Breakthrough T1D Request for Applications: Clinical Trials Advancing Metabolic Therapies for T1D

Summary

- The goal of this funding opportunity is to target metabolic imbalances to improve glucometabolic outcomes in people with established type 1 diabetes (T1D).
- This funding opportunity will prioritize T1D clinical trials evaluating therapies either approved or in development for metabolic diseases such as T2D, obesity, and MAFLD.
- This program will award grants for clinical studies of up to $2,000,000 over 3 years.

Funding Opportunity Description

Key to Breakthrough T1D strategy is supporting development of therapies that improve glucometabolic control in T1D, an autoimmune disease that becomes a metabolic disease. Beyond insulin insufficiency, T1D often comes with other metabolic pathologies including amylin deficiency, insulin resistance, dysregulated glucagon secretion and hepatic glucose production, obesity, and others. Learnings from the growing field of metabolic disease drug development have shown that

comprehensive metabolic control is key for improved outcomes and the prevention of long-term complications. For too long, the metabolic disease therapy field has overlooked T1D.

To advance our goal of expanding the realm of non-insulin therapies available to people with T1D, Breakthrough T1D invites letters of intent to assess metabolic therapies — developed for other diseases—in T1D.

Background

T1D poses a challenge beyond insulin deficiency. It is a complex metabolic disorder necessitating a comprehensive treatment regimen. Current T1D management is almost entirely insulin-centric, but insulin monotherapy often falls short of achieving optimal glycemic and metabolic control. Recent findings from the T1D Exchange demonstrate only 21% of adults and 17% of youth achieve desired glycemic targets.[1] Metabolic challenges beyond glucose control are also poorly addressed.

Metabolic imbalances in T1D arise from multiple factors, starting with depletion of beta cells. Loss of beta cells not only results in insulin deficiency, but also loss of amylin—another metabolic hormone secreted by beta cells— and dysregulated glucagon secretion. Amylin regulates postprandial metabolic control through suppressing glucagon secretion, slowing gastric emptying, and inducing satiety. Dysregulated glucagon secretion not only exacerbates hyperglycemia and disrupts the response to hypoglycemia, but also alters hepatic energy metabolism and lipogenesis. The resulting poor glycemic control promotes oxidative stress and inflammation, further driving metabolic dysfunction.

Another source of metabolic imbalances in T1D is the inability of insulin therapies to recapitulate the biodistribution of insulin secreted form the pancreas. Exogenous insulin therapy fails to reach the liver in adequate amounts, impairing whole-body glucose control. At the same time it distributes too highly to the periphery, resulting in peripheral hyperinsulinemia, which is thought to contribute to insulin resistance in people with T1D; this phenotype is exaggerated in people with T1D and obesity but present even in lean people with T1D. Insulin resistance has been shown to be a key risk factor for cardiovascular disease and kidney disease in T1D.

Compounding these issues, rising rates of metabolic syndrome and obesity among individuals with T1D underscore the need for a multi-target approach to treatment. An estimated two-thirds of adults with T1D live with overweight or obesity, a phenotype that may be exacerbated by intensive insulin therapy. Obesity drives additional pathogenic pathways, including mitochondrial dysfunction, adipose tissue dysfunction, and establishing a chronic low-grade inflammatory state.[2,3]

Interrelated mechanisms, including insulin resistance, oxidative stress and chronic inflammation, are the at the core of metabolic disease development. Recent investments in research and

development have produced promising therapies for metabolic diseases such as T2D, MAFLD, and obesity. This generation of therapies target the underlying pathways that lead to metabolic dysfunction. For instance, renin-angiotensin system inhibitors, commonly used for hypertension, are beginning to be used to promote insulin sensitivity and energy homeostasis in T2D and MAFLD. GLP-1 receptor agonists, dual- and triple-agonists, and amylin analogs initially developed to improve glucose homeostasis have been shown to increase energy expenditure and change eating behaviors. PPARγ agonists improve hyperlipidemia and insulin resistance but also have been shown to decrease inflammation and restore mitochondrial function. Opportunities to reduce oxidative stress, improve mitochondrial function and maintain energy homeostasis in obesity and MAFLD has led to the development of analogs of GDF15, FGF21, and FGF19, and mitochondrial uncouplers. Finally, benefits of immune modulators such as chemokine receptor antagonists, Kv1.3 channel inhibitors, inflammasome inhibitors, and cannabinoid receptor modulators have been shown to address chronic inflammation caused by obesity. Although T1D is too often excluded from these advancements, the metabolic abnormalities these drugs target may also offer significant benefits for T1D. Many of these therapies, and others not listed, merit clinical testing in people with T1D.

