SPECIAL REQUEST FOR APPLICATIONS:

JDRF REQUESTS LETTERS OF INTENT FOR: BIOLOGIC FACTORS AND TARGETS FOR PROMOTING BETA CELL REGENERATION, HEALTH, AND SURVIVAL

PURPOSE

JDRF invites applications from single investigators or teams of investigators to develop and conduct studies towards the goal of discovering and validating druggable targets and biologic factors for promoting pancreatic beta cell regeneration, health and survival in type 1 diabetes.

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 functional beta cell mass and maintain or prevent loss of beta cell function 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 and biologic factors for drug discovery and development. For example, there is mounting evidence that functional pancreatic beta cell mass increases in response to physiologic changes in metabolic demand such as in pregnancy and early childhood growth as well as pathophysiological changes such as obesity/insulin resistance, hyperglycemia, and injury. This increase in beta cell function may be due to mechanisms and pathways promoting beta cell replication and/or the spontaneous conversion of other cell types to become functional beta cells. However, the identification and validation of "druggable" targets or biologic factors to safely increase functional beta cell mass represents a critical gap. Similarly, studies of signaling pathways underlying beta cell stress, inflammation and death and studies of the mechanisms of beta cell dedifferentiation and redifferentiation are yielding new biochemical and mechanistic insights into the loss of functional beta cell mass. The current challenge is to identify and validate beta cell specific or selective drug targets and factors to prevent functional beta cell loss and maintain beta cell health.

The purpose of this RFA is to invite outstanding proposals to characterize and validate novel drug targets or biologic factors that will promote regeneration and survival of functional beta cell mass. Proposed studies should provide a basis for translation to a future drug discovery 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 a top priority.

OBJECTIVES/SCOPE

This RFA will support performance-driven milestone-based research programs aimed at identifying and validating drug targets and biologic factors to promote 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 is strongly encouraged. 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 regulating expansion of functional beta cell mass under conditions of increased metabolic demand in relevant physiologic animal models
- Identification of beta cell specific or selective drug targets in pathways known to promote human beta cell regeneration or beta cell survival
- Testing of the importance of factors, targets, and pathways identified in animal model systems for human beta cell proliferation and function
- Testing of the importance of candidate genes and proteins obtained from gene expression, proteomic, or miRNA expression data sets in beta cell regeneration and survival in human beta cells
- Systematic evaluation of molecular features of human beta-cell biology (cell cycle repressors, epigenetic modifications, etc) that limit human beta cell regeneration relative to rodent systems
- Systematic evaluation of molecular features that limit replication/regeneration in islets from aged rodents, which may relate to limiting features in human islets
- Elucidation of transcriptional networks implicated in beta cell regeneration/survival and identification of potential druggable targets in the network
- Development of novel assays to enable high throughput screening of small molecules and biologic factors promoting human beta cell regeneration and survival
- Development and application of novel mis-expression, siRNA or other genomic-based assays to screen for regulators of beta cell regeneration or survival
- Evaluation of biologic factors for potential use as therapeutics to promote beta cell regeneration and/or for target identification
- Studies aimed at establishing the utility of model systems for pre-clinical testing of chemical and biologic libraries
- Investigation of known drugs or pharmacologic agents for effects on beta cell regeneration taking both efficacy and safety into consideration

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.

MECHANISM

Up to a maximum of $165,000 USD per year including 10% indirect costs for up to 3 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 semi-annual (~2-3 pages) reports will be required from the funded investigator as a basis for continued support.
Applicants must adhere to the following guidelines:

- The budget may not exceed $165,000 USD per year, including 10% indirect costs.
- The total project period may not exceed three years.
- Projected timelines on a semi-annual basis for specific aims must be provided in the application.
- 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.
- The research plan may not exceed a total of 12 pages, including figures, tables, legends, milestones and deliverables

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 non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments. 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 collaborations with academia may be submitted to this initiative; additional information will be requested from for-profit entities if a full application is invited.

LETTER OF INTENT

Prospective applicants should submit a letter of intent on-line via the proposalCENTRAL Web site (https://proposalcentral.altum.com). The LOI template provided on the proposalCENTRAL Web site must be used to complete the application. LOIs will be competitively reviewed based on relevance to the goals of the RFA, strategic fit with JDRF's mission and portfolio and scientific merit/feasibility. Applicants will be notified approximately six weeks after the LOI deadline date if they have been approved to submit a full application.

DEADLINES

- **RFA Release Date**: .....October 1, 2012
- **Letter of Intent Deadline**:.....December 3, 2012
- **Application Deadline**: .....February 11, 2013
- **Response to Applicants**:.....June 2013
- **Earliest Anticipated Start Date**: .....July 2013

PROPOSAL

An approved letter of intent is required for submission of a full proposal.

All applications must be completed using the templates provided on the proposalCENTRAL Web site (https://proposalcentral.altum.com/). Proposal templates in MS Word should be typewritten, 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 may not exceed 12 pages, including figures, tables, projected milestones and deliverables, but excluding references. **Applications with research plans exceeding the page limit will not be reviewed.** 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) Quarterly milestones, projected annual outcomes, and deliverables; 7) References (no page limit); 8) Principle Investigator Assurance; 9) Future development Strategy (limit 1 page); 10) Target description and profile.

All information in items 1-6 must be incorporated in the 12-page limit without exception.

APPLICATION COMPONENTS

- Applicant and Institutional Demographics (including Financial and Administrative Officer)
- 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.)

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 application system proposalCENTRAL (https://proposalcentral.altum.com/). The letter of intent and application must be completed using the templates provided on the proposalCENTRAL Web site.

REVIEW CRITERIA

Applications will be evaluated based on the overall fit with the RFA objectives, potential that the proposed research will have a substantial impact on the mission of JDRF, 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 these studies on the concepts or methods that drive the beta cell biology and T1D fields?
Relevance: Is the proposed research relevant to the objectives of this RFA? What will be the expected impact of these studies on JDRF's mission to find new disease-modifying agents to treat T1D?
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?
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?
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?

Applying for Human Pancreatic Islets for Basic Science Studies:

Investigators at institutions in the United States may apply for human islets through the Integrated Islet Distribution Program or through the JDRF Program for Islets for Basic Research. Investigators in Europe may apply for islets through the JDRF-funded European Consortium for Islet Transplantation (ECIT). Please note: The ability of ECIT members to distribute human islets is subject to national and European Union regulations. Detailed information on applying for human pancreatic islets through these programs is available on the JDRF web site (http://www.jdrf.org/index.cfm?page_id=104491).

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