



*dedicated to finding a cure*

# Targeting Beta Cell Survival in the Treatment of Type 1 Diabetes

JDRF Requests *Letters of Intent* for proposals to discover beta cell selective drug targets and pathways to promote beta cell survival for the treatment of type 1 diabetes

Type 1 diabetes (IDDM) is an autoimmune disease characterized by the destruction of the insulin-producing beta cells of the islet. Programmed cell death (apoptosis) is recognized as the major mechanism, which participates in the destruction of pancreatic beta cells. Pharmacologic agents that would safely block apoptosis of beta cells and promote beta cell survival may have clinical utility in terms of preserving and maintaining functional beta cell mass in early onset type 1 diabetics, in protecting vulnerable, newly formed or regenerated beta cells from destruction, and in the maintenance of functional beta cell mass following transplantation. It is essential that suppression of disease-related beta cell apoptosis be targeted in a manner highly specific to the underlying pathologic mechanism(s) to avoid nonspecific suppression of apoptosis. The possible exception may be for approaches targeting the *ex vivo* treatment of beta cell sources to be used for transplantation.

An ideal therapeutic strategy would simultaneously protect beta cells against disease related apoptosis and promote new beta cell formation. Such agents may also have utility to prolong the viability of the beta cells following transplantation, as measured by graft survival and function.

The purpose of this call for *Letters of Intent* is to invite outstanding proposals to identify and characterize novel drug targets or biochemical intervention points in the beta cell that will promote survival and inhibit the apoptotic cascade of the beta cell in a highly selective and specific manner. Mechanistic studies may be proposed if they are specific to the beta cell and may directly lead to therapeutic compounds.

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

- Discovery of beta cell specific pathways or biochemical intervention points that govern the beta cell fate toward survival versus apoptosis in disease relevant systems and models
- Studies to promote beta cell survival and inhibit apoptosis in the context of the transplantation of beta cells, including anti-apoptotic compounds for *ex vivo* administration of islets prior to transplantation
- Studies with RNAi, known drugs or other molecular tools to discover pharmacologic intervention points to promote replication of functional human beta cells and simultaneously block the apoptotic cascade
- High throughput screens to discover novel factors or small molecules to promote beta cell survival in a highly specific and selective manner
- Hypothesis testing of novel factors or molecules to increase beta cell survival in relevant animal models including human transplant models
- Genetic or other studies in animal models to identify or validate targets to promote survival of mature beta cells or newly regenerating beta cells

This call is *not* intended to support:

- Studies on the beta cell apoptotic cascade that do not lend themselves to achieving specificity and selectivity for the beta cell, or those focusing on mechanistic studies that cannot be translated to a protective therapeutic
- Screens exclusively using transformed cell lines lacking physiological or disease relevance

Applicants who wish to consult with JDRF Program Staff to discuss the responsiveness of their proposal to this program may do so. Enquiries in this area should be referred to Andrew Rakeman, Ph.D., arakeman@jdrf.org, +1-212-479-7664.

**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.

**Mechanisms of Support**

JDRF intends to direct up to \$6 million USD over two years in total costs to fund up to ~12 new grants in response to this RFA. Up to a maximum of \$250,000 USD per year for two years, \$500,000 USD total, may be requested. The level of funding may vary depending on the scope and overall objectives of the proposal.

The JDRF hopes to help investigators to accelerate progress and address bottlenecks through active monitoring of these research programs. Under the terms of the grant application, written quarterly reports (~1 page) will be required from the funded investigator and reviewed by JDRF staff as a basis for continued support. Quarterly reports provide the opportunity for investigators to highlight progress towards research milestones as well as identify bottlenecks or impediments to progress and ways in which JDRF might assist in addressing them.

Applicants must adhere to the following guidelines:

- The budget may not exceed \$250,000 USD per year total costs, including 10% indirect costs.
- The total project period may not exceed two years.
- Projected timelines on a quarterly basis for specific aims must be provided in the application.
- Desired projected major milestones and deliverables for year 1 and year 2 must be provided in the application; these will be reviewed and may be modified as work progresses in discussion with the JDRF Program Director during the course of the research program.