This funding opportunity will drive the development of therapies novel to T1D and provide critical insights into the metabolic challenges of T1D, ultimately leading to improved treatment options and clinical outcomes.

Objectives

Letters of intent (LOIs) are sought from academic and industry applicants to propose (1) clinical trials to evaluate therapies developed for other metabolic diseases that can improve metabolic outcomes in people with T1D or (2) clinical investigation of the underlying mechanisms of metabolic dysfunction in T1D to inform future therapy development.

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

- Clinical trials evaluating therapies or therapy combinations for improvement in T1D metabolic dysfunction, e.g., dysglycemia, insulin resistance, mitochondrial stress, chronic inflammation, other.
- Clinical trials testing therapies or therapy combinations that are approved or in development for T2D, obesity, and MAFLD in the T1D population.
- Clinical trials testing therapies or therapy combinations approved or in development for other autoimmune diseases or non-metabolic diseases where there is a credible hypothesis for efficacy in T1D glucometabolic control.
- Proof of concept (PoC) and proof of mechanism (PoM) interventional clinical trials

- Experimental medicine approaches and mechanistic trials exploring druggable pathways for metabolic control in T1D, including clinical research to determine whether a specific therapy ought to be pursued for T1D.
- Clinical research to investigate how druggable metabolic pathways are altered in T1D in liver, fat, muscle, and other relevant tissues.
- Clinical research to elucidate the influence of clinical phenotype (e.g., weight/BMI, lipid profile, age, duration of T1D, age at diagnosis) on treatment response.
- Opportunities to integrate clinical data and 'omics' data to identify metabotypes to predict disease progression and to inform precision medicine approaches in T1D. Studies to model pathways of metabolic dysfunction common across metabolic disease on the background of autoimmunity will be highly prioritized.

Examples of research **not** covered by this RFA include:

- Breakthrough T1D is not prioritizing research to address MAFLD in T1D. Rather, we seek to support T1D trials with MAFLD therapies to improve other outcomes in T1D, such as insulin resistance and hyperglycemia.
- T1D trials of therapies for metabolic abnormalities such as dyslipidemia, hepatic steatosis, and hypertension, where the proposed benefit to people with T1D is identical to that for the general population, unless there is a strong rationale for why T1D-specific studies are warranted.
- Evaluation of therapies that people with T1D already have access to, unless there is a strong rationale justifying why it is warranted.
- Studies focused on T1D prevention, such as evaluation of therapies intended to improve beta cell survival.
- Development of insulin therapeutics.
- Nonclinical studies except in exceptional cases where they contribute directly to clinical development efforts.
- Studies focused on hypoglycemia unawareness.
- Clinical trials evaluating lifestyle interventions such as diet and exercise.

Deliverables

- Projects should be designed to achieve key inflection points appropriate to project duration, budget, and initial stage of development.
- Successful clinical trials should provide safety and efficacy data to support next steps in a path toward further clinical development, regulatory approval, and/or changes to clinical guidelines.
- Successful experimental medicine and mechanistic clinical studies will provide data that can be used to inform future therapy development efforts.

Applicants are encouraged to consult with the Breakthrough T1D Scientific Staff below to discuss the alignment of their proposal to this RFA and to develop the projected study concept. Applicants are also encouraged to consult the Breakthrough T1D research abstracts database and clinicaltrials.gov to prevent redundancy with ongoing funded trials.

