JDRF REQUESTS LETTERS OF INTENT FOR: OPTIMIZING THERAPEUTIC STRATEGIES FOR HUMAN PANCREATIC BETA CELL REGENERATION

- **Discovery of drug targets and combination therapies to simultaneously promote regeneration, survival and health of human pancreatic beta cells**

PURPOSE

JDRF invites applications from single investigators or teams of investigators to develop and conduct studies to identify and prioritize pathways, mechanisms, combination approaches and therapies to safely promote human beta cell regeneration while maintaining beta cell survival and function.

BACKGROUND

Type I diabetes (T1D) is characterized by the declining function and loss of the insulin-producing beta cells of the islet resulting in a need for life-long insulin replacement therapy. Therapies to safely restore and maintain functional beta cell mass are needed for all stages of T1D. Even partial restoration or maintenance of endogenous beta cell function may have benefit by reducing insulin requirements, improving glucose control, and reducing the risk of complications.

Critical to achieving JDRF's therapeutic goals is the identification and validation of targets, biologic factors and drug combinations for simultaneously promoting beta cell regeneration and survival. There is increasing evidence that functional pancreatic beta cell mass is dynamic and responds to physiologic changes and metabolic demands. Insight into the mechanisms and pathways mediating these changes have led to the discovery of several small molecules, growth factors, hormones and nutrients capable of inducing beta cell replication. While these factors and agents have been shown to reliably promote replication of rodent beta cells, the demonstration of similar effects with adult human beta cells has been far more challenging. In cases where replication of human beta cells has been observed, only small subsets of human cells appear to respond. Induction of replication of adult human beta cells may be further confounded by triggering of a DNA damage response, incomplete cell cycle progression, and loss of beta cell function and survival upon exposure of beta cells to a proliferative signal. Thus, the difficulty in translation to human beta cells might be explained, in part, by a paradoxical loss of beta cell function and death upon exposure of beta cells to a pharmacologic or mitogenic signal.

To achieve an effective therapeutic strategy for restoring and maintaining functional beta cell mass in T1D, an integrated view of adult human pancreatic beta cell regeneration and survival is critical. Studies on mechanisms underlying beta cell loss and dysfunction in T1D are pointing to signaling pathways and targets underlying beta cell stress, inflammatory response, autophagy and other death pathways, and induction of beta cell dedifferentiation. Therapies simultaneously promoting beta cell regeneration and preserving functional beta cell mass in T1D require taking into account all-encompassing aspects of beta cell growth, survival, function and health.

The purpose of this RFA is to invite outstanding proposals to characterize, validate and prioritize drug targets, biologic factors, combination approaches or therapies that will simultaneously promote regeneration and survival of pancreatic beta cells. Proposed studies should provide a basis for translation to a future drug discovery and development platform. In addition, most of the molecular insights into regulation of beta cell mass come from studies in animal models, and relevance to human beta cell regeneration and function is essential.

Objectives/Scope

This RFA will support performance-driven, milestone-based pre-clinical research programs aimed at identifying and validating drug targets and biologic factors to simultaneously promote human beta cell regeneration and prevent beta cell loss. It is expected that RFA-sponsored studies may ultimately have implications for treatment of type 1 diabetes and that the data generated may be used to support longer-term drug discovery efforts. Inclusion of studies with human islets/beta cells will be prioritized. Resources for obtaining human islets are described below.

Examples of pertinent topics include (not intended to be exclusive or all-encompassing):

- Discovery of drug targets and biologic factors to safely induce human adult beta cell replication with demonstration of maintenance of beta cell function, health and survival (in vitro and transplant models)
- Testing of the importance of candidate genes and proteins obtained from gene expression, proteomic, or miRNA expression data sets to prioritize their role in adult human beta cell regeneration and survival as drug targets (in vitro and transplant models)
- Systematic evaluation of molecular features of human beta-cell biology (cell cycle repressors, epigenetic modifications, etc.) that limit regeneration capacity and supporting identification and prioritization of tractable drug targets
- Elucidation of transcriptional networks implicated in beta cell regeneration/survival and identification of potential druggable targets in the network to simultaneously optimize regeneration and functional beta cell survival
- Development and application of novel mis-expression, siRNA or other genomic-based assays to concurrently screen for dual regulators of beta cell regeneration or survival
- Evaluation of biologic factors for potential use as therapeutics to jointly promote beta cell regeneration and survival

- Pre-clinical and clinical investigation of known drugs or pharmacologic agents, alone and in combination, for effects on restoring and maintaining function beta cell mass taking both efficacy and safety into consideration
- Identification and validation of targets or therapeutic strategies to promote expansion and subsequent recovery of function of de-differentiated or non-functional beta cells that appear spontaneously during development of disease

This RFA is **not** intended to support:
Studies of embryonic development of beta cells; efforts to expand or differentiate beta cells *in vitro*; efforts aimed at expansion of abnormal, non-functional or oncogenic beta cells or differentiation of stem-cell derived pancreatic progenitors; *ex vivo* studies based solely on rodent beta cell lines/islets.

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

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. Proposals with significantly higher cost may still be considered at the discretion of JDRF scientists. If you believe that your project requires a greater budget, please contact the Programmatic Contact listed below to discuss possible options for submission.

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.

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 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.

PROJECTED DEADLINES

- **LOI Release Date**:.....May 8, 2014
- **Letter of Intent Deadline**: ..... July 17, 2014
- **Notification of Full Application Request** .....September 4, 2014
- **Application Deadline**:..... ....October 9, 2014
- **Response to Applicants**:..... ……January 2015
- **Earliest Anticipated Start Date**: ..... ……February 2015

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 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

The research plan may 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; 7) Quarterly milestones, projected annual outcomes, and deliverables; 8) Intellectual Property or commercial efforts associated with the current application; 9) References (no page limit); 10) Principle Investigator Assurance. All information in items 1-7 must be incorporated in the 10-page limit without exception. Proposal exceeding this page limit will not be considered.

Other proposal components include:

- Applicant and Institutional Demographics (including Financial and Research Officer). Please note: Only the Signatory Authority or Authorized Institutional Official within your Institution's Research Office can approve proposal submission to JDRF.
- Approved LOI
- 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
- Informed Consent
- Resources
- Supporting Documents (i.e. Letter(s) of Collaboration, etc.)

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? 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?

CONTACTS

PROGRAMMATIC

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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.