

Breakthrough T1D Request for Applications: Mitigating stress-related cell loss in islet replacement therapy for type 1 diabetes (T1D)

September 2026

Summary

- This funding opportunity will support projects aimed at reducing the fraction of islet cells lost in the post-transplant period with a focus on improving stress resilience of engrafted cells to enable more durable therapies.
- This call is open to approaches aiming to limit post-transplant stressors or improve resilience to this stress. The proposed strategy must be beyond the discovery stage and translatable to stem cell-derived islet sources.
- This initiative will award grants to academic investigators and industry partners with a maximum budget of \$750,000.00 over 3 years.

Funding Opportunity Description

Breakthrough T1D is soliciting Letters of Intent (LOI) from investigators in academic and industry settings aiming to develop strategies aimed at limiting post-transplant stress experienced by islet cells or by improving the resilience of islets to these stressors. Prioritization will be given to projects with a validated target, identified lead program, and well-articulated plan for clinical translation.

Background

Transplanted islets must survive a period of limited oxygen and nutrient availability before host vasculature is established, and a substantial fraction of transplanted islet mass is lost within the first days to weeks after implantation (Langlois et al., Cells 2024). Oxygen tension in transplanted islets is lower than in endogenous islets in the native pancreas irrespective of implantation site and may remain reduced even after revascularization (Carlsson et al., Diabetes 2001; Olsson et al., Diabetes 2011; Miao et al., Am J Transplant 2006). This is exacerbated by the fact that β cells are particularly sensitive to such conditions (Acharya et al., Islets 2010). In addition, SC-derived β cells

exposed to low oxygen show a progressive decline in cell identity and metabolic function (Wang et al., Nat Commun 2025). Stress can therefore reduce graft potency as well as graft mass, and cells may persist in a dedifferentiated state that further decreases function. This is especially relevant for manufactured stem cell-derived products, in which β -like cells occupy a range of maturation states and continue to mature after transplantation (Augsornworawat et al., Nat Cell Biol 2023).

Recent clinical results indicate both the potential of these cell replacement therapies and the remaining efficiency gap. Manufactured islet cell therapies have restored endogenous insulin secretion and achieved insulin independence with either hepatic portal vein infusion or extrahepatic implantation (Wang et al., Cell 2024; Reichman et al., N Engl J Med 2025; Shi et al., Lancet Diabetes Endocrinol 2026), and hypoimmune engineering has supported islet survival and glucose-responsive function at an intramuscular site without immunosuppression for one patient (Carlsson et al., N Engl J Med 2025; Carlsson et al., N Engl J Med 2026). In donor islet transplantation, primary graft function measured shortly after the final infusion is associated with five-year outcomes independent of the number of infusions, total transplanted islet mass, and immunosuppressive regimen (Chetboun et al., Lancet Diabetes Endocrinol 2023), suggesting that conditions in the early post-implantation period influence long-term performance. While multiple extrahepatic sites are currently being pursued for islet transplantation and offer better retrievability and monitoring accessibility compared to the conventional hepatic vein delivery, these sites are generally less vascularized. There are indications that stem cell-derived islets may have greater intrinsic hypoxia resistance than primary human islets, which could widen the range of feasible transplantation sites (Kato et al., Am J Physiol Cell Physiol 2026), although the basis for this difference and its behavior at therapeutic doses are not well characterized. Manufactured products offer a further practical advantage as cell banks may be engineered before differentiation and implantation. Protective pathways can be upregulated through genetic modification and assessed as part of characterization and release testing.

These considerations are complementary to the immune protection strategies central to Breakthrough T1D's Cell Therapy program. Cellular stress can alter the expression and presentation of β cell antigens and increase their recognition by autoreactive T cells (Marré et al., J Autoimmun 2016). Improving the capacity of islet grafts to withstand the transplant microenvironment therefore represents a distinct and comparatively underdeveloped approach to improving outcomes across cell sources and delivery sites through effectively reducing the dose of cells needed to achieve a desired therapeutic effect via improved cell survival. With this comes considerations for lower dosing, decreased manufacturing costs, and more economically accessible therapies. In summary, a better understanding of the pathways governing islet stress responses after transplantation, and the

development of approaches to strengthen them as a defined and measurable attribute of the cell product, remains a gap in realizing the durable benefit of islet replacement therapies for T1D.

To complement ongoing initiatives focused on manufacturing, immune protection, vascularization, and mitigation of the foreign body response (FBR), Breakthrough T1D is soliciting Letters of Intent (LOIs) focused on mitigating stress-related cell loss to enable more durable islet cell replacement therapies for T1D. While applications leveraging primary islets for initial development will be considered, all proposed strategies must be transferable to scalable manufactured islet sources (i.e., stem cell-derived islets) and projects using manufactured cell sources with benchmarked functional metrics will be prioritized.

