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**Special request for Information**

**JDRF Request for Information (RFI): Biomarkers of Pancreatic Beta Cell Stress and Health Non-Competitive Consortium**

**Purpose**

JDRF, the world’s leading non-profit organization with the mission to cure type 1 diabetes (T1D), is seeking information from research investigators having interest in participating in a Non-Competitive Consortium of major pharmaceutical and biotechnology companies in partnership with JDRF to support and advance the discovery and development of biomarkers of pancreatic beta cell stress and health. To help accelerate the launch of this initiative, JDRF is requesting information from investigators having a potential interest in participating in the scientific goals and objectives for this program to support and advance the discovery and development of biomarkers of pancreatic beta cell stress , health and dysfunction. Information will be used to evaluate the timeliness and feasibly and to determine the scope and scale of a potential Non-Competitive Consortium. Please note whilst this RFI is for JDRF planning purposes only and should not be construed as a funding opportunity or grant program, the response to the RFI may help guide a potential RFA in the area at a future time.

**Background**

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, however, 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. Specific biomarkers enabling earlier detection of subtle changes in beta cell health and function are critically needed for disease staging as well as for non-invasive monitoring of treatments aimed at preserving or restoring functional beta cell mass, including islet transplantation.

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. Prior to the onset of frank T2D, the beta cells compensate by hyper-secreting insulin to overcome insulin resistance in peripheral tissues. Eventually, the beta cells fail to meet this increasing metabolic demand, beta cell loss occurs, and the majority of type 2 diabetics eventually become insulin-dependent. Studies on the mechanisms initiating beta cell destruction are revealing the critical role of beta cell stress in early stages of both T1D and T2D.

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. The unfolded protein response (UPR) is an adaptive signalling pathway designed to prevent accumulation of misfolded proteins in the ER lumen and minimize the stress of oxidative protein misfolding. However, due to its high secretory demand on beta cells, the beta cell ER is more susceptible to stressors such as systemic metabolic and immune/inflammatory mediators. Thus, hyper-activation of the UPR in beta cells results in the shift from an adaptive response to activation of apoptotic pathways.

Emerging insights into ER and oxidative beta cell stress 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.

To evaluate potential strategies for supporting this biomarker objective, JDRF sponsored a workshop at the Lisbon, Portugal EASD meeting in 2011 with representatives from pharmaceutical and biotechnology companies and academic Key Opinion Leaders to assess the clinical and medical need for biomarkers of beta cell stress and health and mechanisms to coordinate and advance the field. During the discussions, the proposed concept for a Non-Competitive Consortium of pharmaceutical and biotechnology companies and academia was well received. JDRF has since developed a framework to initiate such a Consortium and has begun discussions with potential company participants. Under the proposed framework, the Non-Competitive Consortium of industry participants would provide support to academic and biotechnology investigators through awards administered by JDRF.

To help accelerate the launch of this initiative, JDRF is seeking information from investigators having a potential interest in participating in the scientific goals and objectives for this program to support and advance the discovery and development of biomarkers of pancreatic beta cell stress and dysfunction.

JDRF is interested in further information from researchers working in the following areas:

* *Ex vivo* studies with human islets/beta cells to identify potential biomarkers (such as misfolded proteins, microRNAs, alternatively spliced proteins, unique post-translational protein modifications , etc.) which are enriched in beta cells and are shed or released in response to stress induction in the beta cells
* 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; plans for early validation with human beta cells/islets should be included in the plan
* 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 type 1 diabetes 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
* Studies based on use or validation with human beta cells/islets and clinical samples or tissues will be of special interest.

JDRF is particularly interested in potential collaborative efforts that would engage investigators with complementary expertise.

The RFI is not soliciting information regarding studies in the following areas:

* The discovery or development of beta cell imaging technologies
* Discovery of apoptotic markers of beta cell death without correlation to early events in changes in beta cell dysfunction or lacking specificity for beta cells
* Discovering markers of beta cell dysfunction lacking relevance to type 1 and type 2 diabetes
* Developing markers of immune status
* Research 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

**HOW TO SUBMIT A RESPONSE AND DEADLINE FOR SUBMISSION**

Please fill out the JDRF Request for Information (RFI) form [HERE](http://jdrf.org/files/General_Files/Research/RFI_Form_Final.pdf). Please complete and submit to BiomarkersRFI@jdrf.org no later than Friday, September 28, 2012.

**USE OF INFORMATION AND CONFIDENTIALITY**

JDRF is seeking the above mentioned information for determining the scope and scale of the proposed Non-Competitive Consortium activities and establishing a pipeline of potential investigators/studies that would be considered by the proposed Non-Competitive Consortium. Non confidential information such as broad overall summation of research scope and JDRF assessment of overall strength of the replies relating to the RFI may be shared with potential funding parties to the Non-Competitive Consortium. Confidential information, including names of applicants, titles or description of a potential research study, participating institutions or potential collaborators will not be shared outside JDRF.

**INQUIRIES**

**Note that terms and conditions for the awards will be provided upon release of an RFA.**

Scientific inquiries should be directed to the following individuals:

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