JDRF Request for Applications: Glycemic and beta cell monitoring in individuals at risk of Type 1 Diabetes.

December 2023

Summary

- The main goal of this funding opportunity is to improve glycemic biomarkers of disease progression in individuals at high risk of type 1 diabetes (T1D), as they transition from presymptomatic disease (Stages 1 and 2) to clinical diagnosis (Stage 3). LOI's are sought for projects that will aid the translation of risk assessment tools for T1D into clinical use. The focus of this call is the improvement of current or new metabolic risk assessment tools and their integration into clinically and commercially utilized testing platforms.
- Proposals should prioritize validating optimal measurements for glycemic control, with a focus on monitoring alternatives such as blood glucose dysregulation (using fingersticks or CGMs) and beta cell function (C-peptide). This emphasis aims to enable the timely detection of individuals as they transition to Stage 3 T1D. Importantly, the correlation of data measurements from the classic measurements of HbA1c, oral glucose tolerance tests (OGTT) and mixed meal tolerance tests (MMTT) is essential to provide context on how they compare to alternative approaches. Of particular interest is the development of glycemic approaches that are implementable in clinical or public health laboratories, as well as at home testing.
- A key goal of this RFA is to profile the decline of C-peptide before clinical onset. The RFA will support the analysis of existing datasets from natural or clinical studies that include measurement of C-peptide used to monitor endogenous insulin production before and after diagnosis in individuals at risk.
- This program will award grants to non-profit and for-profit entities such as academic institutions and industry partners of up to $900,000.00 and up to 3 years. JDRF International will consider applications with increased scope (time and/or budget) where there is a strong justification (e.g. clinical studies) and interested applicants should discuss with the JDRF scientific contact.

Funding Opportunity Description

JDRF is the world's leading non-profit organization with the mission to improve the lives of people with T1D by accelerating breakthroughs for T1D. JDRF eagerly awaits the submission of pioneering research proposals aimed at advancing our understanding of glycemic changes during disease progression in presymptomatic individuals, with the potential to improve progression biomarkers and monitoring their transition to clinical diagnosis. The knowledge gained in this RFA may eventually be applicable to support regulatory decisions and be part of monitoring guidelines, enabling more effective early identification and timely intervention by

healthcare professionals, including the use of innovative treatments like the recent FDA-approved teplizumab treatment, as well as other immunotherapies currently in clinical trials. As such, its implementation would mark a significant milestone in the pursuit of delaying or preventing T1D and its associated complications.

Background

T1D risk is influenced by several factors including genetics, age, ethnicity, BMI, and environmental determinants. The early stages of T1D can be detected by the presence of islet autoantibodies in serum and these are well correlated with the later development of clinical disease. Persistent positivity of 2 or more of the most common T1D autoantibodies (insulin - IAA, glutamic acid decarboxylase - GADA, insulinoma-associated antigen 2 – IA2A, and zinc transporter 8 - ZnT8A) indicates active autoimmunity and is classified as Stage 1 T1D. The presence of autoantibodies and signs of dysglycemia (Stage 2) such as impaired fasting glucose (100-125 mg/dL), or impaired glucose tolerance (140-199 mg/dL), or A1c 5.7-6.4% or >10% increase [1] is linked to a higher risk of progression to symptomatic disease (Stage 3).

Pre-symptomatic T1D (Stages 1 and 2) represents a critical period in the disease progression where interventions can potentially delay or prevent the onset of clinical symptoms. This RFA seeks to support research projects aimed at understanding the intricate interplay between autoantibody positivity, glycemic control, and beta cell loss in individuals with presymptomatic T1D. Preservation of functional beta cells and effective glucose control are central to managing T1D. It is imperative to explore the dynamic relationship between these factors during the pre-symptomatic phase to develop strategies that can sustain beta cell function, minimize beta cell loss, and optimize glucose management in individuals at risk.

One of JDRF's goals is to develop and execute a global universal screening strategy that identifies high-risk pediatric and adult individuals and monitors them to ensure a smoother transition, improve their quality of life, and reduce complications at disease onset such as diabetic ketoacidosis (DKA). Please refer to the [Research Strategy Document](#) for further details. Further investigation is needed to establish appropriate guidelines for monitoring individuals with presymptomatic T1D. This RFA will support grants that identify and/or further validate biomarkers of progression to clinical T1D such as but not limited to:

- HbA1c measurements that fall outside of the optimal range, but also ≥10% increases within optimal ranges.
- Fasting or pre/post-prandial home fingerstick blood glucose monitoring.
- Percentage of CGM time spent above 120-140 mg/dL, using time in range (TIR) and/or glucose management indicators (GMI).
- In-clinic vs at-home measures of beta cell function by OGTT, their timing and serial approaches.

