JDRF Requests Expressions of Interest for the Discovery and Validation of Biomarkers for Recent-Onset Human Type 1 Diabetes

Key Dates:

**September 10, 2014:** Expressions of interest (EOI) release date

**November 14, 2014:** EOI due date

(EOIs must be submitted via RMS360 website: [https://jdrf.smartsimple.us/s_Login.jsp?null](https://jdrf.smartsimple.us/s_Login.jsp?null))

**Dec 12, 2014:** EOI decision notification

**January 23, 2015:** Full application due date (for accepted EOIs)

**May 2015:** Award notification

**PURPOSE OF REQUEST**

The purpose of this RFA is to support biomarker research in the recent onset setting, both at the early stages of discovery and development as well as at the more advanced stages of biomarker confirmation and validation. Expressions of Interest (EOI) are requested for:

i) The **confirmation** and **validation** of biomarker assays that are supported by robust preliminary data and statistical analysis. These assays should be at stage of development that is translatable to other laboratories, and if validated, can be clinically implemented at multiple sites.

ii) The **discovery** and **development** of biomarkers in the recent onset setting that allow staging of disease progression, predict the rate of C-peptide decline, stratify patients for therapy, or identify responders/non-responders to therapy.

**BACKGROUND**

JDRF believes that T1D recent onset clinical trials could be better optimized to allow smaller size and shorter trials. It has become apparent that the pathogenesis and progression of T1D is quite heterogeneous. Furthermore, it is likely that combination therapies may be required to restore insulin independence in recent onset T1D. Thus, multiple interventions agents will need to be tested singly and in combination, which will necessitate performing multiple trials or adaptive trial designs. Validated prognostic biomarkers that allow clinical trial subject stratification or predictive biomarkers that can serve as informative earlier occurring trial endpoints would allow accelerated clinical development. JDRF is interested in supporting biomarker research in the recent onset T1D setting that will allow the establishment of biomarker assays that can be ultimately combined to create informative integrated, biomarker panels to optimize design of recent onset clinical trials.

There is widespread recognition that a vital gap in current biomarker research has occurred in the transition from discovery research to validation, where most assays fail. A more systematic approach towards identifying robust biomarkers early must involve reproducibility testing for independent assessment of assay precision/reproducibility, followed by biomarker confirmation that involves replicating clinical correlations. Importantly, these efforts need to be guided by a uniform set of statistical parameters.
early in the process. JDRF would like to facilitate the movement of mature biomarker development towards large scale validation. To this end, JDRF has established a Core and Validation Center (CAV) that is capable of functioning as a clinical coordination center as well as a centralized facility for assay testing and confirmation (for details, contact: jodegard@benaroyaresearch.org).

**SPECIFIC GOALS OF REQUEST**

The goal of this RFA is to support biomarker research that address the following clinical questions:

1- Predict rate of loss of C-peptide after disease onset
2- Stratify subjects for specific types of therapy in the recent onset setting
3- Distinguish responders from non-responders in recent onset clinical trials

Preference will be given to efforts that aim to interrogate common sample sets with more than one biomarker assay. As such, collaborative project are encouraged, and higher budgets may be allowed for such projects. Please contact JDRF prior to submission of an EOI for approval of such a project.

Investigators may apply to one or both sub-sections of this RFA:

**i-Validation:** Expressions of interest (EOI) are sought from investigators who have ‘validation ready’ biomarkers- i.e. strong preliminary data using human samples, plus information on statistical methods and thresholds that have been used to analyze the early data. Please note that investigators interested in this sub-section of the RFA will be required to interface with the Core and Validation Center (CAV) prior to submitting their application and during the validation process, if funded. While not required, investigators are strongly encouraged to consult with the CAV prior to EOI submission.

EOIs should be tailored to the following two part investigation plan:

**Step1: External reproducibility testing.** This step is technical and assay-centric. It does not address the clinical application of the assay.

Investigators must specify the type and quantity of samples proposed for this step. The CAV will perform the centralized function of sample aliquoting and distribution. Samples may be proposed from a cross-sectional RO cohort, and may be facilitated via the CAV via access to in-house samples, or via initiation of requests on behalf of the PI, prior to application submission. (Proof of access to a sample resource for this step, while encouraged, is not required at the time of application submission).

Investigators must provide an overview of their proposed plans in the EOI, which includes the following: 1-Precision testing if needed 2-Blinded reproducibility testing at the investigator’s laboratory 3-Assay reproduction at CAV (exceptions may be allowed depending on assay type/technology; strong justification will be needed, if so) 4- Statistical analysis plan to qualify for Step2 – external biomarker confirmation (see below).

Note:
- Results from step 1 for all projects, including statistical analysis, will be subject to input from the CAV on an ongoing basis and will undergo an independent evaluation by CAV statisticians for a go/no-go decision prior to proceeding to Step2 below.

