RFA: Accelerating clinical trials evaluating disease-modifying therapies for T1D

Introduction

Purpose

Breakthrough T1D (formerly JDRF) is committed to accelerating the development of curative therapies from discovery research through clinical development and approval for type 1 diabetes (T1D). To this end, we invite applications that propose clinical trials to test small molecules, biologics, and combination therapies to delay, halt, or reverse the progression of T1D.

Background

Despite recent advancements, there is no cure for T1D, an autoimmune disease characterized by the loss of pancreatic beta cell mass and function, resulting in insulin deficiency and dependency[1]. Following clinical diagnosis, exogenous insulin replacement therapy is the only established treatment, and people with T1D require insulin administration for life and constant glucose management. While increases in the use of continuous glucose monitors has led to improvement, over 70 percent of people living with T1D fail to achieve optimal glycemic outcomes, and face significant risk of long-term complications, mental burden of constant disease management, financial burden due to medical care, and loss of income and productivity[2–4]. New interventions to prevent, slow, or halt disease progression are urgently needed to improve outcomes for the increasing number of people diagnosed with T1D each year.

Recent advances in disease-modifying therapies (DMTs) for T1D include the approval of teplizumab (Tzield™) for individuals prior to clinical diagnosis (stage 2) in the USA. Several therapies have

shown efficacy following diagnosis (stage 3) in phase I/II clinical trials, including teplizumab, abatacept, verapamil, rituximab, anti-thymocyte globulin (ATG), baricitinib, and golimumab[5–11]. These results highlight that interventions aimed at rebalancing the immune system to disrupt autoreactivity or to support endogenous beta cells have the potential to modify the course of disease and provide for the extension of beta cell function to delay or halt T1D progression. Unfortunately, there remains a significant deficit in the transition of these therapies from Phase 2 to Phase 3 trials and registrational approval. Therapeutic approaches focused on enhancing the regulatory elements of the immune system such as broad Treg transfer therapy and low dose IL-2 have shown mixed efficacy in human trials[12–15]. Novel approaches and strategies to induce tolerance in the clinical setting are of high priority for establishing therapies that promote sustained protection of beta cells. Finally, approaches to regenerate beta cells to increase functional beta cell mass have shown promise in pre-clinical studies, however, the clinical translation of these has been delayed due to the need for targeted delivery of these reagents to overcome safety concerns.

To achieve the Breakthrough T1D Cures Program goal of advancing disease-modifying therapies that delay, halt, or reverse the progression of T1D, multiple shots-on-goal are needed to build a robust clinical pipeline and accelerate development. The continued identification of novel therapies that exhibit clinical efficacy, or the assessment of therapies that have shown efficacy in other autoimmune diseases in T1D, is a key component of successfully building that pipeline. In addition, T1D is a complex disease, suggesting that success may require intervention towards multiple targets or pathways, or the development of therapies that address both immune rebalancing and beta cell support or expansion. Therefore, the clinical assessment of combinations of assets that have shown efficacy or have the potential to increase efficacy is of high priority.

To these ends, Breakthrough T1D is soliciting proposals aimed at the clinical assessment of novel or untested disease-modifying therapies, or combinations of molecules that have shown preliminary clinical efficacy as single agents, with the potential to delay, halt, or reverse the progression of disease in individuals in Stage 3 of disease. Expanding the repertoire of therapeutic approaches showing efficacy following diagnosis will increase the probability of success in meeting an unmet need for patients, provide critical data for the establishment of endpoints to increase trial efficiencies, and develop a path for testing these therapies in populations earlier in disease (or in those with established T1D in combination with beta cell replacement therapy).

Funding Opportunity

Objectives

Letters of intent (LOI's) are sought from academic and/or industry applicants for clinical trials to evaluate drugs and biologics to delay, halt, or reverse T1D through supporting or expanding

endogenous beta cell survival and function, disrupting autoimmune pathobiology, or combinations of the above.

Breakthrough T1D is requesting applications that propose Proof of Concept (POC) human subject research trials to provide the data necessary to enable further clinical development, and Phase 1 or 2 trials to determine safety and efficacy. Trials should be powered for the stage of clinical development proposed and include the appropriate and justified endpoints. Phase 3 trials may be considered, however, approval must be obtained from the scientific contact below prior to submission of an LOI so that the budgetary and timeline needs of the trial can be assessed.

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

- Trials evaluating novel small molecule drugs or biologics in people with T1D.
- Clinical trials evaluating the repurposing of small molecule drugs or biologics with demonstrated efficacy in non-T1D populations that have clear rationale or preclinical data for assessment in T1D.
- Inclusion of people with T1D in existing or planned clinical trials evaluating small molecule drugs or biologics in a non-T1D population.
- The inclusion of an additional arm to an ongoing T1D trial to test an additional intervention or new patient population.
- T1D-focused real world studies collecting efficacy and safety data on drugs or biologics with expected benefits for people with T1D.

Examples of research that will not be considered for this RFA include:

- Non-clinical and preclinical studies.
- Observational research on T1D-specific pathophysiology or epidemiology.
- Clinical trials that do not include people with T1D (however, trials may include other populations in addition to people with T1D).
- Clinical trials assessing therapies in populations other than Stage 3 (unless approved in advance of submission).
- Clinical trials assessing combinations of more than 2 interventions, unless approved by the scientific contact below prior to submission of the LOI.
- Clinical trials assessing nutraceuticals such as Vitamin D as a monotherapy.
- Clinical trials evaluating lifestyle interventions such as diet and exercise.

