporated into approaches tailored towards increasing beta cell mass. Functional and dysfunctional beta cells can be detected prior to diagnosis and 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 increase beta cell mass- either through proliferation, differentiation from another cell type, or new growth. This program has and continues to support the discovery of and validation of pathways to increase beta cell mass as well as to reveal novel pathways that influence beta cell function. Beta cell survival and beta cell regeneration therapies, combined with appropriate immune therapies, will be necessary to alter the course of T1D to prevent, halt, and cure T1D.

Beta Cell Regeneration therapies would provide a non-invasive curative option for people living with T1D by providing therapeutics that increase the number and function of a person's own remaining beta cells. There are two strategies to cure the beta cell deficiency in T1D: 1) implant insulin producing cells into the individual (Beta Cell Replacement) or 2) treat the individual with agents that increase the number and function of insulin producing cells in their body (Beta Cell Regeneration). The relative benefits and liabilities of Beta Cell Replacement are discussed as part of JDRF's Replacement strategy. Regenerative therapies would allow stage 3 individuals to achieve improved glucose control and eventually insulin independence. They would also replenish beta cell mass and/or improve residual cell function in stage 2 individuals preventing onset of insulin dependence. Both Beta Cell Regeneration and Replacement strategies will need to be combined with a strategy to combat the auto- or transplant directed- immune response against the beta cell.

Testing of beta cell directed (and other curative) therapies in T1D has been reliant on a single clinical trial design and a single clinical outcome – preservation of meal stimulated insulin secretion 1 year after the start of an intervention. This makes testing of candidate therapies expensive and prolonged and highlights a need to better **enable clinical development** of therapies. Innovating on this standard trial design paradigm will be required to expedite the bench to bedside transition of novel therapeutic approaches. Recent application of ‘platform’ trial designs, combination treatment regimens, novel patient populations (e.g. testing of agents in the most clinically relevant patient population (stage 2 versus stage 3)), and novel therapeutic readouts aim to address this gap. The INNODIA consortium, for example, plans to utilize a multi-site platform trial design reliant on a common control group to greatly increase the efficiency, enable combination drug approaches, and reduce the cost associated with testing therapies in T1D. Several groups are pursuing novel patient populations and unique metabolic measures to address this need. Similarly, the application of continuous glucose monitoring devices in T1D trials may provide a useful and early measure of drug efficacy for those agents that, by maintaining or increasing beta cell mass, result in an improvement in glucose control.

Strategy

The priorities of this program are to develop therapies to preserve beta cell mass and function at all stages of T1D and to restore insulin production after onset of T1D. Focusing on findings from human beta cells and human T1D, we have identified and continue to support two critical therapeutic classes to address these goals- survival and regenerative therapies. Strategies common to these two classes of therapies are as follows:

- Discovery and validation of pathways and targets in human beta cells stemming from knowledge of human biological processes specific to type 1 diabetes
- Early partnering of academic and industry groups to accelerate preclinical drug development
- Clinical testing and generation of proof of concept data to enable partnering activities and, when available, the use of repurposed drugs to allow for early entry into clinical testing
- Reliance on core academic or private laboratories to efficiently generate partner ready preclinical data packages

Beta Cell Survival Therapies

As a priority, this program continues to support research to identify and validate novel pathways modulating beta cell survival. A particular focus is to support the generation of data packages that would allow for partnering and further preclinical and clinical development with biotechnology or pharmaceutical company partners. The availability of repurposed drug candidates has resulted in multiple ongoing clinical trials and others awaiting appropriate partnering. These have begun to report and demonstrate efficacy in preserving insulin production in stage 3 adults. In these situations, the program’s focus has been to support appropriate follow on studies (expansion, other ages, other stages) in collaboration with large T1D trial consortia and with input from regulators and regulatory experts, so as to ensure these continue to move towards drug approval. It should be noted that repurposing of drugs from other indications can be hindered by accessibility issues. JDRF, through the generation of partner ready preclinical data packages with such agents and advocacy for the clinical need for such agents strives to address such accessibility issues with the owners of such assets when possible.

