JDRF Juvenile Diabetes Research Foundation International

dedicated to finding a cure

SPECIAL REQUEST FOR EXPRESSIONS OF INTEREST:

STUDY OF MODIFICATIONS OF BETA CELL ANTIGENS IN THE IMMUNOPATHOGENESIS AND TREATMENT OF TYPE 1 DIABETES

PURPOSE

JDRF is soliciting expressions of interest (EOI) for the study of modifications of beta cell antigens in the immunopathogenesis and treatment of type 1 diabetes (T1D). JDRF is committed and most interested in investigator-initiated proposals that focus on research that will translate to clinical results.

BACKGROUND

The mechanism(s) by which immune tolerance is broken in autoimmune disease is complex and poorly understood. In several human autoimmune diseases, such as celiac disease and rheumatoid arthritis, the antigens targeted by the autoimmune process have been modified by post-translational modifications (PTM). Introduction of tissue-specific or tissue-generated PTMs may lead to the generation of neoepitopes that are not expressed in the thymus and thus escape central tolerance. Furthermore, peptides that have been modified by PTMs may have altered MHC-TCR binding leading to altered T cell signaling and may activate a response in the periphery that bypasses peripheral tolerance. In addition to the alteration of proteins by PTMs, alternative splicing of mRNA may lead to changed expression of proteins and generation of neoepitopes at sites of novel junctions, translational infidelity through misacylation of tRNA may lead to amino acid changes, and protein misfolding may lead to altered antigen processing and presentation. Immune responses to neoepitopes may lead to loss of immune tolerance to naturally occurring self-antigens.

Cells undergoing either oxidative or ER stress are prone to changes in PTMs, alternative splicing, translational infidelity, and misfolding. The beta cell is highly susceptible to undergo oxidative and ER stress and is thus potentially a site of prominent alteration in protein expression. In fact, alternative splicing is prominent in the face of cytokine-induced beta cell stress and there is some evidence for immune recognition of PTMs of beta cell autoantigens. However, the overall role of modification of beta cell antigens in the immunopathogenesis of type 1 diabetes has not been elucidated. Novel diagnostic and therapeutic approaches could be developed if protein modifications were shown to play a critical role in the disease.

OBJECTIVES

Expressions of interest are sought from investigators interested in elucidating the existence of and potential role for beta cell antigen modifications in type 1 diabetes immunopathogenesis. The translational potential of the investigations should be highlighted and thus, research plans involving human samples should be emphasized and will be given priority. This initiative encourages collaborations between experts in the fields of T1D, biochemistry, proteomics and other autoimmune diseases. We also welcome investigators with assays or hypotheses relevant to this initiative.

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

- Are beta cell antigen modifications necessary for the initiation or amplification of the autoimmune response in T1D?
- What are these antigenic modifications, do these conserved modifications target specific proteins, and how do they occur?
- Can beta cell antigen modifications be used as a biomarker of disease progression or response to therapy?
- Are there responses to antigenic modifications that have downstream effects that can be measured peripherally?
- Can we apply knowledge from other autoimmune diseases where antigen modifications contribute to disease pathogenesis (e.g., rheumatoid arthritis, celiac disease) to T1D?

- Can model antigens and their modifications be used to understand the role of beta cell antigen modifications in T1D?
- Can beta cell antigen modifications be targeted with therapies to prevent or reverse autoimmunity associated with T1D?
- Do environmental factors or inflammatory events contribute to beta cell specific protein modifications that impact the autoimmune response in T1D?

Investigators with ideas or resources that might benefit this initiative should also submit their ideas via an expression of interest.

ELIGIBILITY

Applications may be submitted by for-profit entities as well as nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments.

MECHANISM

Research will be supported for a maximum of 24 months (2 years).

LEVELS OF FUNDING

JDRF intends to award grants a maximum of $200,000/year total costs (including 10% indirect costs).

DEADLINES

- **Release Date**: .....July 1, 2011
- **Expression of Interest**: .....September 9, 2011
- **EOI Notification** .....October 12, 2011
- **Application Due Date**:.....December 2, 2011
- **Response to Applicants Date**: .....March 2012
- **Earliest Anticipated Start Date**: .....June 2012

EOI COMPONENTS

Expressions of interest proposals should be no more than two pages in length including the following information:

- Name, title and institution of principal investigator (PI), co-investigator and/or key collaborator(s)
- Brief details of approach proposed, including hypothesis, scientific rationale and references to published or preliminary data (preliminary data need not be presented in detail)
- Description of potential for translation into therapies including short and long-term development goals
- Biosketches of PI and co-investigators/collaborators (does not count towards page limit)

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 both their EOI and application using the templates available at JDRF's on-line application system proposalCENTRAL (https://proposalcentral.altum.com/). The completed templates are to be submitted via the on-line application system.

As a courtesy, please email the scientific contact, Jessica Dunne (jdunne@jdrf.org) to inform us of your intention to submit an EOI.

REVIEW CRITERIA

Submitted expressions of interest will be acknowledged with brief responses as to their suitability for further development by the JDRF no later than October 12, 2011.

SCIENTIFIC CONTACTS

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