JDRF REQUESTS LETTERS OF INTENT FOR: OVERCOMING OBSTACLES TO ACHIEVING IMMUNE TOLERANCE IN TYPE 1 DIABETES

PURPOSE

JDRF is soliciting letters of intent (LOI) for the identification of key barriers in the way of therapeutically restoring immune tolerance in type 1 diabetes (T1D) after the onset of autoimmunity (i.e., in at-risk autoantibody positive pre-diabetic, recent-onset diabetic, and established disease subjects). Such efforts are intended to support the ultimate goal of identifying targets, combination therapies, and treatment strategies for T1D. JDRF is committed to translation of research findings towards clinical results and is most interested in projects that have clinical translation potential.

BACKGROUND

Because T1D results from a failure to maintain immune tolerance to pancreatic islet antigens, targeting the immune response to these autoantigens may provide a safe and effective means of preventing and controlling the autoimmune response while avoiding the harmful effects associated with non-specific immunosuppression. Immunotherapeutic approaches for preventing or halting T1D have involved both autoantigen-specific immunotherapies (ASIs) and non-autoantigen immunomodulatory (IM) interventions such as antibody therapeutics targeting pathogenic immune cell surface molecules and cytokines. While disease prevention or treatment trials with ASI or IM agents have not demonstrated robust, durable effects on immune tolerance or metabolic disease outcomes, such studies have provided compelling evidence of enhanced regulatory T (T_{reg}) cell numbers and functions and reduced memory T effector (T_{eff}) cell subsets, suggesting that immune tolerance might be achieved with the appropriate improvements to therapy. Because ASIs are expected to be a safe approach for restoring and maintaining immune tolerance, it is critical to understand the physiological conditions (and identify barriers) that allow for optimal ASI performance. Such barriers that adversely influence the capacity of ASIs to achieve tolerance include 1) the pathogenic immune/inflammatory environment driven by autoreactive T_{eff} cells, 2) any functional defects of T_{reg} cells relevant to T1D, 3) the specific antigenic component(s) of ASIs, and 4) specific therapeutic requirements of a defined disease stage or patient subpopulation. It is expected that many such barriers can be removed with combination therapies that “help” ASIs enhance regulatory cells and reduce pathogenic cells.

OBJECTIVES/SCOPE

Letters of Intent are sought from investigators interested in 1) investigating the role of disease-associated immunological changes in T1D subjects that are barriers to the optimal performance/selection of ASIs to achieve immune tolerance, 2) exploring mechanisms of establishing durable (vs. transient) tolerance using IM, ASI, and a combination of both, 3) testing combinations of IM therapies with ASIs in preclinical models to achieve tolerance, and 4) performing preclinical studies with such rationally selected combinations to determine optimal dosing and timing of administration for modeling combination therapies in clinical trials. The clinical translation potential of the investigations should be emphasized.

Examples of pertinent topics include, but are not limited to:

- Use of relevant preclinical models to evaluate the ability of IM therapies to enhance the performance of ASIs to achieve immune tolerance to beta cells at different disease stages
- Addressing whether pathogenic cell-mediated pancreatic inflammation and beta cell destruction negatively influence the performance of ASIs in restoring immune tolerance
- Determination of the functional status of T_{reg} cell populations in T1D subjects (or appropriate mouse models) with respect to whether any functional defects identified are cell-intrinsic and/or a consequence of disease activity, thus affecting the performance of ASIs
- Investigation of the therapeutic benefit of achieving immunoregulation/tolerance via a single- vs. multiple-antigen ASI that may be linked to a T1D disease stage
- Elucidation of the degree and mechanism-of-action of autoantigen-specific T_{reg} cell by-stander suppression that leads to restoration of immune tolerance upon ASI treatment (use of inducible autoimmune models is appropriate)
- Addressing the relative roles of cell ablative vs. immunomodulatory therapies as necessary prerequisites for success with ASI (use of inducible autoimmune models is appropriate)
- Establishing a mechanistic rationale for 'when' beta cell therapies are best combined with ASI or IM therapies.

This RFA is not intended to support: efficacy readouts only in preclinical models of disease, efforts aimed at development of cellular therapies or gene therapy approaches; studies without potential for translation or informing future clinical approaches.

Applicants who wish to consult with JDRF Program Staff to discuss the responsiveness of their proposal to this program or to discuss ideas or resources that might benefit this initiative may do so. Enquiries in this area should be referred to contacts as shown below.

Collaborative efforts engaging investigators with complementary expertise are highly encouraged.

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A

JDRF will hold announcement introduction meeting via web and teleconference on **November 13, 2015 at 1-2 PM** US Eastern 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 new grant application portal (RMS360) will also be given.

Click here to Join WebEx meeting
Meeting number: 730 000 222
Meeting password: research2015

Join by phone
Dial in (US): 877-261-5012
Dial in (International): https://www.intercallonline.com/listNumbersByCode.action?confCode=5908746746

Conference code: 59 08 74 67 46

MECHANISM

Up to a maximum of $250,000 USD per year including 10% indirect costs for up to 2 years may be requested. The level of funding will vary depending on the scope and overall objectives of the proposal. Under the terms of the grant award, written quarterly (~2-3 pages) reports will be required from the funded investigator as a basis for continued support. 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/

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

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.

LETTER OF INTENT

Prospective applicants should submit a Letter of Intent, [**2 pages maximum**] on line via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application. Applicants will be notified approximately eight weeks after the LOI deadline date if they have been approved to submit a full application.

PROPOSAL

An approved Letter of Intent 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 (http://jdrf.smartsimple.us). Proposal section templates in MS 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 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:
http://jdrf.org/grant-center/information-for-applicants/how-to-apply/application-guidelines/#human-subject-requirements

SCIENTIFIC REVIEW CRITERIA

Applications will be evaluated based on JDRF's confidential evaluation including:

- Significance
- Relevance
- Approach
- Innovation
- Investigator Experience
- Environment

Significance: Does this study address an important problem? Will the expected results have an impact on the performance of ASIs or IM therapeutics?
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?

PROJECTED DEADLINES

- **LOI Release Date**: ....October 19, 2015
- **Announcement Intro Meeting.**……November 13, 2015
- **Letter of Intent Deadline**: ..... ……..December 3, 2015
- **Notification of Full Application Request** ……....January 19, 2016
- **Application Deadline**: ..... ……..March 2, 2016
- **Response to Applicants**: ..... ……..July 2016
- **Earliest Anticipated Start Date**: ..... ……..September 2016

CONTACTS

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RMS360 (http://jdrf.smartsimple.us)
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