Breakthrough T1D Request for Applications:

Understanding the Foreign Body Response in Islet Cell Replacement: Accelerating Clinical Translation

Summary

- Breakthrough T1D is launching a new funding opportunity to support innovative research that advances the clinical translation of biomaterial-based immune-isolation strategies for islet cell replacement therapy in Type 1 Diabetes (T1D).
- The Foreign Body Response (FBR) to implantable devices used in islet cell transplantation remains a major barrier to achieving long-term survival and function of transplanted islet cells. The primary objective of this funding opportunity is to better understand the underlying mechanisms, improve monitoring approaches, and be able to mitigate and control the FBR, thereby accelerating progress toward clinically viable cell replacement therapies for T1D.
- This Request for Applications (RFA) will provide grants of up to $900,000 each over a maximum duration of three years. Both non-profit (e.g., academic institutions) and for-profit (e.g., biotech companies) entities are eligible to apply.

Funding Opportunity Description

Despite decades of research and promising advances in biomaterial science, the clinical translation of islet cell replacement devices remains severely constrained by the unresolved challenge of the FBR, which continues to impede long-term graft function and survival.

Breakthrough T1D is committed to closing this fundamental translational gap between model system outcomes and the biology of beta cell replacement in humans. Through this funding opportunity, we invite

Letters of Intent (LOIs) from investigators in academic and industry settings aimed at advancing our understanding of the FBR and its impact on beta cell replacement therapies. Proposals should aim to:

- Identify key limitations from current preclinical models that hinder accurate prediction of the human FBR;
- Advance mechanistic understanding of the human immune and stromal response to implanted cell therapy devices;
- Develop human-relevant experimental platforms or analytical approaches that can address this translational gap.

By prioritizing research that directly addresses these modeling and translational limitations, this initiative aims to establish the foundation for clinically successful beta cell replacement therapies.

Background

Breakthrough T1D is the world's leading nonprofit organization dedicated to curing type 1 diabetes (T1D) and improving the lives of those affected by it . As part of our Cell Therapy Research Strategy, Breakthrough T1D is focused on advancing islet cell transplantation as a curative approach for T1D. The goal is to develop an off-the-shelf cell replacement product that 1) utilizes scalable, stem cell-derived islet cells, 2) provides islet cell survival and function without the need for systemic immunosuppression, and 3) achieves durable glycemic control without exogenous insulin. This strategy aims to address major limitations of current treatments, including the scarcity of donor islets and the substantial health risks associated with lifelong immunosuppressive therapy.

Significant progress has been made in developing manufactured islet cells and immune-isolation technologies (Kieffer et al, Cold Spring Harb Perspect Med. 2025; Hering et al, Diabetes 2025) however, major challenges remain—particularly those related to implantable biomaterials. Among the most significant barriers is the FBR, a complex, multifaceted immune reaction, characterized by inflammation, macrophage activation, fibrotic capsule formation, and impaired diffusion, all of which contribute to compromised graft survival and long-term function (Sholl et al, Bioengineering 2025). While many materials and devices have demonstrated minimal fibrosis and sustained function in preclinical animal models, none have translated successfully into humans without eliciting a significant FBR, regardless of biomaterial or implantation site. In nearly all human trials to date, implanted devices have provoked varying degrees of fibrosis and tissue remodeling, eventually leading to loss of cell viability and/or therapeutic function. These clinical outcomes highlight a persistent disconnect in the success of these

approaches between preclinical findings and human efficacy, pointing to a lack of predictive models and an incomplete understanding of the FBR in humans (Padmanabhan et al. Adv. Wound Care 2019). To bridge this gap, future efforts must move beyond preclinical models and approaches that focus on biomaterials or cells in isolation, overlooking the critical influence of their reciprocal interactions. While preclinical models have inherent limitations and important xenogeneic vs. allogeneic considerations, priority should be given to studies that elucidate the mechanisms underlying the human FBR, identify predictive markers of immune response, and develop models that more accurately recapitulate human tissue and immune environments. Doing so is essential to unlocking the full potential of beta cell replacement therapies for people living with T1D.

Objectives

Breakthrough T1D invites LOIs from investigators in academia and industry aiming to address persistent biomaterial-related challenges in beta cell replacement therapy, particularly focusing on understanding and overcoming the FBR in human-relevant settings. We are especially interested in proposals that explore the disconnect between preclinical and clinical outcomes, advance mechanistic understanding of the human FBR, and develop more predictive models and tools to guide device design and evaluation. Proposals may address, but are not limited to, the following areas:

