Breakthrough T1D Request for Applications:

In vitro Disease Modeling: Type I Diabetes-on-a-Chip Platforms for Translational Research

Summary

- Breakthrough T1D is launching a new funding opportunity to support advancement of cutting-edge *organoid- and organ on a chip-based* disease models of Type I Diabetes (T1D).
- This initiative aims to validate and refine existing human-relevant *in vitro* models of T1D as tools for evaluation of pharmacological and genetic interventions with the goal of accelerating translation to clinical studies.
- This Request for Applications (RFA) will provide grants to academic investigators and industry partners of up to $300,000 over one year.

Funding Opportunity Description

Advancement of Islet Cell and Disease-Modifying Therapies (DMTs) for T1D is often constrained by the limited availability of *in vitro* and *in vivo* models that accurately recapitulate human disease mechanisms and predict treatment responses. Traditional two-dimensional cultures show limited physiological relevance, while animal studies are costly, time-intensive, and frequently fail to predict human outcomes. Thus, there is an urgent need for human-relevant, validated experimental systems that can support the evaluation of novel interventions at higher throughput and lower cost.

Breakthrough T1D seeks Letters of Intent (LOIs) focused on validating the predictive power of already established advanced *in vitro* models of T1D pathophysiology and therapeutic response,

including organ-on-chip, 3D tissue constructs, and multi-cellular co-culture systems incorporating human stem cell-derived islets, immune and/or vascular components, and relevant tissue microenvironments.

This RFA aims to support accelerated translation and regulatory pathways of Disease Modifying and Islet Cell Replacement Therapies for Type 1 Diabetes by prioritizing the use of validated and standardized organ-on-chip systems and other New Approach Methodologies (NAMs) and in this fully aligns with the NIH's commitment to advancing human-relevant research while reducing reliance on animal models. Validated NAMs, including organ-on-chip and integrated human-cell models, could cover all critical safety and efficacy endpoints. Conventional animal testing would only be considered when a specific scientific question cannot yet be addressed with NAMs, and even then, only with minimal use and strong justification.

Background

Breakthrough T1D is the world's leading nonprofit organization dedicated to curing T1D and improving the lives of those affected by it. Disease-Modifying Therapies (DMTs) and Cell Therapies are aimed at restoring durable insulin independence by protecting and/or replacing functional β cells (Research Strategy). The Disease-Modifying Therapies (DMTs) focus on restoring immune tolerance and preserving β-cell mass and function through various approaches including disabling autoreactive immune responses, enhancing regulatory mechanisms, and regenerating and protecting β cells, ultimately combining immune and β-cell–targeted therapies. Islet Cell Therapies aim to develop β-cell replacement products capable of restoring glucose control and achieving long-term insulin independence without broad immunosuppression.

While advances in immune engineering, stem cell biology, genome editing, and biomaterials have enabled significant progress in DMT and Cell Therapies, significant challenges remain in the translation from pre-clinical to clinical studies within both therapeutic areas. DMT development is stalled by limited next-generation candidates progressing to the clinic, incomplete delivery systems for targeted immunotherapy, lack of early biomarkers of efficacy, and limited understanding of patient-specific treatment responses and disease heterogeneity—particularly in adult-onset T1D. The translation of Cell Therapy efforts remains challenging due to limited vascularization and slow engraftment, foreign body response to the transplanted devices, incomplete immune protection, and

variability in cell maturity and function. Together, DMT and Cell Therapy strategies underscore a shared need for human-relevant, physiologically representative experimental systems that can accurately model the reciprocal interactions between islet and other cell types and predict clinical outcomes of the many emerging interventions.

Organoid and organ-on-a-chip (OoC) technologies can address these needs by offering unique opportunities to recapitulate the structural, cellular, and functional complexity of human pancreatic, vascular, and immune systems—providing high-content, human-relevant data that complement or surpass what is achievable in 2D cultures or animal models. These advanced systems can directly address key mechanistic and translational questions critical to the Breakthrough T1D Cures Program and help establish standardized, predictive preclinical models across the field.