Beta Cell Regeneration Therapies

Discovery work in regeneration of beta cell mass and function has yielded a number of novel targets in the areas of proliferation, neogenesis, and transdifferentiation. This program will continue to support discovery work to provide additional drug targets in this area, leveraging industry collaborations when available. In addition, we will continue to validate appropriate model systems (such as stem cell derived beta cells) that will enable more efficient preclinical testing of candidate regenerative agents. Lastly, therapies that 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 to specifically deliver such drugs to the islet or beta cell.

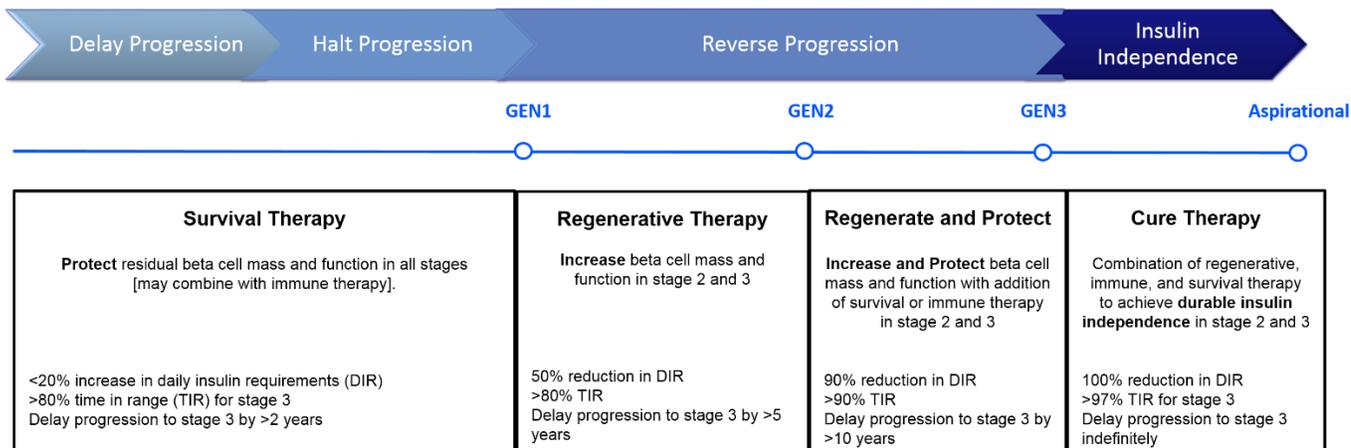
Enabling Clinical Development

In parallel with its therapeutic objectives, the JDRF Beta Cell Regeneration Program has also prioritized the need to enable clinical development of beta cell-directed therapies to allow for more efficient testing of these therapies. This includes efforts to test innovative clinical trial designs as well as the discovery and development of biomarkers of beta cell function and mass. Earlier detection of beta

cell dysfunction will enable earlier diagnosis of T1D, improve disease staging, and aid in the design and execution of more efficient and effective clinical studies by allowing selection of target subject groups as well as providing more specific endpoints. The JDRF Beta Cell Regeneration Program is initially focusing on: (1) the validation and development of biomarkers of early beta cell stress, death and dysfunction; (2) the discovery of markers of beta cell mass and function; and (3) the testing of novel clinical trial paradigms.

Roadmap

Our clinical goals are based upon the characteristics of those currently living with T1D with the goals of halting and reversing T1D progression to restore and/or preserve insulin independence. The roadmap below describes a path towards the ultimate goal of preventing and curing T1D. Based on recent success in proof-of-concept studies using repurposed survival therapies (Gleevec; Verapamil) we feel that Gen 1 therapies are achievable in the near term using currently available drugs. Later generations rely on discovery and development of novel regenerating therapies and combination approaches that employ survival, regenerating, and immune therapies. Later generations will increase durability, efficacy, and patient reach to ultimately achieve durable insulin independence at all stages.



