Breakthrough T1D Request for Applications: Translational Strategies to Define, Enhance, and Monitor Vascularization for Durable Islet Replacement Therapies

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Summary

- Breakthrough T1D is launching a new funding opportunity to support translational research that advances the clinical application of vascularization- and engraftment-focused strategies for islet replacement therapy in type 1 diabetes (T1D).
- Funded projects must address at least one of the following areas: 1) define vascular features that correlate with or predict graft function and long-term durability; 2) advance strategies to enhance vascular integration, perfusion and graft resilience at extrahepatic transplant sites; or 3) advance non-invasive technologies to monitor neovascularization, perfusion, vascular stability, and oxygenation *in vivo*.
- This Request for Applications (RFA) will provide grants of up to $900,000 for a maximum duration of three years. Both non-profit (e.g., academic institutions) and for-profit entities (e.g., biotechnology companies) are eligible to apply.

Background

Breakthrough T1D is the world's leading nonprofit organization dedicated to accelerating life-changing breakthroughs to cure, prevent, and treat type 1 diabetes and its complications (Link to Research Strategy Here). Over the past two decades, significant advances have been made in islet replacement therapies for T1D, with clinical trials demonstrating meaningful therapeutic benefit and the potential to substantially improve quality of life for individuals with T1D[1]. Despite these achievements, further innovation is required to ensure that islet replacement therapies are safe, effective, and durable, ultimately delivering a functional cure across a broad patient population. Next generation islet replacement products will require advances across all three key areas of Breakthrough T1D's cell therapy strategy: (1) Cell Source, to provide a renewable and scalable source of insulin-producing cells; (2) Cell Survival, to enable robust engraftment, vascularization, and long-term function; and (3) Cell Protection, to eliminate or greatly reduce the need for systemic immunosuppression[2]. Because early graft failure is largely driven by severe hypoxia and nutrient deprivation in the first few days post-transplant[3], improving cell survival by accelerating vascular integration and engraftment is an essential unmet need that this Request for Applications is designed to address.

Objectives

This RFA seeks to overcome persistent barriers to long-term success of islet replacement therapies by advancing understanding, engineering, and monitoring of graft vascularization at extrahepatic transplant sites.

Although meaningful advances have been made in cell sourcing and immune protection, insufficient vascularization and inadequate integration with the host microenvironment remain central obstacles to long-term graft success, particularly at extrahepatic transplantation sites[4].

In the native pancreas, arterioles supply blood regionally that branch into a dense network of capillaries, ensuring near-complete vascular coverage[5]. In contrast, transplanted primary and SC islets lack this organized vasculature and often undergo hypoxia and nutrient deprivation until new vessels form, causing cell loss and delayed function[3,6]. Inflammatory and fibrotic responses during implantation can further disrupt nascent vascular networks exacerbating graft failure[7]. Overcoming these challenges will require strategies that promote rapid, stable perfusion and recreate complex endothelial, stromal, and immune cell interactions that define a functional islet vascular niche.

A primary objective of this RFA is to define the vascular parameters that predict long-term graft outcomes. Currently, metrics such as vessel density, perfusion kinetics, endothelial maturity, oxygenation, and spatial organization are measured inconsistently using non-comparable endpoints, limiting the ability to identify determinants of successful engraftment, rationally engineer vascularized grafts, and compare strategies across models and sites.

A second objective is to develop technologies that enable faithful, non-invasive, longitudinal monitoring of graft development *in vivo*. Existing tools rely on terminal or invasive assessments and cannot track dynamic processes such as neovascular formation, vessel maturation, blood-flow kinetics, tissue oxygenation, or early metabolic stress. Clinically adaptable monitoring platforms are needed to evaluate vascularization strategies, support iterative optimization, and assess graft health in alignment with clinical standards.

A third objective is to bridge gaps between preclinical and human extrahepatic transplant environments. Many vascularization approaches lack clear translational paths due to limitations in scalability, manufacturability, surgical feasibility, and regulatory compatibility. This RFA therefore encourages development of strategies that incorporate human-relevant vascular biology, leverage robust large-animal T1D models, and emphasize practical clinical implementation.

Funding Opportunity Scope

Breakthrough T1D invites Letters of Intent (LOIs) from investigators in academic and industry settings proposing strategies or technologies to enhance or monitor engraftment of islet replacement therapies in T1D. LOIs may address 1) mechanisms that govern vascular integration and maturation, 2) approaches that improve perfusion, oxygenation, and long-term function of

implanted islets within extrahepatic transplant sites, or 3) non-invasive longitudinal monitoring of engraftment. Priority will be given to proposals with clear translational potential and well-defined plans for advancing toward clinical application.

