
SPECIAL REQUEST FOR APPLICATIONS

JDRF REQUESTS LETTERS OF INTENT FOR: TARGETING BETA CELL NEOGENESIS AND TRANSDIFFERENTIATION TO RESTORE FUNCTIONAL BETA CELL MASS

PURPOSE

The Juvenile Diabetes Research Foundation (JDRF) and Sanofi, a multinational pharmaceutical company committed to innovative therapies for diabetes management, invite applications from single investigators or groups of investigators to identify and characterize cellular targets and mechanisms to promote beta cell neogenesis and transdifferentiation for regenerative therapies for the treatment of insulin-dependent diabetes.

BACKGROUND

Diabetes is the result of inadequate functional beta cell mass, therefore restoration of normal, endogenous glucose control and ultimately curing diabetes will require therapeutic strategies to restore or regenerate beta cells in individuals with type 1 diabetes. While mounting evidence suggests that replication of pre-existing beta cells is the primary driver of homeostatic maintenance of beta cell mass in animal models, several lines of research also suggest that beta cell neogenesis, the formation of new beta cells from non-beta cells (i.e. dedicated progenitor cells or other mature cell types), can be induced by a variety of experimental injuries or pathophysiological conditions. Beta cell neogenesis as a therapeutic strategy is of considerable interest for the treatment of patients with long-standing type 1 diabetes in which few or no functional beta cells are remaining.

Studies of embryonic development support the existence of a progenitor cell residing in the pancreatic duct that can give rise to multiple cell types, including beta cells. In adult animals, it has been demonstrated that injury to the pancreas, including duct ligation, can induce the appearance of cells sharing many of the same markers as the embryonic progenitor, but it remains controversial whether these cells have the potential to give rise to new functional beta cells. Recent data has revealed a previously unappreciated plasticity in the adult pancreas as it has been demonstrated that other mature cell types, including acinar cells and alpha cells, can adopt a beta cell fate either through forced expression of a small number of key transcription factors or spontaneously in response to near-total ablation of beta cell mass. This raises the possibility that, even in the absence of an embryonic-like progenitor cell, beta cell neogenesis could be driven through the transdifferentiation of non-beta cells towards a beta cell fate.

Rational design of therapeutic strategies to stimulate beta cell neogenesis for the treatment of type 1 diabetes requires an understanding of the cell types that can give rise to new beta cells in the adult as well as the factors and pathways that can trigger their expansion and differentiation. The purpose of this call for *Letters of Intent* is to invite proposals to identify and characterize cells that can give rise to new beta cells, either *bona fide* adult progenitor cells or mature cells capable of transdifferentiation into beta cells, the pathways and cellular processes that regulate their expansion and differentiation and to validate observations made in experimental animal models on human tissues. Strategies that

mimic the response to physiological or pathophysiological stimuli are most likely to lead to safe and effective therapeutics; therefore priority will be given to proposals that take advantage of physiologic or pathophysiological conditions that drive beta cell neogenesis.

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

- elucidation of pathways and factors regulating beta cell progenitor cell expansion and differentiation or beta cell transdifferentiation in response to physiologic or pathophysiological stimuli
- identification and characterization of biologics capable of promoting beta cell neogenesis or transdifferentiation in appropriate animal models
- application of lineage tracing techniques to identify the exact cells responsible for beta cell neogenesis in response to physiologic or pathophysiological stimuli
- isolation and characterization of stem/progenitor cells giving rise to functional beta cells in relevant animal models
- investigation and development of novel markers to support isolation and characterization of adult human stem or progenitor cells capable of giving rise to mature beta cells
- characterization of adult, human pancreatic stem or progenitor cells capable of regenerating functional beta cells in relevant animal models
- proof-of-concept studies to validate putative target pathways and mechanisms using pharmacologic or genetic means to promote neogenesis and restore glucose-responsive insulin secretion and beta cell mass in an animal model of diabetes
- identification and validation of potential biomarkers of beta cell neogenesis

Collaborative efforts engaging investigators with complementary expertise are highly encouraged.

This call is *not* intended to support:

- studies of embryonic beta cell development
- efforts to differentiate embryonic stem cells towards the beta cell fate in vitro or in vivo
- efforts aimed at generating sources of beta cells for replacement therapy through the differentiation or expansion of cells in vitro or ex vivo
- efforts aimed at developing gene therapy approaches to promote beta cell neogenesis or reprogramming

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.

MECHANISM

JDRF and Sanofi wish to help investigators accelerate the progress and address critical research gaps through active partnering and feedback on the research programs. Under the terms of the grant application, written quarterly reports (~1-2 pages) will be required from the funded investigator with evidence of progress toward achieving research milestones as a basis for continued support. Quarterly reports will be reviewed by both JDRF and Sanofi staff with the investigator, and, thus, will provide the opportunity for investigators to highlight progress towards research milestones as well as identify bottlenecks or impediments to progress – allowing Sanofi and JDRF the opportunity to identify ways to help address the bottlenecks.

