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SPECIAL REQUEST FOR APPLICATIONS FOR:

[Roles of Innate Immunity and Inflammation in Type 1 Diabetes](#)

Release Date: January 23, 2008

Statement of Intent to Apply Date: March 7, 2008

Full online Application deadline: April 17, 2008

This RFA contains the following information:

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Purpose of this RFA

The Juvenile Diabetes Research Foundation International (JDRF) invites applications to pursue studies of innate immunity with a specific focus on type 1 diabetes (T1D). The goals of this initiative are to: (1) define the role of innate immunity and inflammation in the etiology of T1D; (2) delineate the contribution of innate immune and inflammatory mechanisms to beta cell sensitization and destruction; (3) employ innate and inflammatory biomarkers to predict T1D disease risk, onset, and progression; (4) develop innate immune and inflammatory modulators for treatment of diabetes or for disease prevention; (5) exploit innate immune and inflammatory mechanisms to achieve immunoregulation in T1D; The long-term goal of this initiative is to identify novel strategies for modulation of innate immunity and inflammation for early treatment and prevention of T1D.

Background

Type 1 diabetes (T1D) is an autoimmune disorder characterized by the presence of activated, self-reactive lymphocytes that invade the pancreas and destroy the insulin producing beta cells found therein. Although the etiology of T1D is incompletely understood, it is recognized to be due to both genetic and environmental determinants. In mouse models, disease can be transferred by T lymphocytes, demonstrating that this immune cell population is critical to disease development. Multiple factors appear to play a role in the activation of diabetogenic T cells, including antigen presentation, cytokines, co-stimulation, and defects in central and peripheral tolerance. Once the autoimmune process is initiated, epitope spreading and continuous antigenic exposure is thought to lead to the expansion of effector T cells that attack beta cells. A role for antigen-specific B cells has also been identified in the pathogenesis of T1D in animal models.

Activation of adaptive autoimmune T and B cell responses requires participation from components of the innate immune system, comprised of both cells and soluble factors. Multiple recent investigations have implicated a role of innate immunity and inflammation in T1D, including:

- Innate immunity associated genes associated with susceptibility to human T1D, including genes encoding MDA-5, which recognizes RNA viruses, and genes affecting vitamin D metabolism, which may be acting through antigen-presenting cells
- Evidence of a pro-inflammatory state associated with an IL-1 signature pattern in the periphery in new onset human T1D
- A role for inflammation and TLR signalling in stimulating antigen presenting cells and priming diabetogenic T cells, and converting T-cell autoreactivity to overt autoimmune disease in animal models of diabetes
- Requirement for TLR signalling in virus-induced autoimmune diabetes in the biobreeding diabetes-resistant rat model
- Role of NKT cells and innate lymphocytes, antigen presenting cells, cytokines, and chemokines in animal models of T1D

Understanding the role of innate immunity in the pathogenesis of human T1D may provide novel therapeutic approaches for its prevention and reversal.

Research Objectives and Scope

This RFA will initiate a research program in the area of mechanisms of innate immunity in T1D. It is hoped that the recruitment of new scientific expertise into the T1D field will foster development of new approaches and tools for the prevention, early diagnosis, and treatment of T1D.

Applications should focus on pursuing studies aimed at elucidating the role of the innate immune system or inflammation in T1D and developing respective modulators for the treatment and prevention of the disease. Although highest priority will be given to studies involving **human** T1D, applications can also propose to develop new human-relevant animal models that will: 1) help address the basic mechanisms underlying the interplay between innate and adaptive immunity in the context of T1D; 2) help identify inflammatory components in disease pathogenesis and/or 3) facilitate the pre-clinical testing of new inflammation/innate immunity-based therapeutic agents in T1D.

Examples of pertinent topics include (not intended to be exclusive or all-encompassing):

- Characterization of innate immune cells and their mechanism of function in T1D in human T1D and human-relevant animal models of T1D
- Characterization of innate immune receptors, and their signalling pathways in human T1D and human-relevant animal models of T1D
- Characterization of novel inflammatory mediators in T1D and their specific role in disease pathogenesis
- Delineation of the role of inflammation in different stages of T1D
- Use of innate immune/inflammatory biomarkers to predict the risk of developing T1D and for potential use in T1D therapy
- Development and application of innate immune- or anti-inflammatory strategies to block the autoimmune and inflammatory processes contributing to T1D

This RFA will not support:

- Clinical trials
- Islet transplantation studies
- Complications studies on inflammation induced by chronic hyperglycemia
- General studies on basic mechanisms of Innate Immunity and Inflammation not directly applicable to T1D
- Studies of Innate Immunity and Inflammation in autoimmune diseases other than T1D

Funding Mechanism

JDRF intends to direct up to US \$3 million for a new Special Emphasis Program to investigate the roles of Innate Immunity and Inflammation in T1D. The total project period of applications submitted in response to this RFA must not exceed three years.

