Breakthrough T1D Request for Applications: Establishing immune tolerance in islet cell replacement therapy for type 1 diabetes (T1D)

November 2025

Summary

- This funding opportunity aims to support the development of tolerance induction approaches for islet cell therapy that enables graft-specific immune protection without compromising natural immune defenses.
- This call is open to both central and peripheral tolerance induction strategies with prioritization given to technologies closest to clinical translation.
- This initiative will award grants to academic investigators and industry partners of up to $900,000.00 over 3 years.

Funding Opportunity Description

Breakthrough T1D is soliciting Letters of Intent (LOI) from investigators in academic and industry settings aiming to develop therapies that induce specific tolerance to transplanted islet cells without compromising requisite immune functions such as infection defense and cancer surveillance. LOIs may address central and/or peripheral tolerance pathways and must be compatible with scalable manufactured islet cells (i.e., human stem cell-derived islets). While this funding opportunity is open to highly innovative projects at early stages of development, prioritization will be given to projects closer to clinical testing with a well-articulated plan for translation. All applicants are suggested to review Breakthrough T1D Research Strategy before applying.

Background

Successful organ and cell transplantation requires overcoming the host immune system's natural tendency to recognize donor tissues as foreign and mount a rejection response. In the case of Type 1 Diabetes (T1D), this is further complicated by the recurrence of autoreactive immune responses targeted to islet-specific

antigens (Burke et al., Curr Diab Rep 2014; Piemonti et al., Endotext 2025). Historically, this allogeneic rejection has been addressed through chronic broad immunosuppressive medication which, while effective at reducing rejection rates, carries significant side effects including increased risk of infections and certain cancers, metabolic complications, and drug specific toxicities (Desai et al., Transplantation 2023; Diker Cohen et al., Eur J Endocrinol 2025).

Given the risks associated with current immunosuppression drugs, emerging islet cell transplantation therapies are only indicated for people with T1D that experience severe hypoglycemic events and hypoglycemia unawareness (Marfil-Garza et al., Lancet Diabetes Endocrinol 2023; Chetboun et al., Lancet Diabetes Endocrinol 2023; Catarinella et al., Lancet Diabetes Endocrinol 2025). To broaden the population for which these therapies are appropriate and expand the benefits of islet cell transplantation, alternative immune protection strategies are being developed in order to realize the full potential of islet transplantation (Grattoni et al., Nat Rev Endocrinol 2025; Marinac et al., Diabetes 2025). As a result, a central goal in Breakthrough T1D's Cell Therapy program is to expand and accelerate the development of immune protection strategies that can enable widespread adoption.

One path towards immune protection without the complications of broad immunosuppression is the induction of immune tolerance - a state in which the recipient’s immune system accepts an islet graft as self while simultaneously retaining the ability to respond to pathogens and malignancies (Ohm et al., Semin Immunopathol 2025). Previous strategies working towards achieving immune tolerance largely relate to one of two key mechanisms. The first is central tolerance, which is the reshaping of the immune cell repertoire to delete donor (allogeneic) and self (auto) reactive immature T and B cells. This strategy is commonly associated with concomitant bone marrow (i.e., HSC) transplantation and mixed chimerism to achieve an accepting immune environment as has been trialed in solid organ transplant with mixed success (e.g., kidney, lung) (Lee et al., Transplantation 2020; Sommer et al., Transplant Direct 2021). However, the conditioning regimens required to achieve this state of mixed chimerism in T1D will require risk-benefit ratio considerations (Mineo et al., Am J Transplant 2008; Pathak and Meyer, Front Immunol 2021). The second is through peripheral tolerance, which aims to regulate mature immune responses by inducing an unresponsive state or promoting apoptosis of self-reactive cells in the periphery or via activation and expansion of counteracting regulatory cells. For example, in recent years significant research has focused on immune cell-based therapies aimed at rebalancing the immune system via the introduction of in vitro engineered T regulatory cells specific to donor or autoantigens (Wardell et al., Sci Transl Med 2025; Passerini et al., Eur J Immunol 2025). Additionally, continued research into the development of costimulatory blockade therapies such as anti-CD40 ligand and anti-CD80/86, which prevent full T cell activation, may promote pro-tolerogenic immune states, albeit less specific to transplant type (Wisel et al., Transpl Int 2023; Perrier et al., Transplant Rev 2025).

