JDRF REQUESTS LETTERS OF INTENT FOR: TARGETING ISLET CELL PLASTICITY FOR REGENERATION OF BETA CELL FUNCTION IN T1D

PURPOSE

JDRF invites applications from single investigators or teams of investigators to develop and conduct studies to identify and prioritize pathways, mechanisms, factors and drug targets to guide therapeutic approaches to drive formation of new beta cells by targeting islet cell plasticity.

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 to prevent and reverse insulin dependence. 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. Efforts supported by JDRF and other entities are underway to discover and develop therapies to maintain, expand and improve functional beta cell mass in early stages of T1D where there is significant beta cell function present. However, alternative therapeutic strategies to restore functional beta cell mass in more advanced stages of T1D where there is little or no significant beta cell function remaining are needed and represent a critical gap.

To achieve the therapeutic objective to restore beta cell functionality, there is growing interest from two primary targeted research approaches involving plasticity of pancreatic islet cells. The first is to convert or reprogram other cell types in the body to become functional beta cells. In line with this approach, there is a growing interest in the potential of reprogramming or converting other cell types in the islet to behave as functional beta cells. Of particular interest are the observations that pancreatic alpha cells and possibly other non-beta endocrine cells in the islet can spontaneously transdifferentiate towards a beta cell phenotype under certain experimental condition. Insights are being gained into the pathways mediating these cellular conversions. However the majority of these observations have been restricted to rodent systems. Developing tools and experimental strategies to validate candidate pathways and evaluate the potential for beta cell transdifferentiation in human cells remains a critical challenge.

The second approach to achieve this therapeutic objective is to understand mechanisms underlying the loss of beta cell function and the potential to prevent or exploit this phenomenon to restore and even expand functional beta cell mass. Emerging evidence suggests that beta

cells may de-differentiate to a less mature status thus contributing to loss of beta cell function during the development of diabetes. While the majority of evidence to date implicating beta cell de-differentiation comes from models of type 2 diabetes, preliminary evidence suggests that a similar process occurs during the development of T1D. If validation of mechanisms regulating de-differentiation in T1D can be identified and understood, expansion and re-differentiation of de-differentiated beta cells would represent an attractive target for T1D therapies.

Rational design of therapeutic strategies exploiting islet cell plasticity requires an understanding of the pathways and mechanisms regulating cell fate changes in the islet. The purpose of this RFA is to invite outstanding proposals to characterize pancreatic islet plasticity and identify and validate pathways and targets regulating islet cell plasticity with the goal of identifying potential therapeutic approaches to exploit islet cell plasticity to drive the formation of beta cells and/or prevent the loss of beta cell function in T1D. Translation of observations made in rodent models to human cells and human disease is critical and priority will be given to proposals utilizing human tissues to validate observations made in other experimental systems.

Objectives/Scope

This RFA will support performance-driven, milestone-based research programs aimed at identifying and validating mechanisms, pathways and potential drug targets regulating islet cell plasticity. It is expected that the 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 efforts aimed at drug discovery and translation. Proposals that include studies on human islets will be prioritized. Resources for obtaining human islets are described below.

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

- Elucidation of pathways and factors regulating transdifferentiation of non-beta islet cells towards a functional beta cell phenotype in response to physiologic or pathophysiologic stimuli
- Identification and characterization of biologics capable of promoting beta cell transdifferentation in appropriate animal models including validation on primary human tissue
- Elucidation of mechanisms regulating beta cell de-differentiation in response to disease-relevant pathological stimuli and identification of mechanisms and pathways to expand and re-differentiate de-differentiated beta cells in vivo
- Proof-of-concept studies to validate putative target pathways and mechanisms using pharmacologic or genetic means to promote transdifferentiation of non-beta cells to become functional beta cells or re-differentiation of de-differentiated beta cells to restore glucose-responsive insulin secretion and demonstrate an increase in beta cell mass in an animal model of diabetes
- Identification and validation of potential biomarkers of beta cell de-differentiation
- Establishment of novel *in vitro* cell culture systems with human primary cells to model islet cell plasticity and fate conversions observed *in vivo*
- Studies using tissues from human T1D donor pancreata or pancreata from other relevant human conditions to validate the importance of pathways and mechanisms identified in animal models

Collaborative efforts engaging investigators with complementary expertise are highly encouraged.

This RFA is **not** intended to support: studies of embryonic development of beta cells; efforts to expand or produce beta cells *in vitro*; efforts aimed at expansion of abnormal, non-functional or oncogenic beta cells; differentiation of stem-cell derived pancreatic progenitors; forced conversion of non-islet cells to a beta cell phenotype; *ex vivo* studies based solely on rodent beta cell lines/islets or strategies targeting expansion or replication of mature beta cells.

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.

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 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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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