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SPECIAL REQUEST FOR APPLICATIONS FOR:

[Role of the GI Tract and Mucosal Immunity in Type 1 Diabetes](#)

Release Date: January 22, 2008

Statement of Intent to Apply Date: March 17, 2008

Full online Application Deadline: May 5, 2008

This RFA contains the following information:

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Purpose of this RFA

The Juvenile Diabetes Research Foundation International (JDRF) invites research to pursue studies of mucosal immunity in type 1 diabetes (T1D). The goals of this initiative are to: (1) define the role of 'environment', including the role of gut microflora, infection, or diet in the etiology and pathogenesis of T1D (2) employ mucosal related markers to predict T1D disease onset and progression; (3) identify key components of mucosal immunity and their mode of action in T1D; (4) develop GALT (Gut Associated Lymphoid Tissue) modulators for prevention or treatment of disease; (5) exploit mechanisms of mucosal tolerance and immunoregulation on behalf of T1D. The long-term goal of this initiative is to establish novel strategies for modulation of the gut microbiome, epithelium, and/or mucosal immunity/immunoregulation for prevention and treatment of T1D.

Background

Although much has been learned about the pathogenesis of T1D over the past several decades, the etiology and pathogenesis of human T1D are incompletely understood, which has hampered the development of effective approaches for prevention and cure. T1D is an autoimmune polygenic disorder, including susceptibility genes such as HLA DR, DQ, and other non-HLA genes, with a strong epigenetic or environmental contribution.

Multiple environmental factors that could involve the gut or its immune system have been invoked but unproven in the etiology or pathogenesis of T1D, including pathogens (viruses, bacteria, and parasites), gut microflora, and dietary antigens. These environmental factors could act to initiate, perpetuate, and/or alter the rate of progression to onset of clinical diabetes. Recent investigations have begun to demonstrate critical and complex interactions among the microbiome in the gut, intestinal epithelia and its integrity, gut innate immunity, and adaptive immunity and immunoregulation. Microbial colonization begins after birth and confers onset of adaptive immunity and immunoregulation to environmental antigens. Alterations in this mucosal-microbial-immune environment have been suggested to contribute to the etiology/pathogenesis and increased incidence of T1D.

It has been recognized for a number of years that exposure to antigen via the oral route can result in unresponsiveness or tolerance. Thus, there is increasing interest in the use of the oral administration of antigens to induce tolerance to prevent or treat various autoimmune diseases. In contrast, it is known that oral administration of certain infectious agents such as poliovirus can elicit protective systemic immunity, and this route is now encouraged in vaccines for the production of immunity to infectious agents. Studies with oral insulin in the NOD mouse demonstrated that oral administration of islet cell autoantigens was effective in delaying the onset of type 1 diabetes. In addition, ingestion of glutamic acid decarboxylase (GAD), a beta-cell antigen, by NOD mice also inhibited the development of diabetes. These results suggested that tolerance provoked by presentation of oral insulin or GAD to the immune system via the intestinal mucosa could attenuate pancreatic islet autoimmunity, leading to a delay in the onset of type 1 diabetes. The specific mechanisms by which one antigen leads to tolerance and another to immunity are unknown at this time.

The increased incidence of T1D is most marked in the young child. Prospective studies have demonstrated recently that initial production of beta-cell specific antibodies begins in the first two to three years of life in the majority who develop T1D in their first decade. The overall increase in allergic disease and autoimmune disease, especially in developed countries has been attributed to the so-called 'Hygiene Hypothesis', which suggests that the increase is due to lack of sufficient exposure of the maturing mucosal immune system to critical microbes or pathogens, with subsequent alteration in the gut microbiome and induction of protective immunoregulation. Conclusive experimental evidence to date for the Hygiene Hypothesis, however, is lacking. It is also unclear whether the environmentally-induced increased incidence of T1D is acting at the stage of initiation of T1D or is conferred by failure to induce or maintain proper immunoregulation to prevent onset or progression of immune-mediated beta-cell loss. The role of gut closure in this regard is also not determined.

Research Objectives and Scope

This RFA will initiate a research program in the area of the role of mucosal immunity in T1D. The overall objective of the RFA is to stimulate new research projects in this area with specific emphasis, whenever possible, on studies of the **human** mucosal immune system in T1D. It is hoped that this RFA will recruit scientific expertise from diverse fields to foster the development of new approaches and tools for the prevention, treatment, and early diagnosis of T1D.

Applications should focus on pursuing studies aimed at elucidating the role of the mucosal immune system in T1D and developing respective modulators for the prevention and treatment of the disease. Applications can also propose to develop new animal models that will: 1) help identify gut-associated pathogenesis of T1D; 2) help identify microbial or dietary causative agents in disease pathogenesis and/or 3) facilitate the pre-clinical testing of new mucosal immunity-based therapeutic agents in T1D.

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

- Characterization of the mechanisms of the mucosal immune system, the gut microbiome, mucosal triggers, or gut epithelial function in the pathogenesis (initiation, progression, perpetuation) of T1D
- Delineation of the contribution of mucosal exposure/immunization/antibiotics to systemic immunoregulation in healthy humans and in T1D
- Approaches to modify or “mature” mucosal-induced immunoregulation to establish ‘normal’ systemic immunity in T1D
- Development and application of innate mucosal immunity-based strategies to block the autoimmune and inflammatory processes in T1D
- Use of gut/mucosal immunity biomarkers for determine risk of developing T1D and for potential use in T1D therapy.

This RFA will not support:

- Clinical trials/studies
- Islet transplantation studies
- Complications studies on inflammation induced by chronic hyperglycemia
- General studies on basic mechanisms of mucosal Immunity not directly applicable to T1D

Funding Mechanism

JDRF intends to direct up to US \$4 million for a new Special Emphasis Program to investigate the roles of Mucosal Immunity in T1D. The total project period of applications submitted in response to this RFA must not exceed three years. ***Applications involving***

collaborative efforts between T1D and other autoimmunity or allergy research groups are welcome.

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 17, 2008**. Applicants will be informed if their LOI has been successful by March 28, 2008. No written critiques will be distributed at the LOI stage.

Proposal

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 May 5, 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	3/17/2008	3/28/2008	5/5/2008	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:


Teodora Staeva, Ph.D.
Program Director, Immunology
Juvenile Diabetes Research Foundation International
120 Wall Street, 19th Floor
New York, NY 10005, USA
Tel: +1 (212) 479-7547
Email: tstaeva@jdrf.org

Or

Simi T. Ahmed, Ph.D.
Scientific Program Manager, Immunology
Juvenile Diabetes Research Foundation International
120 Wall Street, 19th Floor
New York, NY 10005, USA
Tel: +1 (212) 479-7595
E-mail: sahmed@jdrf.org

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 <https://proposalcentral.altum.com/Login.asp>

 pcsupport@altum.com

 (301)-916-4557 ext. 227, or toll free in the US, (800)-875-2562 ext. 227

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