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Breakthrough T1D Request for Applications

Beyond Pediatrics: Advancing Early Detection in Adult-Onset Type 1 Diabetes

May 2025

Summary

- The main goal of this funding opportunity is to improve adult diagnosis of type 1 diabetes (T1D), with special emphasis on the early stages of the disease.
- This request for application (RFA) will award grants to non-profit and for-profit entities such as academic institutions and industry partners of up to $900,000.00 each and up to 3 years.

Funding Opportunity Description

Breakthrough T1D is the world's leading non-profit organization dedicated to curing and improving the lives of people with T1D by accelerating breakthroughs for T1D. T1D is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas, resulting in hyperglycemia and lifelong dependence on exogenous insulin. While T1D has traditionally been viewed as a childhood disease, approximately 62% of new T1D diagnoses occur in adults (≥20 years of age) worldwide[1-2]. An important consideration is that around 40% of these cases are misclassified as type 2 diabetes (T2D)[3], leading to delays in appropriate treatment and care. This shift presents urgent and significant challenges, as well as opportunities for research, accurate diagnosis, and timely intervention.

Through the Early Detection of T1D research portfolio, Breakthrough T1D is committed to applying our understanding of the disease's etiology, progression, and autoimmune pathogenesis – especially in historically understudied populations, such as those with adult-onset T1D – to improve the diagnosis of T1D. Understanding disease progression requires distinguishing between early stages (Stage 1 and 2), where individuals show the presence of persistent multiple autoantibodies without or with dysglycemia, and Stage 3, the clinical diagnosis, when symptoms appear due to significant beta cell loss and impaired glycemic control. Gaining deeper insight into this progression in adults may accelerate clinical research and facilitate access to emerging disease-modifying therapies that have the potential to delay or prevent the onset of clinical symptoms. Knowledge generated through this RFA may ultimately

inform regulatory decisions and contribute to the development of screening and monitoring guidelines in adults.

Background

Although several natural history and screening studies have included adults, most have focused on pediatric individuals or a limited adult range, and have primarily involved first-degree relatives. Notable examples include the Diabetes Prevention Trial–Type 1 (DPT-1)[4] and the TrialNet TN01 Pathway to Prevention Study[5], which enrolled participants between the ages of 3 and 45 years. More recently, efforts have expanded to include the general adult population, such as the T1D Risk in Adults (T1DRA) study in the UK, which is enrolling individuals aged 18 to 70 years,[6] and the Autoimmunity Screening for Kids (ASK) study in the Unites States, which has broadened its eligibility criteria to include adults as well. In addition, population-based registries like the UK Biobank and the German Diabetes Study (GDS) provide valuable data on individuals with adult-onset diabetes. However, despite these efforts, there remain multiple critical gaps in our understanding of the natural history and adult-onset T1D progression.

During a past Breakthrough T1D-hosted workshop, experts identified key knowledge gaps in adult-onset T1D [7], including the need to reduce ethnic disparities, extend longitudinal screening studies (of genetically high-risk and autoantibody-positive individuals) into adulthood, evaluate disease-modifying therapies given their greater efficacy in children, address challenges in misdiagnosis, assess the benefit and risks of adjunctive therapies, and strengthen post-diagnosis education, psychosocial support and long-term care. A recent manuscript has also highlighted similar gaps in the field,[8] including genetic risk, immunologic profiles and metabolic outcomes such as the type and number of autoantibodies present, the rates and persistence of C-peptide decline, and glycemic control. This RFA aims to address several of these unmet needs from a research perspective by supporting studies that advance our understanding of disease mechanisms specific to adult-onset T1D.

In pediatric T1D, significant progress has been made in elucidating the disease's etiology, progression, and underlying immunological mechanisms. These studies have contributed to the identification of genetic and environmental risk factors, early immune activation, and the role of diabetes-associated autoantibodies—such as those against insulin, GAD65, IA-2, and ZnT8. Despite this robust body of research in pediatric populations, adult-onset T1D remains significantly understudied. Emerging evidence indicates that adult-onset T1D may differ in its clinical presentation, rate of progression, and underlying immunological characteristics, underscoring the need for dedicated research in this area. Addressing these knowledge gaps is essential to improving the diagnosis, treatment, and long-term management of adult-onset T1D. By advancing our understanding of the distinct clinical and immunological features of T1D in

adults, we can enhance our capacity to deliver timely, personalized care and better support this growing population of individuals living with the disease.