Given the progress in these areas, it is anticipated that further research and development into underexplored pathways and novel therapeutic modalities will further improve tolerance induction efficacy and translatability. Taken together, these strategies reflect the research community’s continued efforts in developing alternatives to broad immunosuppression that are more precise and patient friendly.

Understanding the mechanisms underlying tolerogenic immune states and developing therapies to promote them is a critical gap in broadening the T1D patient population for which islet replacements are appropriate.

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

- Further development of co-stimulatory blockade therapies targeting T cell activation pathways such as CD28-CD80/86, CD40-CD154/CD40L, LFA-1/ICAM-1, or underexplored pathways.
- Co-administered regulatory cell therapies such as engineered T regulatory cells, tolerogenic dendritic cells, or B regulatory cells that offer significant improvements over current generation immune cell therapies.
- Co-transplantation of thymic organoids toward establishing mixed HSC development and tolerance to islet grafts.
- Nanoparticle or microparticle technologies that present allo- and autoantigens and deliver tolerogenic signals to transplanted islets.
- Biomaterial-based approaches that present pro-tolerogenic signals locally at the islet graft site capable of providing durable protection and integration beyond the early engraftment phase.

Topics out of scope for this funding opportunity:

- Protection of islet cells via genetic modification.
- Co-transplantation of mesenchymal stem/stromal cells.
- Antigen specific therapies for the protection of endogenous beta cell mass.
- Tolerance induction approaches for the acceptance of xenogeneic islets.

Eligibility

- Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants must hold an M.D., D.O., 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.

- 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, applications may request up to a **total of $900,000.00 USD for up to three years**.

- The level of funding will vary depending on the scope and overall objectives of the proposal. Breakthrough T1D may consider applications with increased scope (time, budget) where there is a strong justification, and applicants interested in such should discuss with the Breakthrough T1D scientific contact below.

- Note that the above budget figure is the maximum, and Breakthrough T1D will also consider projects with substantially smaller budgets. In all cases, the level of requested funding should be commensurate with the studies proposed and non-Breakthrough T1D resources (funds, personnel, other) available to successfully complete the project. Appropriateness of budget in relation to scope will be considered as part of the review criteria.

Letters of Intent (LOI) can be submitted under the following mechanisms:

Strategic Research Agreement (SRA)

Strategic Research Agreements are intended for support of research activities at non-for-profit entities such as academic institutions. For more information on the SRA grant mechanism, please refer to the Grant Handbook. SRA applications may include up to 10% indirect costs as part of the total request.

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 including company matching funds. If you would like to submit an IDDP project LOI to this RFA, please see 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. IDDP applications that are invited to a full proposal will receive their own timeline for completion of due diligence and finalization of an agreement.

Submission

Letter of Intent (LOI)

Prospective applicants should submit a letter of intent (LOI) using the template provided online via RMS360. The LOI should be 2 pages and submitted online to be considered for a full proposal invitation.

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. Complete

information should be included to permit a review of each application without reference to previous applications.

Clinical studies

- 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 U.S. National Institutes of Health (NIH) Public Health Service Policy 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.
- More details can be found in the Human Subject Research Guidelines section of the Grant Handbook.

Review Criteria

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

- Significance
- Relevance to RFA topic
- Approach
- Translational plan and potential for clinical impact
- Environment
- Resource sharing plan

Projected Timeline

Milestone	Date
Information webinar and Q&A	December 16, 2025 (11AM – 12 PM EST)
LOI deadline	January 7, 2026
Notification of LOI outcome	January 22, 2026
Full proposal deadline	February 24, 2026
Award notification	July 2026
Earliest anticipated start	September 2026

Please register for the webinar by December 15, 2025. The registration link is - https://breakthrought1dorg.zoom.us/webinar/register/WN_N20qazx4T_KZSjiWO4Mh7w#/registration. After registering, you will receive a confirmation email containing information about joining the webinar.

Program Contacts

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