

JDRF REQUESTS LETTERS OF INTENT FOR:

INNOVATIVE STRATEGIES TO DEMONSTRATE “IMMUNOLOGICAL PROOF-OF-MECHANISM” AND TO EXPLORE EARLY OUTCOME MEASURES IN IMMUNOTHERAPY TRIALS

PURPOSE

JDRF is committed to addressing key hurdles in accelerating the clinical path towards approval of effective immunotherapies for the prevention and treatment of T1D. To that end, JDRF is soliciting letters of intent (LOIs) for the development of revised outcomes for clinical trials of immunotherapies that will allow faster and more efficient studies to establish proof-of-mechanism and proof-of-concept. Efforts are urgently needed in the T1D community to define measures that will allow evaluation of the therapeutic effects of candidate immune therapies in a shorter time frame and utilizing fewer subjects to evaluate therapeutic benefit.

BACKGROUND

In all T1D immunotherapy trials to date, efficacy has been defined as preservation of beta cell function measured in a mixed meal tolerance test (MMTT). However, the high burden and high variability in MMTTs, and the need for a long observation period (typically twelve months) results in overly burdensome trials that require large numbers of patients and take a long time to execute, significantly slowing progress for evaluating candidate therapies.

Retrospective mechanistic analyses of samples from several T1D trials, are providing compelling evidence for enhanced regulatory T (T_{reg}) cell numbers and function and reduced or disabled memory T effector (T_{eff}) cell subsets in responders to immunotherapies, suggesting that immune regulation might be achieved with the right type of therapy(ies) in the right subjects with the right treatment regimen. This rationale underscores the potential to identify robust early markers or predictors of immune efficacy and to link such to early markers of beta cell health, early metabolic measures, and possibly relevant patient reported outcomes.

OBJECTIVES/SCOPE

Letters of intent are sought from investigators/groups that will address any or all of the following:

- 1) Define a measure or measures that will allow evaluation of candidate immune therapies for treatment effect, in a shorter timescale and with fewer subjects than current practice.
- 2) Explore early outcome measures that are surrogates for clinical efficacy in immunotherapy trials.
- 3) Define a lower burden outcome measure that may be frequently sampled with easier tools and technologies than currently available.
- 4) Define a measure/score for therapeutic effect, incorporating measures that represent early alterations in disease course after interventions.
- 5) Other novel approaches to determine early readouts of immune therapeutic effect and/or link such to improved, earlier outcomes in T1D immunotherapy trials.

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

- Small prospective intervention trials designed to collect and link mechanistic, metabolic and patient outcome data for exploration of early endpoints after treatment with immunotherapies.
- Evaluation of the impact of immunotherapies (if any) on early features of beta cell function that go beyond overall stimulated C-peptide secretion (e.g. early phase insulin secretion, rapid control of post-prandial glucose excursions, appropriate counter-regulation to avoid hypoglycemia, etc.)
- Evaluation of datasets from relevant non-immune intervention trials to generate early surrogates of positive metabolic effects that can be tested/incorporated in future immune intervention trials.
- Validation studies of novel scores or measures of clinical benefit in new data sets, trials or cohorts.
- Standardization and harmonization of definitions of responders in immunotherapy trials and for achieving comparable surrogate measures of treatment effect across future trials.

Please note that cross-disciplinary projects involving multi-functional teams (modelers, statisticians, clinicians, epidemiologists, endocrinologists, immunologists, health economists, regulatory affairs subject matter experts), and involving industry-academia collaborations are highly encouraged and will be given top priority.

This RFA is not intended to support: studies involving preclinical models of disease, or prospective studies with devices or non-immune interventions.

Also, while outside the scope of this RFA, any applicant with access to high quality (worldwide) health record data to trace QoL trajectory and clinical parameters through natural history of T1D, are encouraged to contact JDRF staff to gauge relevance to other related JDRF efforts.