Current Status

To date, no approved therapy exists to specifically preserve or increase beta cell mass in any stage of T1D. However, recent clinical findings have shown for the first time that beta cell survival therapies are capable of halting or slowing the loss of insulin production that occurs after diagnosis. These particular repurposed agents are moving towards repeat or expansion studies while we await the first trials with novel survival therapies. Beta cell regenerative agents, specifically those targeting proliferation, have been developed and are in the late preclinical development to improve their safety profile. Much of the focus of this therapeutic area is devoted to discovery and validation of other pathways to increase beta cell mass and function.

Beta Cell Survival Therapies and Repurposing of Drugs from Other Indications

JDRF-supported studies have been pivotal in demonstrating the role of the endoplasmic reticulum stress response and closely linked oxidative stress response as likely causes in the initiation and progression of T1D and have identified key regulators of the process. As a result of these efforts, a number of pathways have been identified where there are existing drugs, approved for different indications, which have beneficial effects on beta cell survival. Trials using Gleevec or Verapamil have reported positive results- halting or delaying the loss of insulin production in stage 3 adults. Current activities have been devoted to ensuring these findings are repeated and expanded into additional ages and stages of T1D and in combination with appropriate immune therapies. Three other clinical studies (TUDCA, DFMO, GABA) are ongoing.

Beta Cell Regenerative Therapies

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/insulin resistance, and pregnancy in the adult. Increasing knowledge of the mechanisms regulating the physiologic expansion of beta cells is providing insight into potential pathways and targets for therapies to restore 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, transdifferentiation, plasticity, and neogenesis may all contribute to this heterogeneity. Current discovery and validation efforts based on these recent works aim to generate novel targets for increasing beta cell mass and function. Clinical studies with first generation regenerative agents (GABA) are ongoing and will report in the next few years.

Targeted Delivery of Beta Cell Therapies

Recent advances have led to the discovery of several small, drug-like molecules that are capable of driving human beta cell replication. However, none of these molecules act on pathways that are sufficiently selective for the beta cell. Achieving sufficient beta cell selectivity and an appropriate safety margin for beta cell regeneration therapies may require the use of targeted delivery approaches. Cell-selective targeted drug delivery has advanced considerably in recent years, particularly in the oncology setting, raising the possibility of adapting such technology for use in T1D. In the past year, 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. Validation of these findings are ongoing yet there still exists a need to develop additional strategies. These targeted delivery strategies have the potential to improve the safety profile of multiple classes of drugs: regenerative, survival, and immune.

Enabling Clinical Development

Biomarkers of Beta Cell Stress, Death and Dysfunction

Mounting evidence suggests that beta cell stress, dysfunction, and loss occur at the earliest stages of T1D development. Sensitive markers of these would enable improved understanding of pathogenic mechanisms, improved staging of T1D, identification of patients likely to benefit from beta cell survival therapies, and could serve as endpoints in clinical proof-of-mechanism studies. A number of candidate markers of beta cell stress and death have been proposed in recent years. Current efforts are focused on clinical validation of candidate markers and assay development. Inappropriate hormone processing is a direct result of beta cell stress. Circulating levels of proinsulin or proIAPP are readily detectable in patients with undetectable levels of stimulated c-peptide secretion. Circulating proinsulin can also be found in the circulation of those in stage 1 and 2 of T1D. Such biomarkers may provide powerful tools to better identify those at risk of progressing to insulin dependence or to determine the effect of therapies directed at improving beta cell survival or function.

Circulating Biomarkers and Imaging of Beta Cell Mass and Function

Non-invasive biomarkers that accurately and sensitively measure beta cell mass and function would provide the ultimate measure of T1D progression and effectiveness of disease-modifying therapies. To this end, we have pursued the discovery and validation of circulating biomarker as well as imaging approaches to measure beta cell mass. Imaging approaches have long been pursued as the ultimate direct measure of beta cell mass. However challenges such as the anatomic depth of the pancreas, relatively low number and wide distribution of beta cells within the pancreas, and the dearth of beta cell-selective imaging probes have stymied the field. Multiple groups are performing proof of concept imaging studies with candidate beta cell tracing agents and should present results in the next few years. Preclinical and early clinical findings from such imaging studies have demonstrated that beta cell mass and function do not perfectly correlate. The combination of beta cell imaging technologies and available metabolic testing will offer a powerful approach to measure therapies that may impact mass or function or both. MRI of the pancreas, while not directly informative on beta cell mass, has recently been shown to track with T1D disease progression; the pancreas volume is reduced at diagnosis and continues to decline after. This may prove to be a useful tool to assess risk or report on therapeutic efficacy and current efforts are focused on generating and dissemination of standard operating procedures for this tool.