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

**Deadlines**

RFA Release Date	LOI Deadline	LOI Decision Notification	Full Online Application Deadline	Response to Applicants	Earliest Activation Start Date
09/18/08	11/24/08	01/09/09	03/02/09	June, 2009	09/01/08

**Letter of Intent**

**An approved letter of intent is required for submission of a full proposal.**

Prospective applicants should submit a letter of intent on-line via the proposalCENTRAL website, using the template provided therein (<https://proposalcentral.altum.com/>). **Letters of Intent should be no more than two pages in length including, where applicable, the following information:**

- List of proposed specific aims
- Brief details of approach proposed, including rationale and references to published or preliminary data
- Short and long-term development goals set forth as milestones
- Total estimated budget and project duration (up to \$250,000 USD per year for 2 years)

Letters of intent will be reviewed by members of the scientific community, lay community and JDRF staff based on the following criteria:

*Relevance:* Is the proposed research relevant to the objectives of this RFA? What will be the expected impact of these studies on JDRF’s mission to find new agents to promote regeneration or enhance replacement of beta cell mass in T1D?

*Programmatic fit:* Do the proposed studies address an unmet critical gap in our understanding of beta cell regeneration or replacement?

*Scientific merit:* Do the proposed studies appear to be innovative, feasible and within the expertise of the investigator?

Applicants will be notified four weeks after the LOI deadline date if they have been approved to go forward to submit a full application.

**NOTE:** If your LOI is approved, you will be able to access the full proposal template through proposalCENTRAL. Under the “Manage Proposals” tab you will find a list of applications “In Progress”. If the LOI status changes to **LOI: Approved**, you may click the [Edit](#) button to gain access to the full application. All application sections must be completed and submitted by 03/02/09.

## Proposal

All applications must be completed using the templates provided on the proposalCENTRAL website (<https://proposalcentral.altum.com/Login.asp>). 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.

The research plan may not exceed 10 pages, excluding figures, tables and references. **Applications with research plans exceeding the page limit will not be reviewed.** The Research Plan must be organized as follows: A) Specific Aims; B) Rationale for the Study; C) Significance of this work to Type 1 Diabetes; D) Background and Preliminary Data; E) Research Design and Methods; F) Projected timelines and major milestones on a quarterly basis; G) Desired outcomes and deliverables at end of year 1 and year 2; H) Literature Cited (no page limit); All information in items A-G must be incorporated in the 10-page limit without exception.

## Review Considerations

Applications will be evaluated in accordance with the criteria described below. Evaluations will be competitive and performed by an appropriate peer and lay review group convened by the JDRF.

Scientific Review: 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.

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

*Relevance:* Is the proposed research relevant to the objectives of this RFA? What will be the expected impact of these studies on JDRF's mission to find new agents to promote regeneration of beta cell mass in T1D or to impact Beta cell Replacement?

*Significance:* Does this study address an important problem? What will be the expected effect of these studies on the concepts or methods that drive the beta cell biology and T1D fields?

*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 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?

*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?

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 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.

#### **JDRF Staff Contacts:**

##### **PROGRAMMATIC**

Andrew Rakeman, Ph.D.  
Scientific Program Manager, Regeneration  
Juvenile Diabetes Research Foundation  
120 Wall Street, 19<sup>th</sup> Floor  
New York, NY 10005  
☎ 212-479-7664  
✉ [arakeman@jdrf.org](mailto:arakeman@jdrf.org)

Patricia Kilian, Ph.D.  
Scientific Program Director, Regeneration  
Juvenile Diabetes Research Foundation  
120 Wall Street, 19<sup>th</sup> Floor  
New York, NY 10005  
✉ [pkilian@jdrf.org](mailto:pkilian@jdrf.org)

##### **ADMINISTRATIVE**

Kathryn Leslie  
Research Assistant  
Juvenile Diabetes Research Foundation  
☎ 212-479-7643  
✉ [kleslie@jdrf.org](mailto:kleslie@jdrf.org)

##### **PROPOSALCENTRAL**

🖨 <https://proposalcentral.altum.com/Login.asp>  
✉ [pcsupport@altum.com](mailto: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.