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

1. Longitudinal studies: Introducing an additional parameter to existing longitudinal studies with the goal of incorporating glycemic monitoring approaches such as CGMs or C-peptide. This expansion aims to enhance the follow-up of current individuals enrolled, providing a more comprehensive understanding of measurements and contributing valuable insights to refine diabetes management strategies.

2. Retrospective studies: Conducting a retrospective analysis across longitudinal studies to deepen our understanding of historical data related to different glycemic monitoring approaches, including CGMs or C-peptide. This analysis aims to assess the effectiveness of these alternatives on identifying individuals at risk of disease progression and compare their reliability to traditional monitoring methods such as HbA1c and OGTT/MMT analysis.

3. Comparative studies between children and adults with clinical onset of T1D: Explore and compare data from longitudinal and interventional studies to understand the unique aspects of disease progression in pediatric populations versus adults. Additionally, we are keenly interested in adult monitoring follow-up from research studies, aiming to comprehensively assess and analyze the long-term outcomes and inform tailored strategies for the effective management of and interventions in this population.

4. Monitoring of immunotherapy treatments: Implementing follow-up glycemic monitoring for individuals undergoing disease modifying therapies, whether in FDA-approved treatments (e.g. teplizumab) or enrolled in other ongoing clinical trials. Establishing a robust system for continuous monitoring, allowing for better follow-up of patients and aiming to improve their outcomes through optimized glycemic management.

5. Clinical trials and the impact of glycemic monitoring approaches: Investigate the relationship between clinical outcomes and C-peptide data for use in clinical trial settings. This aspect aims to elucidate the potential value of C-peptide as a biomarker of disease progression in the context of clinical trials, contributing to the development of more effective and targeted monitoring approaches.

6. Advanced monitoring technologies: Develop and evaluate innovative monitoring technologies that provide real-time data on beta cell function and glucose control in presymptomatic individuals before and after they progress to clinical disease. The integration of cutting-edge monitoring devices with C-peptide assessment is critical for a comprehensive understanding of the disease progression.

7. Biomarker validation: Research projects focused on validating novel biomarkers of disease progression and beta cell loss (e.g. immune or beta cell biomarkers), while also evaluating their relationship with C-peptide levels and glycemic control. These biomarkers will be proven as indicators of disease progression before clinical diagnosis.

8. Ethnic and gender diversity and disparities: Investigate the impact of ethnicity on glucose management and C-peptide levels in T1D progression.

Out of Scope for this request:
- Assay development for improved islet autoantibodies
- While the inclusion of genetic data is encouraged in studies involving data analysis, the improvement of Genetic Risk Score (GRS) tools is out of scope.
- Psychosocial impacts of screening in high-risk individuals with pre-symptomatic T1D.
- Studies focused on disease progression following clinical diagnosis.

Understanding how glycemic control and beta cell loss are interconnected during the pre-symptomatic phase is pivotal for advancing our knowledge of T1D. This research is not only essential for identifying individuals at high risk of clinical onset, but also for developing more effective management strategies that can enhance the lives of individuals at risk of 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., Ph.D., or equivalent 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 JDRF 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, JDRF 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 JDRF 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.
➢ **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 JDRF. If you want to submit an IDDP project, applicants must contact the JDRF scientific contact below before submitting their 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. JDRF may consider applications with increased scope (time and/or budget) where there is a strong justification (e.g. clinical studies requiring additional funds to cover patient enrollment or payment of clinical sites) and interested applicants should discuss with the JDRF 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.

JDRF 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:

- o Significance
- o Relevance
- o Approach
- o Innovation
- o Environment

- o Resource sharing plan

Informational Webinar and Q&A

JDRF will hold an announcement introduction meeting via Zoom on **December 20, 2023, from 10-11am Eastern Time** to which all prospective applicants are invited. JDRF scientists will give an overview of the goals of this initiative, explain the application process, and answer initial questions on applications.

Please register for the webinar here:
https://jdrf.zoom.us/webinar/register/WN_tcUo1u7qSy6skDyoY8w83w

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

Projected Timeline

- ➢ Information webinar and Q&A   December 20, 2023
- ➢ Letter of Intent (LOI) deadline   January 25, 2024
- ➢ Notification of LOI outcome   February 1, 2024
- ➢ Full Application deadline   March 8, 2024
- ➢ Award notification   July 30, 2024
- ➢ Earliest anticipated start date   October 01, 2024

Program Contacts

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References

[1] American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S20–S42