Improving Clinical Trial Design

Despite the ability to rapidly advance some candidates to the clinic, current clinical testing approaches due to patient heterogeneity, current surrogate endpoints, and duration of trials, do not allow efficient mechanism-driven testing of beta cell-directed therapies. Current work is probing whether certain defined patient populations would allow for more efficient proof of

concept testing. Platform trial designs also aim to address this lack of efficiency in T1D clinical testing but this has yet to be demonstrated empirically and will be employed in the coming year.

Critical Gaps

■ Launching a First Gen Therapy

1. Survival Therapy

The availability of repurposing opportunities has greatly accelerated this program. Advancing successful candidates to and through clinical testing is of high priority.

- **Repurposing of Drugs from other Indications**
 - Preclinical and clinical testing of repurposing candidates for beta cell survival therapies and the advancement of drug discovery projects towards preclinical and clinical development.
 - Progressing successful clinical candidates through multiple ages and stages of T1D.
 - Assessing the durability of their clinical effects.
 - Determining if immune agents will be needed in concert to durably halt progression.
- **Identification and Development of Novel Targets**
 - Focused on understanding of the pathological events and responses that drive beta cell loss in T1D.
 - Generating preclinical data packages for partnering and future clinical development.
 - Establishing partnerships to sponsor commercialization of agents on patent.
- **Dual Immune and Beta Cell Therapies**
 - Advancing potential therapeutic targets into drug discovery projects and towards preclinical and clinical development.
 - Establishing partnerships to sponsor commercialization of agents on patent.

2. Regenerating Therapies

Beta Cell Regeneration Program supports two major approaches to increase beta cell mass and function as well as the development of technologies to allow the targeted and selective delivery of therapeutics to human beta cells. The availability of an appropriate targeted delivery strategy will accelerate these therapeutic programs

- **Targeted Delivery of Beta Cell Therapies**
 - Discovery of beta cell selective “addresses” to enable targeting, adaptation of existing targeting technologies being developed in other fields for use in beta cell targeting, and testing of candidate targeted molecules in appropriate preclinical models.
- **Beta Cell Expansion Therapies**
 - Discovery and validation of physiologically relevant biochemical pathways to promote beta cell expansion.
- **Reprogramming Therapies**
 - Discovery and validation of physiologically relevant biochemical pathways to promote cellular reprogramming of other cell types towards a functional beta cell identity.

3. Enabling Clinical Development

To enable more efficient, cost-effective clinical testing of beta cell-directed therapies, the biomarkers projects are focused on discovering, validating and developing biomarkers of beta cell health, function, and mass. Drug accessibility and current clinical trial designs have slowed the development of beta cell directed therapies. The availability of biomarkers for beta cell function, dysfunction, and mass will accelerate clinical testing of novel therapeutics. In addition, the use of novel patient populations (longstanding T1D; autoantibody negative FDR) for proof of concept clinical testing will address the competition for the finite numbers of recent onset individuals classically used for this purpose.

- **Biomarkers of Stress, Death and Dysfunction**
 - Clinical validation of candidate markers and assay development
 - Discovery and validation of molecules detectable in circulation that accurately reflect beta cell health
- **Circulating Biomarkers and Imaging of Beta Cell Mass and Function**
 - Clinical validation of candidate markers and assay development.
 - Discovery and validation of molecules detectable in circulation that accurately reflect beta cell mass
- **Improving Clinical Trial Design**

- Development of novel clinical proof-of-mechanism testing paradigms, utilizing specialized patient populations, novel biomarkers and/or innovative study designs.
- **Clinical Development Paths** for beta cell survival and regenerative therapies will need to be defined and refined and are be critical for the long-term success of the program
- **Define Regulatory Path** for approval of beta cell therapies

Towards the Aspirational Therapy

In order to achieve true and durable insulin independence, it is likely that a combination of beta cell survival, regenerative, and immune therapies will be needed. Similarly, beta cell survival and immune therapies will be able to increase the longevity of replacement cell therapies.

