JDRF REQUESTS EXPRESSIONS OF INTEREST FOR:
COMBINATION THERAPIES IN TYPE 1 DIABETES

PURPOSE
JDRF, the world’s leading non-profit organization with the mission to cure type 1 diabetes (T1D), invites Expressions of Interest for the clinical evaluation of combination therapies in the setting of T1D.

BACKGROUND
JDRF has an unprecedented opportunity to make progress in the clinical assessment of combination therapies for T1D that tackle the immune, beta cell and metabolic pathways involved in the disease process. Like many other complex human disorders of unknown etiology, T1D may be controlled via a therapeutic approach that combines multiple agents with different modes of action. The advantages of such a strategy include the ability to reduce toxicities and realize synergies that enhance and prolong efficacy.

At present, nearly two dozen single agents – mostly immune-based – have been tested for the ability to preserve C-peptide production in T1D clinical trials. Yet, less than a handful have shown an ability to preserve, temporarily, C-peptide after disease onset. T1D is a multifactorial and multigenic disease with considerable heterogeneity among patients, suggesting that multipronged therapeutic approaches might be needed to induce durable disease remission. Furthermore, combinations of discrete therapeutic agents may ultimately be needed to customize treatments in T1D sub-groups.

JDRF wishes to solicit expressions of interest for clinical trials in new onset and established T1D to test the safety, efficacy, and potential synergies of combination therapies that target multiple facets of the disease.

Research objectives include but are not limited to:
- Employ combinations utilizing immunomodulators (including antigen specific immunotherapies), beta cell antigen-specific therapies, enhancers of beta cell mass/function, reducers of beta cell stress and/or inflammatory pathways, metabolic control agents, or other relevant therapeutics to prevent or reverse T1D
- Demonstrate safety, biologic effect, and potentially efficacy of combinations in T1D
- Conduct comparative analyses of risk-benefit ratio of the proposed combination vs. the single agent

Desired clinical outcomes can include, but are not limited to:
- **New/recent onset T1D**: maintenance of C-peptide for >1 year or an increase in C-peptide (with MMTT) or achievement of insulin independence; decreased HbA1c, reduced insulin requirements, increased “time in range”.
- **Established T1D**: increase in and maintenance of C-peptide for >6 months; decreased HbA1c, reduced insulin requirements, increased “time in range”

Criteria:
- Proposed studies should: 1) Utilize two or more therapeutic agents targeting mechanisms involved in the following biological pathways: immune modulation (including antigen specific targeting), beta cell function and regeneration/replication, or metabolic control; 2) Have a clear plan for a regulatory path to allow the trial to be done; 3) Be based on a robust scientific
hypothesis and preliminary data; and 4) Use pre-existing infrastructures for rapid recruitment of T1D patients, or at-risk individuals, into the proposed trial(s)

- Clinical trials may be proposed in any of the following disease settings:
  - New (within 3 months of diagnosis) or recent onset (less than 2 years from diagnosis) T1D
  - Established T1D (more than 2 years from diagnosis)

- Applicants are strongly urged to consider pilot or adaptive trial designs to stage investigations and maximize learnings.

- Mechanistic studies should be built into all proposed combination trials, and should utilize established assays to measure immune, beta cell, metabolic status and target engagement/pharmacodynamics. Sample collection and assay feasibility and cost must be taken into account.

- Collaborative efforts engaging investigators with complementary expertise and/or combining multiple agents and patient cohorts are highly encouraged. Likewise, JDRF Staff may propose collaborations between investigators submitting EOI s based on the content therein.

- EOI s should contain information regarding any industry collaborations, and any provisions for obtaining the agents for the proposed trial (at no-cost or at-cost) from the relevant companies.

- Statistical support is necessary for power calculations.

- Proposals may leverage or extend current studies.

- Investigators may propose a budget appropriate to the proposed research according to the general criteria below.

**Further Considerations:**
- Industry collaborations, where necessary, are strongly encouraged
- Willingness to share samples and data with the community, according to JDRF standards
- Validity of the proposed assays
- Potential impact on T1D clinical care

This call is not intended to support pre-clinical efforts aimed at broadly exploring potential combinations for treating or preventing T1D. Focused, IND-enabling pre-clinical studies proposed in direct support of future clinical studies using combination approaches may be considered as part of this RFA – investigators proposing pre-clinical studies should contact JDRF Scientific Staff to discuss the fit and relevance of their proposal prior to submission.

Applicants are encouraged to consult with JDRF Scientific Staff to discuss the alignment of their proposal to this RFA.

**MECHANISM**
EOIs in response to this announcement can be submitted to the following mechanism:

Clinical^ Strategic Research Agreements (supported by strong preliminary data) for a maximum budget of $1,500,000* per year for up to 3 years of funding (including 10% indirect costs)
Pre-clinical support may be requested only for IND-enabling activities.

* Applications whose budget and/or timeline exceeds the above specified guidelines, must obtain JDRF staff approval prior to submitting an LOI.

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.

**EXPRESSIONS OF INTEREST**

Prospective applicants should submit a letter of intent on-line via RMS360 at https://jdrf.smartsimple.us The EOI template located under the LOI Research Plan tab must be used to submit.

EOI submissions will undergo expedited review. Applicants will be notified if they have been approved to submit a full application.

Expressions of Interest 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
- Description of cohort to be studied and inclusion/exclusion criteria
- Brief overview of statistical power, if relevant.
- 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**

EOI Release Date: April 18, 2014
Expression of Interest Deadline: June 20, 2014
Notification, invitation to apply: August 1, 2014
Application Deadline: October 1, 2014
Response to Applicants: January 2015
Earliest Anticipated Start Date: February 2015
PROPOSAL
An approved Expression of Interest 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 website https://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. 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
7) Projected milestones for specific aims, projected annual outcomes, and deliverables; 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) Principal Investigator Assurance

For SRAs, all information in items 1-7 must be incorporated in the 12-page limit without exception. P+F applications will have a 5 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 EOI
- 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.)
- Documented proof of access to samples or written approval from sample access committees

INSTRUCTIONS
Applicants must register as an applicant and submit their expression of interest and invited application in response to this RFA using JDRF’s on-line application system. https://jdrf.smartsimple.us.
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?

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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.