JDRF REQUESTS APPLICATIONS FOR:
PILOT STUDIES FOR MECHANISMS OF T1D DISEASE PATHOGENESIS

PURPOSE
JDRF invites applications to discover or validate mechanisms, processes, and triggers that contribute to human type 1 diabetes (T1D) pathogenesis. Projects funded by this RFA are expected to generate knowledge about early factors that trigger T1D and processes that drive T1D progression. This RFA aims to fund innovative research that will provide insights into mechanisms of disease pathogenesis that will enable future approaches to predict and prevent initiation and progression of T1D.

BACKGROUND
T1D is a complex, chronic autoimmune disease. T1D can be diagnosed at any age, and approximately half of all diagnoses are made in adults. The number of newly diagnosed T1D patients worldwide is accelerating between 3-4% annually. The earliest detectable event in the development of T1D is the appearance of islet autoantibodies in the blood, which denotes beta cell autoimmunity (Stage 1). As T1D progresses, the immune system destroys insulin-producing beta cells in pancreatic islets, leading to dysregulated glucose control (Stage 2) and life-long dependence on exogenous insulin therapy (Stage 3). We do not understand the triggers that impact the development of beta cell autoimmunity (Stages 1/2 T1D) or the progression from Stages 1/2 to clinical T1D (Stage 3). Because of this, there is no cure or method of prevention for T1D.

Several risk factors for developing T1D have been identified. The risk of developing T1D is increased by certain genes, like the inherited susceptibility genes of the HLA family. In addition, non-genetic factors such as an individual's immune system and environmental influences are believed to impact disease pathogenesis and progression. Studies investigating the role of the immune system in driving T1D have been done, but how immune cell/islet interactions drive T1D is still largely unknown. In addition environmental contributions such as diet, stress-induced changes in metabolism, viral pathogens, and carcinogens need further study in T1D pathogenesis.

This RFA is focused specifically on mechanisms of human T1D disease pathogenesis. There are likely multiple factors that simultaneously contribute to the disease. Research generated from this RFA should contribute knowledge to enable the prevention of T1D through the identification and validation of targets for preventative therapies, informing strategies for effective therapeutic modulation of these targets, and/or development of tools that will allow the identification of patients likely to benefit from preventative therapies.

OBJECTIVES
This RFA will support research programs that are aimed at identifying mechanisms of human T1D pathogenesis. Triggers, biological pathways, or cellular targets that contribute to initial autoantibody seroconversion and those that drive progression of T1D from Stage 1 through Stage 3 will be prioritized. Investigators from the T1D field, and those who have identified triggers of other autoimmune diseases and wish to extend those findings into T1D, are encouraged to apply. This RFA will support the generation of new data as well as the interrogation of existing data sets to understand T1D pathogenesis.
Examples of research topics are listed below (examples not intended to be exclusive or all-encompassing):

**Islet/immune interactions**
- Identification of beta cell subsets that are preferentially targeted by or resistant to T-cell killing and the mechanisms by which this occurs
- Mechanistic studies of pancreatic infiltrates, including antigen-specific B and T cells, and other cell subsets that contribute to T1D susceptibility

**Beta Cell Mass and Function**
- Determination of the relative importance of loss of beta cell function and loss of beta cell mass in T1D initiation and progression
- Exploration of how loss of pancreatic mass/function correlates with local and peripheral immune changes and influences autoantibody seroconversion and T1D progression

**Environmental etiologies**
- Exploration of how viral infections influence beta cell survival
- Identification of environmental factors contributing to autoantibody seroconversion and T1D progression and the mechanisms by which they occur

**Pancreatic inflammation**
- Understand the role of pancreatic inflammation in the acceleration of T1D

**Understanding pathogenic mechanisms in non-traditional cohorts**
- Determine the biological or environmental factors, including protective factors, that define onset of T1D in adults

This RFA is **not** intended to support: interventional clinical trials, characterization of biomarkers in the absence of mechanism, mechanisms of type 2 diabetes pathogenesis, studies relying exclusively on the study of animal models, studies exclusively involving other autoimmune indications, microbiome research, or natural history studies.

**ELIGIBILITY**
Preference will be given to early-stage investigators who have not previously received a substantial independent research award. Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent academic degree and a faculty position or equivalent at a college, university, medical school, and for-profit research based organization or other comparable institution.

Applications may be submitted by domestic or foreign, public or private non-profit organizations, such as colleges, universities, hospitals, laboratories, units of state or local governments or eligible agencies of the federal government. 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.

Please note that submissions from for-profit entities or collaborations involving for-profit entities will be reviewed by the JDRF T1D Fund (http://www.jdrf.org/about/t1dfund/) in addition to JDRF 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.
MECHANISM
Applications will be funded by the following mechanism:

**Pilot Grant:** Up to $150,000 USD (total) including 10% indirect costs for up to 2 years may be requested. One or two years may be selected as the investigator deems necessary to complete the proposed research project.

Applications that are not funded in this competition may be resubmitted to other JDRF grant mechanisms according to the deadlines and guidelines described on the JDRF Web site: [http://grantcenter.jdrf.org/rfa/](http://grantcenter.jdrf.org/rfa/)

PROPOSAL
The application must be completed using the templates provided on the JDRF’s grant application portal (RMS360) ([http://jdrf.smartsimple.us](http://jdrf.smartsimple.us)). Proposal section templates in MS Word **[5 page 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 review of each application without reference to previous applications.

The Research Plan must be organized as follows **(5 page maximum):**

- Background and Significance of this work to T1D
- Proposed research (What?)
- Rationale for proposed research (Why?)
- Research Design and Methods (How?)
- Advantages over alternative approaches that would address goal.
- Future plans if research is successful.

Preliminary data is not required in the proposal, but the underlying premise, goal or hypothesis must be plausible and testable. The proposal must be focused with a well-defined goal that is achievable within the timeframe of the award.

Proof of access to biosamples, if not included with the application, will be required prior to activation of any award.

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A
JDRF will hold an announcement introduction meeting via web and teleconference on **Monday October 1, 2018 at 11:00 AM US Eastern Standard Time**, to which all interested 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. A brief introduction on JDRF’s grant application portal (RMS360) will also be given.

**Click here to Join WebEx meeting**
Meeting number (access code): 730 623 489
Meeting password: 6saQtmb3

**Join by phone**
1-866-469-3239 Call-in toll-free number (US/Canada)
+1-650-429-3300 Call-in toll number (US/Canada)
[Global call-in numbers](http://grantcenter.jdrf.org/rfa/) | [Toll-free calling restrictions](http://grantcenter.jdrf.org/rfa/)
DEADLINES
- **Release Date**: September 20, 2018
- **Application Due Date**: November 20, 2018
- **Response to Applicants Date**: April 2019
- **Earliest Anticipated Start Date**: July 1, 2019

SUBMISSION INSTRUCTIONS
Applicants must register as an applicant and submit their application in response to this RFA using JDRF’s on-line research management system RMS360 (https://jdrf.smartsimple.us).

REVIEW CRITERIA
Applications will be evaluated based on JDRF’s standard confidential award policy and according to the following criteria:
- Significance
- Relevance
- Approach
- Innovation
- Investigator Experience
- Environment

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If you have any grant-specific questions as you work within RMS360, please contact the administrative contact listed above. For any non-grant-specific inquiries or technical issues, please contact SmartSimple Support Services via email support@smartsimple.com or phone (866) 239-0991. Support hours are Monday through Friday between 5:00am and 9:00pm US Eastern Standard Time.