Breakthrough T1D Request for Applications: Advancing Technologies to Enhance Engraftment in Cell Therapy for T1D

November 2024

Summary

- The goal of this funding opportunity is to advance technologies that support the engraftment of insulin-producing cells following transplantation at extrahepatic sites for T1D cell therapy.
- Proposals eligible for consideration will focus on strategies addressing the various challenges encountered at alternative transplantation sites during the peri-transplant period due to inflammation, hypoxia, and poor vascularization to enhance survival, engraftment, and function of transplanted cells.
- This program will award grants of up to $300,000 per year for 2 years according to the preliminary data available and scope of work proposed. Awards of increased scope may be considered following discussion with the scientific lead.
- Proposals focused on advancing technologies into late preclinical and early clinical development will be prioritized.

Funding Opportunity Description

Breakthrough T1D requests applications seeking support for preclinical and clinical research projects aiming to accelerate the development of technologies and/or strategies focused on enhancing the survival, engraftment, and function of insulin-producing cells following transplantation at extrahepatic sites. While much progress has been made in the development of alternative renewable sources of insulin-producing cells, several barriers related to the site of implantation, cell delivery, survival and engraftment, and immune protection must be surpassed before cell therapies to cure T1D are widely available. Intrahepatic delivery of cells is currently the gold standard in beta cell replacement therapies given the success of this approach in achieving diabetes reversal and insulin independence. However, this approach is limited due to various constraints of the intrahepatic site and alternative sites of implantation that may offer advantages to novel islet cell therapy approaches are being explored. Through this initiative, Breakthrough T1D aims to promote the advancement of technologies that address the challenges faced during the peri-transplant period that limit the survival and engraftment of insulin-producing cells transplanted at alternative sites. Breakthrough T1D will award grants up to $300,000 per year for 2 years. Awards of increased scope may be considered following discussion with the Breakthrough T1D scientific lead.

Background

Breakthrough T1D is committed to advancing the development of beta cell replacement therapies that can restore glycemic control and eliminate the need for exogenous insulin administration in people with T1D. It has been shown that cadaveric pancreatic islet transplantation is efficacious in improving glycemic control, preventing severe hypoglycemia, reducing exogenous insulin requirements, and improving quality of life in patients with medically unstable T1D. While alternative renewable sources of insulin producing cells like human stem cell-derived islets have advanced into clinical trials, major scientific and technical challenges in ensuring adequate survival and engraftment of cells following implantation at alternative sites. In addition, strategies to overcome allogeneic immune rejection and recurring autoimmunity are needed to ensure long-term graft function without the undue side effects of chronic immunosuppression before beta cell replacement can be widely implemented as a cure for T1D. The major barriers and progress toward addressing these barriers are reviewed here (Grattoni et al. 2024, Nature Rev Endo).

Intrahepatic delivery of cells via infusion into the portal vein is currently the gold standard in beta cell replacement therapies given the success of this approach in achieving improved glycemic control, reduction in exogenous insulin requirements, and protecting against severe hypoglycemia events. However, this approach is limited due to various challenges such as the instant blood-mediated inflammatory reaction (IBMIR), which results in an immediate loss of 50 to 60% of the graft, a relatively hypoxic environment, and increased risk for portal thrombosis and hypertension. Moreover, this site may need to be further explored for safety consideration as the development of genetically modified immune evasive stem cell-products advances toward clinical application. As a result, alternative sites of implantation that may offer advantages for hypoimmunogenic naked cells or other immune protective strategies over intrahepatic delivery are being explored. Nevertheless, these alternative sites have their own limitations, such as poor vascularity and hypoxia, which limit the survival and engraftment of transplanted cells. Moreover, inflammation and immune-mediated reactions, which may depend on the implantation site, can induce stress in insulin-producing cells and lead to cell death. Lastly, methods to monitor the engraftment process are lacking.

As such, Breakthrough T1D requests applications seeking support for preclinical and clinical research projects aiming to advance the development of strategies and technologies to enhance the survival, engraftment, and function of insulin-producing cells transplanted in alternative sites. This funding opportunity focuses on strategies directly targeting the beta cell graft and methods to modify or monitor the graft microenvironment. Proposals focused on advancing technologies into late preclinical and early clinical development will be prioritized.