**Step2: External biomarker confirmation.** This step addresses the clinical application of the assay and is intended to confirm and replicate initial findings of independent studies. Investigators must specify the type and quantity of samples proposed for this step. Samples may be proposed from longitudinal cohorts, including placebo arms of RO Trials as well as relevant arms of Trial
samples. The CAV may be able to co-ordinate sample access and/or provide samples to multiple studies. (Proof of access or conditional access to a sample resource for this step is required at the time of application submission).

Investigators must provide an overview of their proposed plans in the EOI, that includes the following:

1- Outline of experimental plan for interrogation of blinded samples from a 'confirmation cohort' that is separate from the ‘discovery’ cohort. Exceptions may be made for trial samples.
2- Statistical analysis plan.
3- A signed ‘conditional approval’ form for sample access from the ‘confirmation cohort’. (due at time of application submission).
4- Agreement to provide a subset of samples to the CAV for independent confirmation of results.

Note:
- Results from step 2 for all projects, including statistical analysis, will be subject to input from the CAV on an ongoing basis and will undergo an independent evaluation by CAV statisticians at project term, if project is successful.
- While this RFA is focused on biomarker assays pertaining to the recent onset setting, exceptions may be made for compelling assays that are ready for validation and involve pre-diabetic samples. In such cases, only EOIs that are able to provide samples to the CAV or have written access to such samples at the time of application will be considered. Discovery assays involving pre-diabetic samples will NOT be supported by this RFA.
- Investigators with ideas or resources that might benefit this initiative should also submit their ideas via an expression of interest.

**ii-Discovery/development**: To feed the pipeline of biomarkers that may become ready for validation, Expressions of Interest are sought from investigators for biomarker discovery and development efforts in the recent onset (RO) setting. It is required that proposed studies involve human RO samples and that proof of access to samples is provided at time of application submission. Interaction with the CAV is not required for EOIs submitted to this section of the RFA.

**Examples of pertinent categories of biomarkers include, but are not limited to:**

- Immune/inflammatory biomarkers: cellular or secreted
- Genetic/epigenetic biomarkers
- Biomarkers of beta cell function, inflammation, mass, death
- Metabolic biomarkers and surrogates
- Biomarkers that utilize agnostic platforms
- Combination panel of biomarkers that bring together immune, beta cell, or other expertise
- Analysis of existing T1D biomarker data

**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, for-profit research based organization or other 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 EOI, however, additional information will be requested from for-profit entities if a full application is invited.
MECHANISM
Applications in response to this announcement can be submitted via one of the following funding mechanisms:

Validation:
• Strategic Research Agreements (SRAs): Up to $250,000 USD per year including 10% indirect costs for up to two years. Costs for CAV-based research and data analysis should be included as a subcontract to BRI. For any research projects proposed for 3 years, applicants must contact JDRF to discuss its scientific justification. For any budget that exceeds $250,000/yr, JDRF scientific staff must be contacted with a strong justification, prior to EOI submission. SRAs require quarterly milestones, reporting against those milestones and will receive milestone-based payments.

Discovery and Development:
Pilot & Feasibility Grants (P&Fs): up to $110,000 (including 10% indirect costs) for one year only.
• Strategic Research Agreements (SRAs): Up to $165,000 USD per year including 10% indirect costs for up to two years. For any research projects proposed for 3 years, applicants must contact JDRF to discuss its scientific justification. For any budget that exceeds $165,000/yr, JDRF scientific staff must be contacted with a strong justification, prior to EOI submission. SRAs require quarterly milestones, reporting against those milestones and will receive milestone-based payments.

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

EOI COMPONENTS
Expressions of interest proposals should be no more than two pages in length for discovery research and three pages in length for validation research including the following information:

• Name, title and institution of principal investigator (PI), co-investigator and/or key collaborator(s), including industry.
• Brief details of approach proposed, including guidelines provided in this RFA where relevant, hypothesis if relevant, scientific rationale, potential advantages over existing technologies (sample volume, ease in clinical implementation, etc), deliverables, and references to published or preliminary data (preliminary data and statistical analysis is mandatory for validation-based proposals)
• Relevant intellectual property, description of potential for translation into therapies including short and long-term development goals
• Specifics of bio-samples to be utilized, if applicable, (including matching and blinding criteria) and projected time-lines for sample access. Intended utilization of CAV resources must be mentioned here.
• Biosketches of PI and co-investigators/collaborators (does not count towards page limit)
• Total estimated budget and project duration

An approved EOI is required prior for submission of a full proposal. Please see below for complete instructions.

SUMBISSION 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 research management system RMS360 (https://jdrf.smartsimple.us).
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