Examples of projects relevant to this funding call include but are not limited to:

1) Defining Vascular Features That Determine Graft Success

- Quantitative mapping of vascular architecture to identify structural features associated with durable graft outcomes.
- Studies that identify early vascularization-related predictors of long-term graft function.

2) Enhancing Vascular Integration, Perfusion & Graft Resilience

- Engineering or guiding organ-specific endothelial or perivascular phenotypes (e.g., fenestrated capillaries) that support islet maturation and insulin secretion.
- Strategies to improve islet hypoxia resilience, metabolic adaptation, or oxygen utilization.
- Tissue-supportive co-transplantation strategies (e.g., adipose- or stromal-based scaffolds) to improve perfusion in extrahepatic sites.
- Development of pre-vascularized immune-cloaked graft constructs.

3) Non-Invasive Monitoring & Longitudinal Assessment Technologies

- Real-time high resolution *in vivo* imaging of vascularization, blood-flow dynamics, and oxygenation in rodent or large-animal models.
- Development of non-invasive, longitudinal monitoring technologies to track various aspects of vascularization and engraftment with a clear pathway to clinical deployment, including technologies adaptable for human imaging modalities.

Preference will be given to proposals that:

- Perform pilot studies in T1D large-animal models to bridge findings from small animal models into settings that more accurately replicate human clinical transplantation.
- Establish or utilize standardized, quantitative metrics or benchmarks for vascularization, perfusion, or endothelial maturation that can be compared across studies or models.
- Incorporate comparative analyses that assess how differences in graft design (ECM, 3D architecture, cellular composition, implantation site) affect vascularization and graft function.
- Include assessment of long-term graft durability (≥6 months) to demonstrate sustained impact of vascularization strategies.
- Demonstrate strong consideration of translational feasibility, including manufacturability, scalability, surgical practicality, and regulatory alignment.

- Incorporate human-relevant vascular biology (e.g., human stromal or endothelial components, humanized mouse models) to improve predictiveness for clinical application.
- Feature multidisciplinary collaborations that accelerate movement of promising strategies toward late preclinical or clinical readiness.

The following types of proposals are <u>not</u> within the scope of this RFA:

- Mechanistic studies performed solely *in vitro* or in non-transplant contexts that lack substantial preliminary data demonstrating relevance within an islet transplant setting in rodents.
- Projects focused solely on islet differentiation, manufacturing, or stem-cell biology that do not include investigation of vascularization, engraftment, or graft function.
- Development or optimization of encapsulation or immune-isolating technologies aimed at preventing immune rejection.
- Studies focused exclusively on immune modulation, fibrosis, foreign-body response, or biomaterial chemistry without a vascularization or engraftment component.
- Studies relying on stem cell–derived islets that do not include preliminary data that assess islet quality (insulin secretion, cellular composition) following differentiation.

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, for-profit entities, or industry collaborations with academia. Applicants must hold an MD, DO, 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 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 $900,000 USD total costs for up to three (3) years (including 10% indirect costs). 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 $900,000 and/or 3 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. Alex Bashore (abashore@BT1D.org) to discuss proposed scope and budget prior to submitting an application. Indirect costs are not permitted on IDDP applications. IDDP applications that are invited to a full proposal will receive their own timeline for completion of due diligence and finalization of an agreement.

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.

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.

All applications involving human subjects must include supplemental information to address subject safety, study design, and investigational product information. Breakthrough T1D follows the U.S. National Institutes of Health (NIH) guidelines for the humane care and use of animals in research and 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 subjected to confidential external scientific review evaluated on the following:

- Relevance to RFA topic
- Approach
- Translational plan and potential for clinical impact
- Research team and environment

Projected Timeline

Milestone	Date
Informational webinar and Q&A	January 13, 2026 (12PM – 12:45PM EST)
LOI deadline	January 28, 2026
Notification of LOI Outcome	February 11, 2026
Full proposal deadline	March 11, 2026
Award notification	July 2026
Earliest anticipated start	October 2026

Please register for the webinar by January 12, 2026. The registration link is - https://breakthrought1d-org.zoom.us/webinar/register/WN_BMGgFL2dQb6oeCG54km-Vw#/registration. After registering, you will receive a confirmation email containing information about joining the webinar.

Program Contacts

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References

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