Applicants must adhere to the following guidelines:

- The budget may not exceed US \$225,000 per year total costs, including 10% indirect costs.
- The total project period may not exceed three years.
- The research plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 10 pages.
- An annual progress report is required.
- Funded investigators may be asked to participate in a workshop during which grantees will present their work in progress.

Applications that are not funded in this competition may be resubmitted as regular research grant or innovative grant applications using the standard receipt dates for applications described on the JDRF website: <http://www.jdrf.org/>

Eligibility

Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent academic degree and hold a faculty position or equivalent at a college, university, medical school, or comparable institution. Applications may be submitted by domestic or foreign non-profit organizations, public or private, such as colleges, universities, hospitals, laboratories, units of state or local governments, eligible agencies of the federal government, or for-profit organizations. There are no citizenship requirements.

Instructions to Submit Applications

Letter of Intent (LOI):

For this special initiative, a Letter of Intent (LOI) must be submitted and competitively approved prior to being invited to submit a full proposal for an award. A template for the LOI can be found on proposalCENTRAL at the following link: <https://proposalcentral.altum.com/Login.asp>. The LOI must include the following information: 1) Project Title; 2) Applicant name, institution and contact information; 3) Names and institutions of key personnel and collaborators; 4) Specific Aims; 5) Outline of Proposed Research; 6) Relevance to this RFA and T1D; 7) Potential for translation into therapies; and 8) Citations. Applicants are encouraged to limit sections 5-7 to two pages.

The LOI must be submitted online through the following link: <https://proposalcentral.altum.com/Login.asp>, by **March 7, 2008**. Applicants will be informed if their LOI has been successful by March 17, 2008. No written critiques will be distributed at the LProposal.

Principal investigators whose LOI proves competitive and relevant to this RFA will be invited to submit a full proposal. **A Letter of Intent must be approved before gaining access to a full application.** *If your LOI is approved, log back on to your account on proposalCENTRAL to gain access to the full application – this must be completed by April 18, 2008.*

Proposal section templates in MS Word should be typewritten, 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.

Application Review

Review Criteria

Reviewers will be asked to evaluate applications based on the likelihood that the proposed research will have a substantial impact on the mission of JDRF. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighing them as appropriate for each application.

- Significance
- Approach
- Innovation
- Investigator
- Environment
- Relevance
- Access

Significance: Does this study address an important problem? What will be the effect of these studies on the concepts or methods that drive the T1D field?

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?

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: 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?

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?

Relevance: Is the proposed research relevant to the objectives of this RFA as well as the overall JDRF goals?

Access: For studies proposing research with human samples, appropriate documentation regarding access to samples must be provided.

Lay Review

Lay Review Committee (LRC) members will participate in the review. Each of the lay reviewers will be assigned applications in a manner similar to the scientific review committee. In addition to having reviewed applications prior to attending the meeting, they will listen to the deliberations and take the reviewers' commentary into consideration as part of the lay review. The LRC meeting will take place following the scientific review. The applications will be reviewed in a manner similar to the scientific review and those applications meeting both the scientific and JDRF criteria will be recommended for the funding to the JDRF Board of Directors.

Board Review

The recommendations of the scientific and lay review committees will be presented to the JDRF Board for final approval before funds are awarded.

Deadlines:

RFA Release Date	LOI Deadline	Response to LOI	Full Online Application Deadline	Response to Applicants	Earliest Activation Start Date
1/24/2008	3/7/2008	3/17/2008	4/17/2008	7/15/2008	9/1/2008

Award Criteria

Criteria that will be used to make award decisions include:

- Responsiveness to the goals of the RFA
- Scientific merit of the proposed project as determined by peer review
- Programmatic priorities
- Availability of funds

Inquiries

For more information about this RFA, please contact JDRF staff:

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Assistance can be obtained Monday through Friday between 8:30am and 5pm U.S. Eastern Time.