Investigators (and Institutions) selected for grant funding will be required to sign a modified JDRF “Program Award Agreement.” In addition to JDRF’s standard terms and conditions for academic grant awards, this agreement also includes the following requirements:

- Patent applications, public disclosures (e.g., public seminar presentations, press releases, etc.) and publications resulting from the funded research and incorporating Project Research

Results and Project Confidential Information must be provided to JDRF and Sanofi at least thirty (30) days in advance of submission or public disclosure.

- Sanofi is granted non-exclusive rights to use Project Research Results and Project Confidential Information for internal review purposes only for the purpose of determining Sanofi's potential interest in a further collaboration and/or licensing arrangement. In addition, Sanofi is granted a right of first negotiation to enter into such collaboration and/or licensing arrangement. Both of these rights will terminate six (6) months following completion of the funded Project.
- JDRF shall make Project funding payments directly to the Investigator (and Institution) as per the Program Award Agreement.

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 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.

There are no citizenship requirements.

LEVELS OF FUNDING

JDRF and Sanofi intend to support selected 1-2 year proposals with funding ranging between \$100,000-\$250,000 USD per year (amounts to include indirect costs of no more than 10%). The level and duration of funding may vary depending on the scope and overall objectives of the proposal.

LETTER OF INTENT

Prospective applicants should submit a letter of intent on-line via the proposalCENTRAL website (<https://proposalcentral.altum.com/default.asp>). The LOI template provided on the proposalCENTRAL Web site must be used to complete the application. Applicants will be notified approximately eight weeks after the LOI deadline date if they have been approved to submit a full application. Letters of Intent should be no more than two pages in length including, 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 quarterly milestones
- Total estimated budget and Project duration
- Future plans if successful
- Potential translational impact toward finding new treatments and a cure for type 1 diabetes

DEADLINES

- **RFA Release Date:** Friday, September 9, 2011
- **Letter of Intent Deadline:** Monday, November 28, 2011
- **Application Deadline:** Friday, February 24, 2012
- **Response to Applicants:** June 2012
- **Earliest Anticipated Start Date:** July 2012

PROPOSAL

An approved Letter of Intent is required prior to submission of a full proposal.

Upon notification from JDRF that the LOI has been accepted for full application status, the modified JDRF "Program Award Agreement" will be provided to the applicant. As a condition for submitting the full application, a letter of support for the terms and conditions for the award from the

University's Sponsored Research Office must be provided to JDRF within two weeks of notification. JDRF will provide a Letter of Support template; additionally, the letter needs to review any pre-existing (1) 3rd party rights that would impact future project discoveries and any future collaboration/licensing and (2) agreement terms that the institution, by policy or statute, will require in an agreement between Sanofi, JDRF and the grant recipient.

All applications must be completed using the templates provided on the [proposalCENTRAL](https://proposalcentral.altum.com/) website (<https://proposalcentral.altum.com/>). Proposal section templates in MS Word 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. The research plan will need to meet specific page restrictions. This information will be provided to the applicant upon notification of LOI acceptance, and will vary depending on the time frame for the study and proposed budget. **Note that applications with research plans exceeding the page limit will not be reviewed.** The Research Plan must be organized as follows:

- 1) Background and Significance of this work to the goals of the RFA
- 2) Proposed Research
- 3) Rationale for proposed research
- 4) Research Design and Methods
- 5) Advantages over alternative approaches that would address the same goal
- 6) Future plans if research is successful and potential translational impact towards developing new treatments and a cure for type 1 diabetes
- 7) Quarterly milestones, projected annual outcomes, and deliverables
- 8) Intellectual Property or commercial efforts associated with the current application
- 9) References (no page limit)
- 10) Principle Investigator Assurance

All information in items 1-7 must be incorporated in the 12-page limit without exception.

PROPOSAL COMPONENTS

- Applicant and Institutional Demographics (including Financial and Administrative Officer)
- Approved LOI
- Institutional Letter of Support
- Key Personnel
- Lay and Technical Abstracts
- Budget
- Budget Justification
- Subcontract Budget (if applicable)
- Subcontract Budget Justification (if applicable)
- Other Support (for the PI only)
- Organization Assurances (IRB and/or IACUC)
- Biosketches (for all Key Personnel)
- Research Plan
- Human Subject Research plan (if applicable)
- Resources
- Supporting Documents (i.e. Letter(s) of Collaboration, etc.)

INSTRUCTIONS

Applicants must register as an applicant and submit their letter of intent and application in response to this RFA using JDRF's on-line application system [proposalCENTRAL](https://proposalcentral.altum.com/) (<https://proposalcentral.altum.com/>).

REVIEW CRITERIA

Evaluations will be competitive and conducted in a highly confidential manner based on the following criteria:

- Relevance to the RFA objectives
- Significance of proposed study to a critical research gap
- Innovation and quality of the approach
- Expertise and ability of the investigators to carry out the proposed research
- Translational potential of the Project; potential to lead to a novel therapeutic approach to treat insulin dependent diabetes with potential safety/risks taken into account
- Whether there is third party funding (e.g., government, public or private funding) that has been or will be received for the same or closely related work.

CONTACTS

PROGRAMMATIC


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PROPOSALCENTRAL

 <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