Objectives

The **In vitro Disease Modelling: Type I Diabetes-on-a Chip Platforms for Translational Research** RFA directly addresses this need by supporting the validation and refinement of advanced organoid and organ-on-a-chip platforms that integrate human β cells in combination with immune cells, vascular and/or lymphatic elements to model T1D pathogenesis and therapeutic response. Breakthrough T1D encourages applicants to design projects with regulatory relevance in mind, generating data that could support future NAM-based preclinical evaluation. Specifically, projects that contribute to the following FDA-recommended steps will be viewed favorably:

- **Mapping critical endpoints**: NAM-based models should aim to replicate key human-relevant safety and efficacy outcomes, such as β-cell toxicity, immune response, engraftment, and pharmacodynamics of cell- or disease-modifying therapies;
- **Supporting NAM development**: Proposals that refine or validate organoid- or organ-on-chip systems to predict human response directly contribute to FDA's roadmap for NAM adoption;
- **Establishing validation and qualification pathways**: Projects should focus on rigorous benchmarking against clinical data, demonstrating reproducibility, mechanistic insight, and predictive power, critical elements for potential FDA qualification.

By encouraging the use of validated NAMs, this RFA not only accelerates translational research for Type 1 Diabetes therapies but also supports broader regulatory initiatives to shift from animal-based testing toward human-relevant, high-content preclinical models.

Examples of Projects Addressed by This RFA:

- **Test safety and efficacy** of novel pharmacological and gene editing interventions as well as scaffold/device materials and controlled-release drugs.
- **Evaluating Drug Delivery, Pharmacodynamics, and Combination Therapies,**
  such as local immune-modulating drug release or combinations of immune and β-cell–targeted agents—to identify synergistic or adverse interactions and inform rational combination design.
- **Identifying Translational Biomarkers and Surrogate Endpoints**
  OoC systems equipped with integrated biosensors to capture dynamic clinically relevant molecular and functional readouts in real time and inform discovery of early, *in vitro* biomarkers predictive of clinical efficacy. The obtained quantitative human datasets should strengthen regulatory submissions by providing mechanistic evidence of therapeutic safety and activity.
- **Modeling Immune–Islet Interactions**
  OoC or other models that incorporate human β cells, stromal components, and immune cells to illuminate the cellular and molecular mechanisms of autoimmune attack and tolerance.
- **Evaluating Strategies Targeting β-Cell Survival, Function, and Regeneration**
  Micro-engineered β-cell systems that recreate physiologic nutrient and oxygen gradients, enabling detailed study of the stress pathways—including ER stress, oxidative stress, inflammation, and hypoxia—that drive β-cell dysfunction and loss.
- **Modeling Transplant Engraftment,**
  such as tissue-specific oxygen gradients, nutrient diffusion, vascularization, inflammation, fibrosis, and immune activation.

Preference will be given to proposals that:

- Build on established *in vitro* platforms that are clinically relevant, tunable, reproducible, and mechanistically informative;
- Use human cellular components to maximize clinical relevance;

- Validate the predictive power of the model against pharmacological, genetic, or other interventions from ongoing or completed clinical studies;
- Involve collaborations between tissue engineering groups and clinical centers to link *in vitro* findings with *in vivo* biology;
- Integrate clinically relevant metrics: β-cell function, engraftment, vascularization, immune protection.

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

- Use of general *in vitro* platforms without specific relevance to T1D;
- Address broad immunology or diabetes mechanisms without connecting to β-cell function, engraftment, or therapeutic intervention testing;
- Include model development without validation against human islet/β-cell benchmarks;
- Focus solely on murine islets or non-human-only models without human cellular components;
- Focus solely on software or *in silico* modeling without integration into experimental human-relevant systems;

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 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, research proposals 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 $300,000.00 USD (including 10% indirect costs) total costs for up to 1 year. 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 1 year, 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.

Proposal

Applicants should submit a project proposal [4 pages maximum] online via RMS360. The proposal template provided on the RMS360 website must be used to complete the application to be considered for this RFA.

Proposal section templates in Microsoft Word 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.

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

- Relevance
- Approach
- Innovation and Translational Potential
- Environment

Projected Timeline (no extensions will be given)

Milestone	Date
Informational webinar and Q&A	January 15, 2026 (12PM – 12:45PM ET)
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

To register for the webinar, please use the following link: https://breakthrought1d-org.zoom.us/webinar/register/WN_Epua9wfkQsWMYx_OH662CA#/registration. After registering, you will receive a confirmation email containing information about joining the webinar.

Program Contacts

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