Stage 1 – autoimmunity – An immune therapy or beta cell survival therapy could be used to permanently maintain insulin independence.

Stage 2- autoimmunity and metabolic instability – A regenerative therapy, in combination with an immune and/or survival therapy, would be needed to increase the lost beta cell mass and achieve metabolic stability.

Stage 3: autoimmunity and insulin dependence- A regenerative therapy, in combination with an immune and/or survival therapy, would be needed to reverse the loss of beta cell mass and achieve insulin independence.

Regulatory + Reimbursement Pathway

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

Therapeutic Concepts

Gen 1.0

Parameter	Target
Primary Indication	<ul style="list-style-type: none">• Improve glucose control in insulin-dependent diabetes• Delay time to insulin dependence in at risk populations
Target Population	<ul style="list-style-type: none">• Stage 3 individuals with residual beta cell mass• Stage 1 and 2 individuals at high risk of progressing to insulin dependence
Features	<ul style="list-style-type: none">• Oral or injectable treatment (survival therapy) in addition to insulin therapy (stage 3) or to prevent need for insulin therapy (stage 2 and 3)• Can be combined with immune therapy to increase efficacy and/or durability• Daily to intermittent dosing
Efficacy	<ul style="list-style-type: none">• Increased time in range• Reduction in HbA1c• Delay to insulin dependence (stage 1,2)
Risk/Side Effect	<ul style="list-style-type: none">• Acceptable risk/benefit profile

Parameter	Target
Primary Indication	<ul style="list-style-type: none"> • Increase insulin production in insulin-dependent diabetes to delay and reverse disease progression • Prevent insulin dependence in at risk populations
Target Population	<ul style="list-style-type: none"> • All stage 3 individuals • Stage 2 individuals with detectible metabolic dysfunction
Features	<ul style="list-style-type: none"> • Single agent (regenerative) • Oral or injectable treatment in addition to insulin therapy (stage 3) • Oral or injectable treatment to prevent insulin dependence (stage 2) • Daily to intermittent dosing
Efficacy	<ul style="list-style-type: none"> • Increase in endogenous insulin production • Increased time in range • Decreased HbA1c • Increase in metabolic function
Risk/Side Effect	<ul style="list-style-type: none"> • Acceptable risk/benefit profile with monitoring for carcinogenesis associated with regenerative agents

Parameter	Target
Primary Indication	<ul style="list-style-type: none"> • Independence from exogenous insulin • Restore metabolic stability in at-risk populations
Target Population	<ul style="list-style-type: none"> • All stage 3 individuals • Stage 2 individuals with detectible metabolic dysfunction
Features	<ul style="list-style-type: none"> • combination of agents <ul style="list-style-type: none"> ○ regenerative + survival therapies ○ regenerative + immune therapies • Oral or injectable treatment • Intermittent dosing
Efficacy	<ul style="list-style-type: none"> • Completely restore endogenous insulin production • Normal time in range • Normal HbA1c • Normalize metabolic function
Risk/Side Effect	<ul style="list-style-type: none"> • Acceptable risk/benefit profile with monitoring for <ul style="list-style-type: none"> ○ carcinogenesis associated with proliferative agents ○ infections associated with immunosuppression

Aspirational

Parameter	Target
Primary Indication	<ul style="list-style-type: none">• durable insulin independence
Target Population	<ul style="list-style-type: none">• All stage 3 individuals• Stage 2 individuals with detectible metabolic dysfunction
Features	<ul style="list-style-type: none">• combination of 3 agents - regenerative + immune + survival• oral or injectable treatment• single course of treatment
Efficacy	<ul style="list-style-type: none">• Durable restoration of endogenous insulin production• Normal time in range• Normal HbA1c• Normalize metabolic function
Risk/Side Effect	<ul style="list-style-type: none">• Acceptable risk/benefit profile without risk of infection or carcinogenesis

For more information:

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