JDRF SPECIAL REQUEST FOR EXPRESSIONS OF INTEREST:

CLINICAL TRIALS TO PRESERVE BETA CELL FUNCTION AND DELAY ONSET OF SYMPTOMATIC DISEASE IN THE AT-RISK SETTING FOR TYPE 1 DIABETES

PURPOSE

JDRF is soliciting expressions of interest (EOI) for performing secondary prevention clinical trials to preserve beta cell function and delay the onset of symptomatic disease. These EOIs may include proof-of-concept clinical trials with existing and/or novel therapies and with combination therapies that target different aspects of beta cell dysfunction and loss.

BACKGROUND

Prevention of type 1 diabetes (T1D) represents a "cure" for those at-risk of developing the disease, and, in fact, will likely represent the most cost-effective approach to a cure and is becoming increasingly important with the rising incidence of the disease. Over the last three to four decades, the incidence of T1D has increased at an annual rate of 3-5% with penetration to low-moderate human leukocyte antigen (HLA) risk groups, suggesting a lowered threshold for its development. In some countries, the largest increase in incidence has occurred in the age group 1-5 years.

T1D secondary prevention (prevention of symptomatic disease after the onset of autoimmunity) trials are ongoing today and these current trials and new secondary prevention trials have the prospect of demonstrating that progression can be slowed in the at-risk setting, a concept yet to be demonstrated to date. If left untreated, the majority of these individuals will proceed to develop symptomatic T1D. Secondary prevention interventions to robustly arrest disease progression and prevent symptomatic disease will likely require combining therapies that target beta cell-specific autoimmunity, inflammation, beta cell survival and/or metabolic regulation. Smaller and shorter proof-of-concept prevention clinical trials will be prioritized.

OBJECTIVES

Expressions of interest are sought from investigators with access to patient cohorts of individuals with ≥2 T1D autoantibodies to conduct proof-of-concept clinical trials using intermediate trial outcomes/endpoints to inform larger and longer prevention trials. Intermediate endpoints to be considered include: increasing HbA1c, onset of dysglycemia, reversal of dysglycemia, change in C-peptide, etc.). Repurposed and/or novel therapeutics (immune, inflammation, beta cell survival, metabolic, etc.) will be considered. Combination therapies, used either sequentially or simultaneously, for robust prevention will also be considered.

Investigators with ideas or resources that might benefit this initiative should also submit their ideas via an expression of interest. Mechanistic studies should be built into all trials.

JDRF is concurrently releasing an EOI for Combination Therapies in Type 1 Diabetes. This EOI is not meant as a replication of that EOI, which focuses on combination therapies for new-onset and established T1D. Furthermore, EOIs with a focus on primary prevention will not be considered.

ELIGIBILITY

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, 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 EOI, however, additional information will be requested from for-profit entities if a full application is invited.

There are no citizenship requirements.

MECHANISM

EOIs in response to this announcement can be submitted to the following mechanism:

Clinical Strategic Research Agreements (supported by strong preliminary data) for a maximum budget of $1,500,000* per year for up to 3 years of funding (including 10% indirect costs)

Pre-clinical support may be requested only for IND-enabling activities.

* Applications whose budget and/or timeline exceeds the above specified guidelines, must obtain JDRF staff approval prior to submitting an LOI.

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://www.jdrf.org/

DEADLINES

- **Release Date**: ..... April 22, 2014
- **Expression of Interest**: ..... July 11, 2014
- **EOI Notification** ..... August 1, 2014
- **Application Due Date**: ..... October 1, 2014
- **Response to Applicants Date**: ..... December 23, 2014
- **Earliest Anticipated Start Date**: ..... February 1, 2015

EOI COMPONENTS

Prospective applicants should submit an expression of interest on-line via RMS360 at https://jdrf.smartsimple.us The EOI template located under the LOI Research Plan tab must be used to submit.

EOI submissions will undergo expedited review. Applicants will be notified if they have been approved to submit a full application.

Expressions of Interest should be no more than 3 pages in length including the following information:

- Specific aims for the proposed study
- Background and rationale for the proposed study
- Brief description of research plan including preliminary data
- Description of cohort to be studied and inclusion/exclusion criteria
- Brief overview of statistical power, if relevant.
- Future plans if successful and potential translational impact of the proposed study
- Projected deliverables for the project if successful
- Intellectual Property or commercial efforts associated with the current application
- For collaborative projects, description of how the project will be led and coordinated
- References (no page limit)

SUMBISSION INSTRUCTIONS

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

As a courtesy, please email the scientific contact, Jessica Dunne (jdunne@jdrf.org) to inform us of your intention to submit an EOI.

REVIEW CRITERIA

Submitted expressions of interest will be acknowledged with brief responses as to their suitability for further development by the JDRF no later than August 1, 2014.

PROPOSAL

An approved Expression of Interest is required prior to submission of a full proposal.

Upon notification of a request for a full proposal, the application must be completed using the templates provided on the RMS360 website https:// jdrf.smartsimple.us. Proposal section templates in MS Word 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:

1) Background and Significance of this work to the goals of the RFA
2) Proposed Research
3) Rationale for proposed research
4) Research Design and Methods
5) Advantages over alternative approaches that would address the same goal
6) Future plans if research is successful and potential translational impact
7) Projected milestones for specific aims, projected annual outcomes, and deliverables; Projected major milestones and deliverables for year 1 must be provided in the application; these will be reviewed and may be modified as work progresses during the course of the research program in discussion with the JDRF Program Director.
8) Intellectual Property or commercial efforts associated with the current application
9) References (no page limit)
10) Principal Investigator Assurance

For SRAs, all information in items 1-7 must be incorporated in the 12-page limit without exception. Note that applications with research plans exceeding the page limit will not be reviewed.

PROPOSAL COMPONENTS

- Applicant and Institutional Demographics (including Financial and Administrative Officer)
- Approved EOI
- Institutional Letter of Support
- Key Personnel
- Lay and Technical Abstracts
- Budget
- Budget Justification
- Subcontract Budget (if applicable)
- Subcontract Budget Justification (if applicable)
- Other Support (for the PI only)
- Organization Assurances (IRB and/or IACUC)
- Biosketches (for all Key Personnel)
- Research Plan
- Human Subject Research plan (if applicable)
- Resources
- Supporting Documents (i.e. Letter(s) of Collaboration, etc.)
- Documented proof of access to samples or written approval from sample access committees

INSTRUCTIONS

Applicants must register as an applicant and submit their expression of interest and invited application in response to this RFA using JDRF's on-line application system. 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

Significance: Does this study address an important problem? What will be the expected effect of the discovery and development of biomarkers of beta cell stress and health?
Relevance: Is the proposed research relevant to the objectives of this RFA? What will be the expected impact of these studies on the JDRF's mission?
Approach: Are the conceptual framework, design, methods and analyses adequately developed, well integrated and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Is the proposed research feasible within the term of the award? Are resources and knowledge based on prior experience and know-how?
Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?
Investigator Experience: Is the investigator appropriately trained and well suited to carry out the planned studies? Is the work proposed appropriate to the experience level of the principal investigator? If the investigator does not have T1D experience, are there appropriate collaborative arrangements with experts in T1D? For collaborative projects, is the project well led and coordinated?
Environment: Does the scientific environment in which the work will be performed contribute to the probability of success? Do the experiments proposed take advantage of unique features of the scientific environment or employ useful **collaborative** arrangements? Is there evidence of institutional support?

SCIENTIFIC CONTACTS

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ADMINISTRATIVE CONTACTS

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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 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.