JDRF REQUESTS LETTERS OF INTENT FOR: BIOMARKERS OF PANCREATIC BETA CELL STRESS AND HEALTH

PURPOSE

JDRF, the world's leading non-profit organization with the mission to cure type 1 diabetes (T1D), invites applications from research investigators having interest and expertise to support the discovery and advancement of biomarkers of pancreatic beta cell stress and health correlating with early beta-cell loss.

BACKGROUND

Specific biomarkers enabling earlier detection and quantitation of subtle changes in beta cell health and function are critically needed for disease staging, patient stratification, and non-invasive monitoring of treatments aimed at preserving or restoring functional beta cell mass, including islet transplantation.Therapies to promote the preservation and restoration of functional pancreatic beta cell mass are essential for the treatment of T1D as well as type 2 diabetes (T2D). A major challenge impeding the timeline for clinical evaluation and feasibility of development of such therapies is the lack of adequate surrogate biomarkers to assess changes in beta cell health and function with therapeutic intervention and disease stage. Presently, clinical readouts rely on changes in C-peptide and HbA1c levels coupled with metabolic measurements. These markers and measurements are inadequate since changes in C-peptide and HbA1c levels are only observed over a relatively long time frame, and metabolic measurements are not directly indicative of functional beta cell mass but may reflect changes in insulin sensitivity of peripheral tissues.

Both T1D and T2D are characterized by a loss of functional beta cell mass. T1D is an autoimmune disease characterized by selective and progressive loss of functional insulin-producing beta cells. T2D is a metabolic disease characterized by beta cell dysfunction as well as peripheral insulin resistance. Despite differences in the pathophysiology of T1D and T2D, recent studies suggest that beta cell stress is critical in initiating beta cell destruction in both forms of the disease.

Increasing evidence suggests that chronic activation of endoplasmic reticulum (ER) stress and closely linked oxidative stress pathways set off biochemical changes in the beta cell leading to beta cell dysfunction and beta cell loss in both T1D and T2D. These pathways may enable the identification of early, specific markers of beta cell dysfunction in serum and other body fluids. This could include, for example, biomarkers of molecular alterations that occur in the stressed beta cell such as alterations in protein post translational modifications, alternative RNA splicing, translational infidelity, misfolded beta cell proteins, changes in gene expression or micro RNA expression, or changes to the ratio of proinsulin/insulin. Discovery and development of biomarkers based on these insights could help accelerate the clinical assessment of therapies to promote beta cell health and survival as well as the stratification of patients by disease status for targeted therapies.

Ongoing efforts to develop quantitative non-invasive measures of beta cell mass are hampered by first the lack of a beta-cell surface target unique to the beta cell, and second the anatomic structure of the islets in the pancreas. At present, non-invasive imaging methods do not yet have the sensitivity to discern small changes in beta cell mass relevant to early onset of T1D; as such, this topic will be excluded from the present call.

The purpose of this call for *Letters of Intent* is to invite proposals to support and advance the discovery, development, and/or validation of biomarkers of pancreatic beta cell stress and dysfunction. Studies based on use or validation with human beta cells/islets and clinical samples or tissues will be of special interest.

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

- *Ex vivo* studies with human islets to identify potential biomarkers (such as misfolded proteins, microRNAs, alternatively spliced proteins, unique post-translational protein modifications, etc.) which are enriched in beta cells, are shed or released in response to stress induction and would be detectable in blood, urine or other accessible body fluids
- Pre-clinical studies with animal models of diabetes aimed at discovery of potential biomarkers in blood or other body fluids correlating with temporal changes in beta cell stress and function, including plans for early validation with human islets/beta cells
- Studies aimed at validating putative beta cell stress biomarkers in serum or other body fluids based on use of currently available and well characterized clinical samples from people at risk or recently diagnosed T1D or from islet transplant patients
- Identification or validation of serum biomarkers based on studies performed with transplanted human islets in relevant animal models correlating with changes in beta cell stress
- Discovery of a panel of unique metabolomic biomarkers of beta cell stress and early beta cell dysfunction detectable in serum or other body fluids
- Studies based on use or validation of candidate biomarkers with available serum or other body fluid samples from diabetic subjects or clinical studies will be of special interest

Collaborative efforts engaging investigators with complementary expertise are highly encouraged.

This call is *not* intended to support efforts aimed at:

- Discovery or development of beta cell imaging technologies
- Discovery of non-specific markers of beta cell death without further study demonstrating correlation to early events in changes in beta cell health/dysfunction
- Discovery of markers of cell stress that lack specificity for beta cells
- Discovery of markers of beta cell dysfunction lacking relevance to T1D
- Discovery or development of biomarkers of beta cell stress and loss that are *only* applicable in the setting of islet, pancreas or stem cell transplantation
- Discovery and development of markers of immune status unrelated to changes in beta cell stress
- Studies based solely on immortalized beta cell lines without validation with primary human or rodent islets or beta cells
- Discovery of biomarkers of peripheral insulin resistance
- Discovery of biomarkers in pancreatic tissues which will not be detectable in serum, urine or other body fluids available through minimally invasive procedures

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 [to be inserted].

MECHANISM

Applications in response to this announcement can be submitted under one of the following funding mechanisms:

Pilot & Feasibility Grants (P&Fs): up to $110,000 (including 10% indirect costs) for one year only.

Strategic Research Agreements (SRAs): Up to $250,000 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 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

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

There are no citizenship requirements.

LETTER OF INTENT

Prospective applicants should submit a letter of intent on-line via the proposalCENTRAL website (https://proposalcentral.altum.com/default.asp). The LOI template provided on the proposalCENTRAL Web site 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. Letters of Intent 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
- 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)

DEADLINES

- **LOI Release Date**:..... .....March 22, 2013
- **Letter of Intent Deadline**:..... .....June 17, 2013
- **Notification of Full Application Request** .....August 2, 2013
- **Application Deadline**: ....October 4, 2013
- **Response to Applicants**: ....January 2014
- **Earliest Anticipated Start Date**:..... .....February 2014

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 proposalCENTRAL website (https://proposalcentral.altum.com/). 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 towards developing new biomarkers of beta cell stress and health
7) Projected quarterly 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) Principle Investigator Assurance

For SRAs, all information in items 1-7 must be incorporated in the 12-page limit without exception.
For P&Fs, there is a 3 page limit.
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 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 (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/).

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?

CONTACTS

Juvenile Diabetes Research Foundation
26 Broadway, 14th Floor
New York, NY 10004

PROGRAMMATIC

Adrianne Wong, Ph.D.
Senior Scientist, Beta Cell Therapies
☎+1-212-479-7642
💻 awong@jdrf.org

ADMINISTRATIVE

Amanda J. Rieder, Grant Coordinator
☎212) 479-7575
💻arieder@jdrf.org

PROPOSALCENTRAL

💻 https://proposalcentral.altum.com/Login.asp
💻 pcsupport@altum.com
☎ (301)-916-4557 ext. 227, or toll free in the US, (800)-875-2562 ext. 227
Assistance can be obtained Monday through Friday between 8:30am and 5pm U.S. Eastern Time