Applicants who wish to consult with JDRF Program Staff to discuss the responsiveness of their proposal to this program or to discuss ideas or resources that might benefit this initiative may do so via email to the contacts listed in this RFA. Please keep enquiries brief and to the point.

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A

JDRF will hold announcement introduction meeting via web and teleconference on Monday, **August 13, 2018 at 11 am -12 pm US Eastern Time**, to which all interested prospective applicants are invited. JDRF scientists will give an overview of the goals of this initiative, explain the application process and answer initial questions on applications. A brief introduction on JDRF's new grant application portal (RMS360) will also be given.

[Join Webex meeting](#)

Meeting number (access code): 731 561 818

Meeting password: EcaM662D

Join by phone

1-866-469-3239 Call-in toll-free number (US/Canada)

+1-650-429-3300 Call-in toll number (US/Canada)

[Global call-in numbers](#) | [Toll-free calling restrictions](#)

MECHANISM & FUNDING LEVELS

In response to this announcement, LOI's can be submitted as **Strategic Research Agreement (SRA)** and **Pilot and Feasibility** grant mechanisms.

The level of funding will vary depending on the scope and overall objectives of the proposal. Proposals from strong cross functional teams will be given highest priority and a maximum budget (especially when involving prospective human studies) of up to \$2M total (including 10% indirect costs, typically for a 3year period) may be proposed. Intermediate budgets for smaller projects are allowed. **Please note that budgets that are deemed clearly excessive for a proposed study may result in the rejection of an LOI.**

Pilot and feasibility studies on compelling topics, when the pilot is a clear first step to a potential larger effort may be submitted. Each pilot project may request up to total \$110,000 USD [typically \$75k - \$110k] per year for one year (including 10 % indirect costs).

For more information on the Strategic Research Agreement mechanism, please refer to our website: <http://grantcenter.jdrf.org/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/>



Pilot and Feasibility LOIs should follow the same website guidelines as the Strategic research agreements with the smaller budget and focus referred to above.

Under the terms of the grant award, written biannual progress reports will be required from the funded investigator as a basis for continued support.

ELIGIBILITY

Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. 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.

For clinical studies, applicants must hold an appointment or joint appointment in a subspecialty of clinical medicine, and conduct human clinical research.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, JDRF welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

Applicants successfully funded by this RFA must agree to share updates and challenges and identify opportunities to work together on issues of common interest (including interactions with regulatory affairs experts) during teleconferences and annual face-to face meetings organized by JDRF. JDRF firmly believes that a community-wide effort will be needed to incorporate new T1D outcomes into clinical practice.

LETTER OF INTENT

Prospective applicants should submit a Letter of Intent, [**2 pages maximum**] on line via RMS360 (<http://jdrf.smartsimple.us>) to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application. Applicants will be notified approximately four weeks after the LOI deadline date if they have been approved to submit a full application.

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 in RMS360 (<http://jdrf.smartsimple.us>). Proposal section templates in MS Word, [**10 pages maximum**] 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.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design and investigational product information. More details can be found in the Human Subject Research Guidelines: http://grantcenter.jdrf.org/wp-content/uploads/2012/12/JDRF_Scientific_Guidelines_final-Aug2015.pdf

SCIENTIFIC REVIEW CRITERIA

Applications will be evaluated based on JDRF's confidential evaluation including:

- Significance
- Relevance
- Approach
- Innovation
- Investigator Experience
- Environment

Significance: Does this study address an important problem? Will the expected results have an impact on the performance of ASIs or IM therapeutics?

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?

PROJECTED DEADLINES

- **RFA Release Date**.....July 20, 2018
- **Announcement Intro Meeting**.....August 13, 2018
- **Letter of Intent Deadline**... ..September 12, 2018
- **Notification of Full Proposal Request**October 15, 2018
- **Full Proposal Deadline**.....November 14, 2018
- **Earliest Response to Applicants**.....May, 2019
- **Earliest Anticipated Start Date**.....July, 2019



CONTACTS

PROGRAMMATIC

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RMS360 (<http://jdrf.smartsimple.us>)

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