Breakthrough T1D Request for Applications: Mechanisms of Graft Acceptance in Clinical Islet Transplantation

August 2024

Summary

- The goal of this funding opportunity is to expand the understanding of mechanisms contributing to long term survival/function and immune tolerance toward islet grafts following transplantation in type 1 diabetes (T1D) using existing clinical datasets.
- This initiative will award grants to academic investigators and industry partners of up to $750,000.00 over 2 years.
- Breakthrough T1D will consider applications with increased scope (time and/or budget) where there is a strong justification. Interested applicants should discuss with the Breakthrough T1D scientific contact, nmamrak@breakthrought1d.org.

Funding Opportunity Description

Breakthrough T1D aims to fill critical gaps in the understanding of mechanisms contributing to graft acceptance and immune tolerance in islet transplantation. While graft survival rates have improved with more refined immune suppression strategies, islet procurement, and surgical procedures, there is still significant heterogeneity in the therapeutic outcomes for islet transplant recipients. While the alloimmune response is likely to drive rejection in many cases, the interactions between islet graft and host immune system are not fully characterized, particularly in the context of successful islet transplants. In addition, the re-occurrence of autoimmunity despite immunosuppressive protocols occurs in some islet transplant recipients. Lastly, the stress and metabolic state of islet grafts is likely to contribute to long term survival. Overall, the mechanisms that determine why some patients maintain graft function, while others do not, are not entirely clear. This funding opportunity aims to advance our understanding of graft acceptance and immune tolerance in islet transplantation using existing clinical data. Therefore, Breakthrough T1D is soliciting Letters of Intent (LOI) from investigators who have access to such datasets with the aim to

ultimately support long-term islet survival and improve therapeutic outcomes of current and future islet transplantation approaches for T1D.

Relevant datasets may include National Institutes of Health NIDDK Central Repository studies, CIT02 through CIT08, pan-CIT, and Collaborative Islet Transplant Registry samples/data, or center specific datasets from national islet transplant programs and registries, and clinical trials. Industry sponsored trials and/or trials using alternative sources of insulin producing cells (e.g., human stem cell-derived islets or porcine sources) are also of interest.

Examples of topics pertinent to this call include but are not limited to:

- Using clinical datasets to identify biomarkers/signatures of beta cell stress or immune rejection to better measure and predict graft failure prior to decline in c-peptide and/or glycemic control.
- Single cell profiling of immune cells from patients undergoing islet transplantation as correlates of therapeutic outcomes, ideally with longitudinal sampling.
- Analysis of immune populations in clinical datasets testing alternative immune protection strategies such as immunomodulatory therapy.
- High dimensional -omic profiling of banked serum or blood samples from islet transplant recipients as correlates of therapeutic outcomes.
- Investigating common signals within other transplant types, such as liver or kidney, which exhibit immune tolerance that may apply to islet transplant.

Topics out of scope for this funding opportunity:

- This funding opportunity is not designed to support the analysis of data from preclinical experiments such as rodent models.
- Support for new clinical trials.
- Studies of individuals at early presymptomatic or new onset stages of T1D.
- Projects focusing on protecting endogenous beta cell mass from autoimmune destruction.

Background

One of Breakthrough T1D's goals is to accelerate the development of therapies capable of restoring metabolic control and insulin independence in T1D through the transplantation of insulin-producing cells. (Link to Strategy Document Here).

Pancreatic islet transplantation has been efficacious in improving metabolic control and quality of life, and in preventing severe hypoglycemia in a select group of patients with medically unstable T1D. However, further advancements are required in order to recommend islet transplantation for broader patient populations. One of the major barriers limiting the more widespread adoption of islet transplantation is the reliance on chronic systemic immunosuppression to limit immune rejection of the graft. In the context of automated insulin delivery technology, the adverse side effects of systemic immunosuppression create an unfavorable risk-to-benefit profile for islet transplantation in most people living with T1D, thus restricting the patient population for which these therapies are appropriate despite the superiority of islet transplantation in controlling glycemic variability without the need for patient control of the device. Ultimately, people living with T1D should have a choice between device based glycemic management and islet replacement therapy; however, advancements are required to expand the populations for which islet transplant is suitable given the side effects of current immunosuppression protocols. Additionally, in the presence of immunosuppression, graft function after intraportal transplantation varies over time, resulting in a wide range of therapeutic benefits for patients. Lastly, islet grafts experience inflammation and transplant associated stressors leading to high percentages of cell death upon transplantation, necessitating high islet doses to achieve insulin independence.

