JDRF REQUESTS EXPRESSIONS OF INTEREST (EOI) FOR:

NEOEPITOPES IN TYPE 1 DIABETES: PATHOGENESIS, STAGING, AND THERAPEUTIC UTILITY

PURPOSE

A number of beta cell neoepitopes have been described and implicated in Type 1 Diabetes (T1D) pathogenesis. However, the role of neoepitopes in the breakdown of self-tolerance and their utility as biomarkers for improved disease staging remains unclear and their potential as possible therapeutic targets has not been determined. JDRF is soliciting EOIs to support research projects that explicitly address the role and utility of neoepitopes in T1D and facilitate novel findings into the clinic.

BACKGROUND AND OBJECTIVES

In several autoimmune diseases, neoepitope responses have been directly linked to the pathogenesis of the disease and have been successfully utilized as disease biomarkers. One such example is antibodies to citrullinated peptides for the diagnosis of rheumatoid arthritis. However, in T1D, incomplete understanding of the timing and prevalence of neoepitope generation and the immune responses to neoepitopes has limited the utility of neoepitopes for staging, stratification, or to inform therapeutic interventions. To date, multiple lines of evidence demonstrate that neoepitopes can be formed as a result of beta cell stress, metabolic stress, inflammation, and other situations. Both cellular and humoral responses to neoepitopes have been detected in individuals with and those in the early stages of T1D. Given that multiple neoepitopes have now been identified in T1D samples and work informing on their utility as biomarkers has commenced, this RFA prompts investigators to apply these findings to:

- Inform on the role of neoepitope responses in T1D to facilitate a mechanistic understanding of T1D.
- Develop and implement assays that improve on the current stratification and staging paradigms.
- Inform on existing or devise novel therapeutic approaches based on these responses.
- Capitalize on current advances in other fields to apply technologies and learnings to T1D.

SCOPE

Applications are sought from investigators to build upon and/or capitalize on prior findings demonstrating the presence of immune responses to neoepitopes and apply these to questions of clinical significance.

Potential topics to address include, but are not limited to:

1. Demonstration of the role of neoepitopes in the etiology and/or pathogenesis of human T1D.
    a. Does reactivity to a neoepitope or neoepitopes precede reactivity to native beta cell antigens?
    b. What are the mechanisms driving immune reactivity to neoepitopes?

2. Determination of the timing, prevalence, dynamics of neoepitopes and the resulting immune responses to neoepitopes in the progression to T1D in humans.
    a. Can neoepitopes be utilized to improve on current staging paradigms?
    b. Do neoepitopes inform on the progression to and between stages of T1D?
    c. Can a clinical assay be developed utilizing identified neoepitope responses to address these questions?

3. Determination of the utility of a given neoepitope for therapeutic interventions.
    a. Can the therapeutic utility of inhibiting neoepitope production to prevent Stage 2 and/or Stage 3 T1D be demonstrated in preclinical models?
    b. Can neoepitopes be integrated into immune tolerance approaches?

4. Application of novel technology to facilitate discovery and detection of neoepitope generation and responses in humans and/or human derived samples.
    a. Platforms that allow for analyses on small sample volumes or cell numbers
    b. Advanced technologies to facilitate discovery of neoepitopes
    c. Platforms that facilitate identification of circulating antibodies to neoepitopes and timing of T cell reactivity.
        i. The examples above are dependent on the availability of a robust and reliable assay for detection. **Preliminary data demonstrating this will be required.**

Additional details:

- Cross validation using additional cohorts or laboratories is highly desired.
- Sample access must be demonstrated during the application process.
- Awardees will be required to participate in the Neoepitopes Working Group, including participation in monthly calls and collaboration among members.
- Applications proposing the discovery and detection of novel neoepitope generation and responses must utilize human samples.
- Applications proposing the development of animal models are **out of the scope** of this RFA. Please monitor the JDRF Grant Center for upcoming funding opportunities that are tailored for such projects.

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 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 are welcome to submit to this RFA.

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.

EOI COMPONENTS

Prospective applicants should submit an expression of interest **that is no more than 2 pages in length** online via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal request. The EOI template provided on the RMS360 website must be used to complete the application. Applicants will be notified approximately three weeks after the EOI deadline date if they have been approved to submit a full application.

EOI proposals should include the following information.

- Proposed research (What?)
- Brief description of rationale for proposed research (Why?)
- Brief description of research design and methods (How?)
    - Include data regarding assay reliability and robustness, if applicable
- Advantages over alternative approaches that would address goal, if applicable
- Future plans if research is successful and potential translational impact
- Projected deliverables for the project if successful
- Confirmation of sample access (does not count towards page limit)

DEADLINES

- **Release Date**: Thursday, April 4, 2019
- **Expression of Interest Deadline:** Thursday, May 16, 2019
- **Notification of EOI Outcome:** Monday, June 3, 2019
- **Full Proposal Deadline:** Tuesday, July 2, 2019
- **Response to Applicants:** By November 30, 2019
- **Earliest Anticipated Start Date:** January 1, 2020

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 2 years may be requested. The level of funding will vary depending on the scope and overall objectives of the proposal.

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://grantcenter.jdrf.org/rfa/

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 online via JDRF's on-line research management system, RMS360 (http://jdrf.smartsimple.us). Proposal section templates in MS Word [**12 page 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.

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

SUBMISSION INSTRUCTIONS

Applicants must register as an applicant and submit their application in response to this RFA using JDRF's on-line research management system, RMS360 (https://jdrf.smartsimple.us).

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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 technical issues with RMS360, 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.