Critical considerations

- Clinically relevant glucometabolic control outcomes include HbA1c, level 1 and 2 hypoglycemia, time-in-range, glycemic variability, insulin resistance, weight/adiposity, lipids, ketones, and others.
- Proposals to evaluate SGLT inhibitors and once-weekly GLP1 receptor agonists in T1D must be strongly differentiated from historic and ongoing trials in T1D.
- Trials in sub-populations of T1D may be considered, such as people with T1D and overweight/obesity or high HbA1c, people in vulnerable age groups, and others.
- We will consider support of trials at any stage of development (phase 1, 2 or 3; from early trials focused on safety, PD markers, or mechanistic endpoints to later trials with powered effectiveness endpoints).
- Expectation of direct benefits on long-term complications is encouraged, but not required, in selection of therapeutic intervention.
- Breakthrough T1D strongly encourages applications from industry.
- Breakthrough T1D supports collaborative approaches, including between academic applicants and industry partners. **Breakthrough T1D can assist industry applicants seeking an academic partner, or vice versa, prior to submission of the LOI.**
- Breakthrough T1D encourages proposals that seek to leverage existing or planned projects (e.g., proposals that add resources to projects with funding from other sources).
- It is the applicant's responsibility to obtain drug for their study. Breakthrough T1D funding will be contingent on a written commitment from the drug manufacturer to provide study drug and placebo.
- The feasibility of future commercial and regulatory paths will be a key part of the proposal and carefully considered as part of Breakthrough T1D's funding decision.
- Clinical studies should recruit a diverse population representative of the real world in terms of ethnicity, socioeconomic status, and other demographic features.

Clinical Studies

- 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, including the recent Revised Common Rule.

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.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.

- 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 Mechanism

In response to this announcement, Letters of Intent (LOI) can be submitted under the following mechanism(s):

Strategic Research Agreement

Strategic Research Agreements are intended for support of research activities at non-for-profit entities such as academic institutions. Applications proposing clinical trials may request up to a total of $2,000,000 (including 10% indirect costs) over a maximum of three years. Applications proposing non-interventional clinical studies may request up to a total of $1,000,000 (including 10% indirect costs) over a maximum of three years. The level of funding will vary depending on the scope and overall objectives of the proposal. If your project budget exceeds $2,000,000, please discuss with Breakthrough T1D staff (contact information below). For more information on the Strategic Research Agreement (SRA) grant mechanism please refer to the Grant Handbook.

Industry Development and Discovery Program

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 review the IDDP guidelines available in the Grant Handbook for additional information. Applications proposing clinical trials may request up to a total of $2,000,000 over a maximum of three years. Applications proposing non-interventional clinical studies may request up to a total of $1,000,000 over a maximum of three years. 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

Prospective 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.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design, and investigational product information. More details can be found in the Human Subject Research Guidelines section of the Grant Handbook.

Breakthrough T1D follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the Common Rule changes.

Review Criteria

Applications will be subjected to confidential external scientific review evaluated on the following:

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

Projected Timeline

Milestone	Date
LOI deadline	Thursday, October 31, 2024
Notification of LOI outcome	Thursday, November 21, 2024

Full proposal deadline	Tuesday, January 7, 2025
Award notification	May 2025
Earliest anticipated start	July 2025

Program Contacts

Strategic Fit and Scientific Inquires

Courtney Ackeifi, PhD
Senior Scientist, Research
Breakthrough T1D
cackeifi@BreakthroughT1D.org

Administrative Inquiries

Sanjukta Mukerjee, PhD
Program Administrator, Research
Breakthrough T1D
smukerjee@breakthrought1d.org

1. Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol Ther*. 2019;21(2):66-72. **2.** Steenackers N, Feldman AN, Mathieu C, et al. The double burden: Navigating type 1 diabetes and obesity. *Clin Obes*. 2024;14(3):e12645. **3.** Corbin KD, Driscoll KA, Pratley RE, et al. Obesity in Type 1 Diabetes: Pathophysiology, Clinical Impact, and Mechanisms. *Endocr Rev*. 2018;39(5):629-663. doi:10.1210/er.2017-00191