We encourage research proposals that address one or more of the following areas, including but not limited to:

- **Immune Activation and Autoimmunity:** The autoimmune process in adult-onset T1D appears to exhibit distinct patterns of immune activation compared to pediatric cases, including differences in immune cell subsets, cytokine profiles, and the timing and magnitude of the immune response. Proposed studies should aim to characterize these adult-specific immune signatures and investigate their relationship to clinical progression, treatment requirements, and therapeutic responsiveness. Research should leverage established datasets and biobanks with adult-onset T1D cohorts to validate findings across diverse populations. These efforts will be critical to informing the design and timing of disease-modifying therapies targeted at the early stages of T1D in adults.
- **Islet Pathology and Beta Cell Function:** Adults diagnosed with T1D often retain greater residual beta cell function at onset than children, suggesting slower disease progression and potential differences in islet pathology. Research should explore the mechanisms underlying these differences, including the pace of beta cell destruction and the regenerative capacity of the adult human pancreas, with implications for therapeutic timing and response.
- **Autoantibodies and Biomarker Validation:** In early-stage T1D, adults are more likely to test positive for GADA, while children more commonly exhibit IAA, IA-2A, or ZnT8A. We are seeking proposals that aim to better characterize and validate alternative autoantibodies and other established biomarkers of disease progression through Stages 1 to 3 in adults, with the goal of improving diagnostic accuracy and stratification of progression, including adults with slow disease progression.
- **Accuracy in Misdiagnosis and Diagnostic Tools:** We support proposals that aim to address the misdiagnosis of adult-onset T1D, including efforts to distinguish it from T2D through the integration of autoantibodies, C-peptide, and clinical features. Proposals may also include the analysis of existing electronic health record (EHR) data to identify diagnostic patterns and improve classification strategies.
- **Epidemiology Studies:** Evidence suggests that while a family history of T1D increases risk at all ages, the strength of this association appears to be greater in childhood-onset cases. This RFA welcomes studies that aim to advance our understanding of the epidemiology of adult-onset T1D using existing databases, as this area remains poorly defined. Projects examining incidence, prevalence, and age-related trends are encouraged to help clarify population-level risk factors.

Out of Scope for this request:

- For any approaches focused on genetic risk in adult-onset T1D, please refer to the RFA titled “Advancing Genetic Risk Assessment for Type 1 Diabetes: Improving Prediction and Clinical Translation” launched in parallel with this RFA.
- Exclusive pediatric T1D studies with no clear link to adult-onset T1D.
- Support for research screening programs that require additional recruitment and monitoring of adults to understand the natural history of T1D in this population.
- Studies focusing on disease progression after clinical diagnosis or examining environmental triggers that influence adult-onset T1D.
- Testing of beta cell regenerative agents or therapies.
- Basic research using animal models (e.g. NOD mice) without human clinical relevance.

In conclusion, addressing the gaps in knowledge related to adult-onset T1D is crucial for improving the diagnosis, treatment, and management of this condition. By expanding our understanding of the unique features of T1D in adults, we can enhance our ability to provide effective care and support for this growing population. Understanding the early stages and progression of T1D in adults is pivotal in advancing our knowledge and addressing clinical needs, ensuring proper diagnosis, and offering appropriate care. This research will not only help identify individuals in the early stages of T1D but also foster the development of more effective management strategies that can enhance the lives of these individuals prior to developing clinical T1D.

Eligibility

- Applications may be submitted by domestic and foreign non-for-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 welcomed 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 human clinical research.
- 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, LOI's can be submitted to Breakthrough T1D through the following two mechanisms (please refer to their respective website for further information):

- **Strategic Research Agreements (SRA)** are intended for support of research activities at non-for-profit entities such as academic institutions. SRA totals can include up to 10% indirect costs. For more information about our SRA and Clinical SRA grant mechanisms, please refer to our grant handbook.
- **Industry Development and Discovery Program (IDDP)** are intended for support of for-profit entities. They entail additional requirements and typically have a modest royalty payback to Breakthrough T1D. Please refer to our grant handbook for information on the IDDP grant mechanism and descriptions, and contact the Breakthrough T1D scientific contact listed below before submitting your application. Indirect costs are not permitted on IDDP applications.

Proposed budgets for projects should not exceed $900,000.00 total costs for up to 3 years of duration. The level of funding or duration will vary depending on the scope and overall objectives of the proposal. Breakthrough T1D may consider applications with increased scope (time and/or budget) where there is a strong justification, and interested applicants should discuss with the Breakthrough T1D scientific contact below.

Letter of Intent

Prospective applicants should submit a Letter of Intent (LOI) [2 pages maximum] online via RMS360 to be considered for a full proposal request. The LOI template provided through RMS360 must be used to complete the LOI application.

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 our grant handbook.

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

Review Criteria

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

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

Informational Webinar and Q&A

Breakthrough T1D will hold an announcement introduction meeting via Zoom on **May 13, 2025, 11am Eastern Time** to which all prospective applicants are invited. Breakthrough T1D scientists will give an overview of the goals of this initiative, explain the application process, and answer initial questions on applications. Recognizing that the scheduled time may not be convenient for participants in all time zones, the session will be recorded and made available upon request.

Please register for the webinar in advance:

https://breakthrought1d-org.zoom.us/webinar/register/WN_PG9fOQhLQGGI3G-usOe8gQ

After registering, you will receive a confirmation email containing information about joining the webinar.

Projected Timeline [no extensions will be given]

- Information webinar and Q&A — Tuesday, May 13, 2025
- Letter of Intent (LOI) deadline — Tuesday, June 10, 2025
- Notification of LOI outcome — Friday, June 20, 2025
- Full Application deadline — Thursday, July 17, 2025
- Award notification — December 2025
- Earliest anticipated start date — February 2026

Program Contacts

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