Breakthrough T1D's role is to enable the scientific community to address these challenges with the ultimate goal of accelerating the development of safe and effective beta cell replacement therapies that are available to all individuals living with T1D. While a multitude of factors are likely to affect graft survival and function over time, we currently lack a clear mechanistic understanding of what contributes to one patient's transplant success or another patient's transplant failure. For example, in rare cases of islet and solid organ transplant (e.g., liver and kidney), immune tolerance is observed where grafts function and survive with minimized or no immunosuppressive therapy and the mechanisms by which this acceptance is permitted is not fully understood. In total, developing a deeper understanding of the factors contributing to differential survival and function across the spectrum of transplant outcomes will help inform the design of next generation islet replacement that are suitable for a broader patient population.

Eligibility

Applications may be submitted by domestic and foreign non-profit organization, public and private, such as universities, colleges, hospitals and laboratories, units of state and local

governments and eligible agencies of the federal government, for-profit entities, or industry collaborations with academia. Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent and have a faculty position or equivalent at a college, university, medical school, or other research facility.

Please note that applications from for-profit entities or industry collaborations with academia may be submitted in response to this RFA. Additional information will be requested from for-profit entities if invited to submit a full proposal.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, Breakthrough T1D welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

Funding Mechanisms

In response to this announcement, Letters of Intent (LOI) can be submitted under the following mechanism(s):

Strategic Research Agreements (SRAs)

Strategic Research Agreements are intended for support of research activities at non-for-profit entities such as academic institutions. For SRAs, proposed budgets for projects should not exceed $750,000.00 USD (including 10% indirect costs) total costs for up to two (2) years. The level of funding will vary depending on the scope, data available, need to perform additional laboratory assays, access to samples, degree of data analysis to be performed, and overall objectives of the proposal. If your project budget and/or timeline exceeds $750,000.00 and/or 2 years, please discuss with Breakthrough T1D staff (contact information below). For more information on the Strategic Research Agreement (SRA) grant mechanism please refer to our grant handbook.

Industry Discovery and Development Partnerships (IDDPs)

For-profit entities may apply under Breakthrough T1D's Industry Discovery & Development Partnership (IDDP) funding mechanism, which entails additional requirements and typically has a modest royalty payback to Breakthrough T1D. If you would like to submit an Industry Discovery and Development Partnership (IDDP) project LOI to this RFA, please check our grant handbook for additional information and contact Dr. Nicholas Mamrak

(nmamrak@BreakthroughT1D.org) to discuss proposed scope and budget prior to submitting an application. Indirect costs are not permitted on IDDP applications.

Letter of Intent

Applicants should submit an LOI, [2 pages maximum] online via RMS360 to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application.

Proposal

An approved LOI is required prior to the submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided in RMS360. Proposal section templates in Microsoft Word, [10 pages maximum] should be type-written, single-spaced, and in typeface no smaller than 10-point font and have no more than six vertical lines per vertical inch. Margins, in all directions, must be at least ½ inch. Complete information should be included to permit a review of each application without reference to previous applications.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design, and investigational product information. More details can be found in the Human Subject Research Guidelines section of the grant handbook.

Breakthrough T1D follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the Common Rule changes.

Review Criteria

Applications will be subjected to confidential external scientific review evaluated on the following:

- Significance
- Relevance
- Approach
- Environment
- Resource sharing plan

Informational Webinar and Q&A

Breakthrough T1D will hold an announcement introduction meeting via Zoom on August 20, 2024, from 1-2 pm Eastern Time to which all prospective applicants are invited. Breakthrough T1D scientists will give an overview of the goals of this initiative, explain the application process, and answer initial questions on applications.

Registration for Webinar (please register by August 19, 2024):

https://breakthrought1d-org.zoom.us/webinar/register/WN_CbR9rYnZTnS75KHpuZPZPQ

Projected Timeline

Milestone	Date
Information Webinar and Q&A	August 20, 2024, 1-2 PM ET
LOI deadline	September 17, 2024, 5 PM ET
Notification of LOI Outcome	September 24, 2024
Full proposal deadline	October 22, 2024, 5 PM ET
Award notification	March, 2025
Earliest anticipated start	June, 2025

Program Contacts

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