Applicants seeking to further develop technologies to enhance engraftment are encouraged to have preliminary data demonstrating *in vivo* engraftment in rodent models is enhanced with survival lasting for a minimum of 30 days. Demonstration of physiologic glucose response post engraftment is highly recommended via dynamic GSIS or glucose tolerance tests.

Examples of research appropriate for this RFA include, but are not limited to:

- The further development of strategies (e.g. scaffolds, hydrogels, cell delivery devices) that ensure adequate oxygenation of the cell graft *in vivo* and accelerate stable long-term vascularization and integration of the graft at alternative transplantation sites.

- Strategies to improve insulin kinetics through better function of implanted beta cells, with a focus on improved function and glycemic control over purely cell survival.

- Development of methods to quantify engraftment without invasive biopsy such as validating biomarkers of engraftment (e.g., miRNA, prohormone ratios) or developing blood vessel and oxygen imaging.

- Investigation of the relationship between engraftment propensity and various graft features such as cell maturation/metabolism (mitochondrial state, respiration rate), insulin-producing cell source, immunogenicity or site of implantation.

- Characterization of differential immune reactions and inflammation at various extrahepatic sites to better inform immune protection strategies at alternative sites.

- Validation of novel target genes involved in promoting cell engraftment via small molecule or pharmacologic treatment.

Examples of research not supported by this RFA include:

- Genetic modification of the transplanted beta cells.

- Approaches entailing the use of co-transplanted support cells (e.g., mesenchymal stem/stromal cells or isolated microvessels) to promote vascularization or survival and engraftment of transplanted beta cells.

- Delivery of therapeutics targeting beta cells that reduce beta cell stress and death independent of vascularization or engraftment (e.g., GLP-1 pathway).

- The early preclinical development of immunoisolating encapsulation devices to prevent immune rejection.

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 MD, DMD, DVM, PhD, 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 Mechanism

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 $300,000.00 USD (including 10% indirect costs) per year for up to two (2) years. The level of funding will vary depending on the scope and overall objectives of the proposal. If your project budget and/or timeline exceeds this amount, please discuss with Breakthrough T1D scientific staff prior to LOI submission. For more information on the Strategic Research Agreement (SRA) grant mechanism please refer to our grant handbook.

Industry Discovery and Development Partnerships (IDDPs)

Breakthrough T1D's Industry Discovery & Development Partnership (IDDP) funding mechanism is intended for support of research activities at for-profit entities. IDDPs have additional requirements and typically entail a modest royalty payback to Breakthrough T1D. The level of funding will vary depending on the scope and overall objectives of the proposal. Indirect costs are not permitted on IDDP applications. If you would like to submit an Industry Discovery and Development Partnership (IDDP) project LOI to this RFA, please contact Breakthrough T1D scientific staff (contact information below) to discuss prior to LOI submission. For more information on the IDDP grant mechanism please check our grant handbook.

Letter of Intent

Prospective applicants should submit an LOI (2 pages maximum) online via RMS360 to be considered for a full proposal request. The LOI template provided in RMS360 must be used to complete the application in order to be considered for a full proposal request.

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 Public Q&A

Breakthrough T1D will hold an announcement introduction meeting via Zoom on December 5th, 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 December 4th, 2024):https://breakthrought1d-org.zoom.us/webinar/register/WN_e8-0raAnSemNVoUPiVJhsQ?_x_zm_rtaid=L8tBELCPSjSRsHgWiQfPlw.1730918707231.d81e467131beb8da9bd289c713221795&_x_zm_rhtaid=210#/registration

Projected Timeline

Milestone	Date
Informational Webinar and Q&A	December 5th 2024
LOI Deadline	January 10th 2025
Notification of LOI Outcome	January 21st 2025
Full Proposal Deadline	February 21st 2025
Award Notification	July 2025
Earliest Anticipated Start	October 2025

Program Contacts

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