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

- Beta cell-intrinsic approaches to stress resilience such as genetic modification
- Treatment of beta cells prior to and/or after transplantation for increased resistance to hypoxia, cytokine or metabolic stressors with a well-defined druggable target
- Evaluating transplant applications of beta cell support agents that have demonstrated positive effects in endogenous beta cell survival

Topics out of scope for this funding opportunity:

- Strategies focused on reducing the stress of endogenous beta/islet cells for disease modifying therapy applications
- Co-transplantation strategies with mesenchymal stem/stromal cells or extracellular vesicles
- Methods to improve the isolation and recovery of cadaveric islets
- Mechanistic studies determining overlap and discrepancies in drivers of endogenous beta cell stress vs. SC-islets
- Strategies focused on FBR mitigation, reducing instant blood mediated inflammatory response (IBMIR), or vascularization/oxygenation

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 a **total project budget of up to \$750,000.00 USD over a grant period of 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. Asja Guzman (aguzman@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.

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
LOI deadline	November 19, 2026
Notification of LOI outcome	December 3, 2026
Full proposal deadline	January 28, 2027
Award notification	May 2027
Earliest anticipated start	August 2027

Program Contacts

Strategic Fit and Scientific Inquires

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References

- Acharya JD, Ghaskadbi SS. Islets and their antioxidant defense. *Islets*. 2010;2(4):225-235. doi:10.4161/isl.2.4.12219
- Augsornworawat P, Hoglebe NJ, Ishahak M, et al. Single-nucleus multi-omics of human stem cell-derived islets identifies deficiencies in lineage specification. *Nat Cell Biol*. 2023;25(6):904-916. doi:10.1038/s41556-023-01150-8
- Carlsson PO, Hu X, Scholz H, et al. Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression. *N Engl J Med*. 2025;393(9):887-894. doi:10.1056/NEJMoa2503822
- Carlsson PO, Hu X, Scholz H, et al. Long-Term Survival of Hypoimmune Allogeneic Islets without Immunosuppression. *N Engl J Med*. Published online July 10, 2026. doi:10.1056/NEJMc2604408
- Carlsson PO, Palm F, Andersson A, Liss P. Markedly decreased oxygen tension in transplanted rat pancreatic islets irrespective of the implantation site. *Diabetes*. 2001;50(3):489-495. doi:10.2337/diabetes.50.3.489
- Chetboun M, Drumez E, Ballou C, et al. Association between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: a retrospective, multicentre, observational cohort study in 1210 patients from the Collaborative Islet Transplant Registry. *Lancet Diabetes Endocrinol*. 2023;11(6):391-401. doi:10.1016/S2213-8587(23)00082-7
- Dai C, Walker JT, Shostak A, et al. Tacrolimus- and sirolimus-induced human β cell dysfunction is reversible and preventable. *JCI Insight*. 2020;5(1):e130770. Published 2020 Jan 16. doi:10.1172/jci.insight.130770
- Kato H, Shang KM, Mitsugashira H, et al. Enhanced hypoxia resistance distinguishes human pluripotent stem cell-derived islets from primary islets. *Am J Physiol Cell Physiol*. 2026;330(5):C1237-C1245. doi:10.1152/ajpcell.00043.2026
- Langlois A, Pinget M, Kessler L, Bouzakri K. Islet Transplantation: Current Limitations and Challenges for Successful Outcomes. *Cells*. 2024 Oct 28;13(21):1783. doi: 10.3390/cells13211783. PMID: 39513890; PMCID: PMC11544954.
- Marré ML, Profozich JL, Coneybeer JT, et al. Inherent ER stress in pancreatic islet β cells causes self-recognition by autoreactive T cells in type 1 diabetes. *J Autoimmun*. 2016;72:33-46. doi:10.1016/j.jaut.2016.04.009
- Miao G, Ostrowski RP, Mace J, et al. Dynamic production of hypoxia-inducible factor-1 α in early transplanted islets. *Am J Transplant*. 2006;6(11):2636-2643. doi:10.1111/j.1600-6143.2006.01541.x
- Olsson R, Olerud J, Pettersson U, Carlsson PO. Increased numbers of low-oxygenated pancreatic islets after intraportal islet transplantation. *Diabetes*. 2011 Sep;60(9):2350-3. doi:10.2337/db09-0490.

Reichman TW, Markmann JF, Odorico J, et al. Stem Cell-Derived, Fully Differentiated Islets for Type 1 Diabetes. *N Engl J Med*. 2025;393(9):858-868. doi:10.1056/NEJMoa2506549

Shi Y, Feng Y, Li T, et al. Autologous and allogeneic stem cell-derived islet therapy in three recipients with type 1 diabetes and complete loss of endogenous pancreatic β -cell function pretransplant. *Lancet Diabetes Endocrinol*. 2026;14(4):285-288. doi:10.1016/S2213-8587(25)00423-1

Wang S, Du Y, Zhang B, et al. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. *Cell*. 2024;187(22):6152-6164.e18. doi:10.1016/j.cell.2024.09.004

Wang, X., Brielle, S., Kenty-Ryu, J. *et al*. Improving cellular fitness of human stem cell-derived islets under hypoxia. *Nat Commun* 16, 4787 (2025). doi:10.1038/s41467-025-59924-7