Trials should be designed to generate critical data regarding drug or biologic mechanism, efficacy, and safety in people with T1D. Trial results should allow for determination of whether selected

drugs or biologics merit further development toward the ultimate goal of regulatory approval and/or enhancement of clinical guidelines for people with T1D.

Priority consideration will be given to trials that:

- Evaluate an immune agent or therapy with established efficacy in another autoimmune disorder for a novel assessment of an ability to disrupt the immune attack on islets and preserve beta cell function in individuals newly diagnosed with T1D.
- Evaluate multiple agents that have individually shown efficacy in reducing/halting autoimmunity or supporting beta cell health in a combinatorial approach with a clear rationale for increasing efficacy through synergistic or additive mechanisms.
- Evaluate proven beta cell regeneration agents with novel targeting strategies based upon strong preclinical data with a focus on establishing a safety profile for the targeted regenerative therapy.

Applicants are encouraged to consult with the Breakthrough T1D scientific contact listed below to discuss the alignment of their proposal to this RFA and to discuss the projected study concept. To be considered, projects should have goals that align with the Breakthrough T1D Cures aims of delaying, halting, or reversing the progression of T1D, as outlined in the Breakthrough T1D Research Strategy.

Critical Considerations

- Breakthrough T1D strongly encourages applications from industry through the Industry Discovery and Development Partnership (IDDP) program. More information on this program can be found under the Mechanism section below.
- Breakthrough T1D encourages collaborative approaches, including between academic applicants and industry partners, and multi-country collaborations.
- It is expected that clinical trials assessing disease modifying therapies will target new onset (stage 3) individuals. Investigations proposing the assessment of other populations must be approved by the scientific contact below prior to submission of an LOI.
- Participant numbers and target enrollment should be appropriate for the stage of clinical assessment.
- Investigators should plan on including patient-reported outcomes (PROs) as part of the assessment wherever possible.

- It is the responsibility of the applicant to obtain the drug or therapeutic agent for their trial. Breakthrough T1D funding will be contingent on a written commitment from the drug manufacturer to provide study drug and placebo.
- Choice of surrogate and mechanistic endpoints in the trial should be well justified. Endpoints should align with regulatory pathways either established or under consideration, rather than exploratory objectives[16,17].
- Breakthrough T1D encourages proposals that seek to leverage existing or planned clinical trials by adding people with T1D or ancillary studies.

Clinical Study Guidelines

Breakthrough T1D follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the common rule changes. More information can be found in the Breakthrough T1D Grant Handbook.

In addition, proposals submitted under this call must:

- Include an experienced clinical trial manager (CTM) in the trial budget.
- Be powered for assessment of stimulated C-peptide AUC at endpoint (unless otherwise justified for the trial proposed).
- Include an extension period for follow-up measures for evaluation of durability of response.
- Include the use of continuous glucose monitors (CGMs) for all participants.
- Include the assessment of HbA1c, Time in Range (TIR), and other measurements of metabolic function as appropriate.
- Adhere to a harmonized sample collection plan for potential future analysis to be provided to applicants selected for submission of full proposals.

Mechanism

In response to this announcement, LOI's can be submitted to Breakthrough T1D's **Strategic Research Agreement (SRA)** or **Industry Discovery and Development Partnership (IDDP)** grant mechanisms. Please note that for IDDP LOI's, applicants are required to contact the Breakthrough T1D scientific contact below prior to submitting an LOI. For more information on these mechanisms, please refer to the Breakthrough T1D Grant Handbook.

Applicants may request budgets of up to $1.5M per year, for up to 4 years. Consideration of budgets or timelines that exceed these guidelines must be discussed with Breakthrough T1D staff prior to LOI submission.

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. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this RFA; however, additional information will be requested from for-profit entities if a full application is invited.

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.

Letter of Intent

Prospective applicants should submit a LOI online through via RMS360 (instructions below) to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the applications. Applicants will be notified according to the timeline below if they have been approved to submit a full proposal application.

Letters of intent should use the template provided and must include the following information:

- Background/Rationale, preliminary data and references to relevant publications, specific aims, project deliverables, and collaborative framework (if applicable).
- Justification for choice of trial endpoint(s).
- Targeted participant population, recruitment strategy, and inclusion/exclusion criteria.
- Plan for acquiring drugs and placebo/controls used in the study.
- Intellectual property or commercial efforts associated with the current application, including a list of current business partnerships relevant to the proposed work.

Proposal

An approved LOI is required prior to submission of a full proposal. Upon notification of a request for a full proposal, the application must be submitted using the templates provided on RMS360 (instructions below). Complete information should be included to permit review of each application without reference to previous applications.

Review Criteria

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

- Significance
- Approach
- Innovation
- Investigator Experience
- Environment

Administrative

Submission Instructions

Applicants should register and submit their completed LOI (and full proposal, if requested) in RMS360.

An informational webinar will be held on **Wednesday August 28, 2024 at 2:00pm** to provide further information on this opportunity. Please pre-register **here**.

Deadlines (no extensions will be given)

- LOI deadline: **Thursday October 10, 2024**
- Notification of LOI Outcome: **Thursday October 31, 2024**
- Full proposal deadline: **Monday January 13, 2025**
- Response to applicants: **June 2025**
- Earliest anticipated start date: **August 2025**

Contacts

Scientific

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Administrative

For grant-specific inquiries as you work within RMS360:

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