- Mechanistic studies to disentangle the respective roles of implanted cells vs. biomaterials in triggering or modulating the foreign body response.
- High-throughput or semi-high-throughput approaches to evaluate biomaterials (in combination with islets) previously tested in large animal models or human trials* in immune-competent preclinical models that assess key features of FBR progression - macrophage activation, fibrotic encapsulation, vascularization and nutrient/oxygen diffusion, and/or local inflammatory balance.
- Comparative evaluation of implantation sites (e.g., subcutaneous, omental, intramuscular and intraperitoneal) and cross-species immune modeling to enhance predictive value of animal models for islet transplantation by comparing immune responses to biomaterial-islet grafts with known clinical outcomes of the biomaterial*.
- Spatial profiling of immune and stromal responses to implanted biomaterials in human tissue samples or humanized models, using high-resolution technologies to define cellular and molecular mechanisms driving fibrosis, immune rejection, or resolution.
- Leveraging human tissue and explant materials from prior clinical studies or surgical removals to investigate tissue remodeling, fibrosis, and immune infiltration, and conducting prospective

clinical tissue-response studies in accessible surgical contexts (e.g., abdominoplasty or panniculectomy) to directly assess immune and fibrotic remodeling in human tissues.

* Clinical trials in which the biomaterial has been previously tested can include other indications beyond beta cell replacement.

- Identifying and validating predictive biomarkers of the FBR through multi-omic, imaging, or immune-profiling approaches, linking local tissue responses with systemic immune or metabolic signatures to inform non-invasive monitoring and clinical translation.
- Establishing human-relevant experimental platforms, including in vitro and organ-on-a-chip systems incorporating primary or patient-derived immune and stromal cells, designed to recapitulate the human implantation microenvironment and improve predictive accuracy relative to in vivo outcomes.
- Integrate computational and systems-biology approaches to model the dynamic interplay between immune, stromal, and material components, analyze multi-scale or longitudinal datasets, and develop predictive frameworks that enhance the translational relevance or preclinical and human studies.

Preference will be given to proposals that:

- Use GMP-compatible biomaterials to enhance clinical relevance
- Include benchmarking against biomaterials/devices with prior clinical testing
- Use large animal models and NHPs
- Involve collaborations between teams that have tested devices in preclinical models and can compile data towards better mechanistic understanding of the FBR
- Build on previous clinical studies and/or explanted devices to elucidate mechanisms of human FBR

The following topics are not within the scope of this RFA:

- Development of novel anti-fibrotic materials
- Development of immunomodulatory biomaterials, including:
    - Lipid nanoparticles (LNPs)

    - Micro/nanogels
    - Drug-eluting encapsulation materials
- Development of new encapsulation devices
- Oxygen-generating biomaterials or devices
- Biomaterial-only studies in preclinical animal models
- Mechanistic studies relying exclusively on rodent models

Eligibility

- Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals and laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants must hold an M.D., D.M.D., D.V.M., D.O., Ph.D., or equivalent degree and have a faculty position or equivalent at a college, university, medical school, or other research facility.
- For-profit entities, or industry collaborations with academia, are welcome to submit applications in response to this RFA. Please contact the Breakthrough T1D scientific contact below prior to submitting the application. Additional information will be requested from for-profit entities if invited to submit a full proposal.
- For clinical studies, applicants must hold an appointment or joint appointment in a subspecialty of clinical medicine and conduct human clinical research.
- To assure continued excellence and diversity among applicants and awardees, Breakthrough T1D welcomes proposals from all qualified individuals and encourages proposals from a broad cross section of researchers and scientists

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-profit entities such as academic institutions. For SRAs, proposed budgets for projects should not exceed $900,000.00 USD (including 10% indirect costs) total costs for up to three (3) years. The level of funding will vary depending

on the scope, data available, need to perform additional laboratory assays, access to samples, and degree of data analysis to be performed. In case the project duration exceeds 3 years, please discuss with Breakthrough T1D staff (contact information below).

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. Asja Guzman to discuss proposed scope and budget prior to submitting an application. Indirect costs are not permitted on IDDP applications. Details about both mechanisms can be found in the grant handbook.

Letter of Intent

Applicants should submit a 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.

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. 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. Breakthrough T1D follows the U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects in research (45 CFR 46). Breakthrough T1D requires the Grantee Institution to comply with these guidelines.

Review Criteria

Applications will be evaluated based on Breakthrough T1D's standard confidential award policy and according to the following criteria:

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

Projected Timeline (no extensions will be given)

Milestone	Date
Information webinar and Q&A	October 30, 2025 (12 – 1 PM ET)
LOI deadline	November 17, 2025
Notification of LOI outcome	December 15, 2025
Full proposal deadline	January 27, 2026
Award notification	June 2026
Earliest anticipated start date	September 2026

Please register for the webinar by October 29, 2025. The registration link is - https://breakthrought1d-org.zoom.us/webinar/register/WN_MgWoEuqPSaa8hwF5UM3w2Q

After registering, you will receive a confirmation email containing information about joining the webinar.

Program Contacts

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