

**New JDRF Beta Cell Replacement Initiative in Australia**  
Request for Application – Program Project Grant

<b>Release Date:</b>	October 6, 2008
<b>Letter of Intent Receipt Date</b>	December 8, 2008
<b>Application Receipt Date:</b>	March 2, 2009

**This RFA contains the following information:**

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- Purpose and Objectives of this RFA
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**Background**

T1D is an autoimmune disease characterized by the destruction of the insulin secreting beta cells of the pancreas by cytotoxic T cells. T1D is difficult to control with the current therapies available, and as a result patients may suffer devastating consequences including accelerated cardiovascular and peripheral vascular diseases, nephropathy, retinopathy, neuropathy, oral diseases and premature death. Islet transplantation as a therapy for T1D has been an important focus of JDRFI support, and significant progress has occurred in recent years. However, serious obstacles remain for development of islet transplantation as a cure for T1D in the general population, most notably the limited supply of human cadaveric islets. The recent successes in islet transplantation provide additional impetus for research to develop methods to attain an unlimited supply of islets and/or physiologically-responsive insulin-secreting cells from alternative sources (e.g. human embryonic stem cells, reprogrammed and expanded adult somatic cells) in order to provide a basis for cell therapy treatments. In addition, advances are also needed to overcome the xenogeneic barrier for long-term graft survival and function, given the potentially limitless supply of xenogeneic islets,

This Request for Application (RFA) was developed as a component of the JDRF Islet Transplantation Program (ITP) in Australia. The ITP was established by the JDRF with funding from the Department of Health and Ageing, and is designed to help take islet transplantation from being an experimental procedure to one broadly available for people with diabetes. This RFA is not a program being run in isolation. It is created specifically as a supplement to the existing ITP clinical and pre-clinical projects to address the long-term prospects of beta cell replacement therapy. This RFA will fund Program Project Grants that will ultimately assist in the supply of renewable human beta cell sources and/or providing the proof of concept of successful xenogeneic islet transplantation in a preclinical large animal model.

# JDRF Beta Cell Replacement Initiative

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### **Purpose and Objectives of this RFA**

JDRF's role is to facilitate the scientific community in addressing the significant challenges in beta cell replacement with the ultimate goal of developing safe and effective transplantation approaches available to large numbers of individuals with type 1 diabetes. To achieve this, JDRF is soliciting multi-project proposals addressing any combination of the following:

- Projects with the goal of differentiating embryonic stem cells (ESCs) into physiologically responsive, functional beta-cells
  - Understanding the fundamental biological mechanisms governing beta cell development and differentiation –with the overall goal of applying new knowledge to produce a source of replacement beta cells for the treatment of type 1 diabetes
  - Application of knowledge gained from normal embryology to the development of *in vitro* protocols to differentiate ESCs into “mature”, physiologically responsive, functional beta-cells
  - Recapitulation of the temporal regulation of transcription factors by growth factors and/or small molecules to produce beta-cells *in vitro*
  - Improvement of efficiency of existing protocols for beta-cell differentiation from ESCs
  - Generation of human ESC tools for high-throughput screening of small molecules capable of differentiating human ESCs towards the pancreatic beta cell lineage
- Research to develop renewable beta cell sources from non-embryonic stem cell origins
  - Isolation, purification, characterization, expansion, and differentiation of pancreatic stem/progenitor cells towards physiologically functional beta cells
  - Determining the growth conditions required to generate differentiated cells of the endocrine pancreas from adult/fetal pancreatic stem/progenitor/precursor cells in culture
  - Identification of the environmental cues, signaling pathway components, and transcriptional factors that can direct differentiation of stem/progenitor cells towards beta cells *in vitro*
  - Reprogramming/transdifferentiation of non-beta cells to physiologically responsive, insulin-secreting beta cells
  - Strategies to safely expand stem/progenitor/candidate surrogate beta cells suitable for wide therapeutic use in humans, including proof-of-concept studies using non-human cells
  - Development of physiologically responsive, insulin-secreting non-oncogenic/non-tumorigenic cell lines applicable to therapeutic use in humans, including proof-of-concept studies using non-human cells
- Preclinical projects using relevant large animal models to address immunological and physiological issues critical to the engraftment, survival, and function of islet xenografts
  - Elucidation of the mechanisms of acute vascular and cellular rejection as well as chronic rejection of xenografts
  - Characterization of the host innate and adaptive immune responses to the xenograft post-transplantation
  - Evaluation of the immune responses to xenografts from the same animal source but in different stages of development, e.g. neonatal islet-like clusters vs. adult islets
  - Approaches to immune tolerance induction
  - Delineation of the mechanisms of accommodation and/or tolerance induction
  - Development of effective strategies, including genetic modifications of organs/tissues/cells or utilization of encapsulation, to prolong xenograft survival and to eliminate or minimize the use of immunosuppressive drugs

The overall purpose of this RFA, to be funded by the JDRF Islet Transplantation Program in Australia, is to assist in the successful long-term delivery of clinical beta cell replacement therapy. This will complement and not replace other funding available through:

- ITP clinical program grants (initial commitments already made)
- Joint JDRF / NHMRC Program Grants

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- JDRFI direct funding programs
- The Diabetes Vaccine Development Centre

Please note that experience in islet transplantation is NOT required or expected for applications submitted in response to this RFA. Collaborative responses and proposals that include extensions of existing skills and projects are most welcomed.

### **Funding Mechanism**

JDRF Australia intends to direct up to AUD\$2.4 million over two years to fund Program Project Grants addressing the basic science surrounding pre-clinical approaches to resolve cell source issues for beta cell replacement therapy.

Program Projects should be composed of 2-6 projects and 1-3 cores, with component projects being highly interactive and benefiting from the use of common cores. In general, the component projects will have interdependent outcomes. An overall Program Project principal investigator is required. Generally, administration of the Program Project will rely on mutually agreed-upon leadership and common consent of the individual project principal investigators. In many instances, an administrative core will not be necessary, and any budget requests for administrative support must be strongly justified in the Program Project Grant application.

The initial stage of review will require the submission of a brief Letter of Intent. Applicants who are invited to submit a full application must adhere to the following guidelines:

- The budget may not exceed AUD\$600,000 per year total costs, including 10% indirect costs.
- The total project budget period may not exceed two years.
- An annual progress report is required

Applications that are not funded through this program may be resubmitted to JDRF using the standard receipt dates for applications described on our website: <http://www.jdrf.org/>

### **Eligibility**

**ONLY INVESTIGATORS AND INSTITUTES BASED IN AUSTRALIA ARE ELIGIBLE.** Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent and have a faculty position or equivalent at a college, university, medical school, or other research facility. Applications may be submitted by non-profit organizations, public and private, such as colleges, universities, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. The applicant may want to collaborate with investigators at other non-profit or with for-profit institutions and multi-institutional and university-industry collaborations are encouraged.

### **Instructions to Submit Applications**

#### **Letter of Intent**

Prospective applicants **must** submit, by **December 8, 2008**, a Letter of Intent (LOI) using the template provided on the JDRF on-line application system, proposalCENTRAL: (<http://proposalcentral.altum.com/default.asp?GMID=16>).

The LOI should include the following:

- A descriptive title of the proposed Program Project Grant (PPG) and a clear mission statement;
- The name, address, telephone number, and email address of the PPG Director;
- An estimated budget;
- The identities of other key personnel and participating institutions;
- The titles and a short description of component projects and cores;

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- Research project descriptions indicating the significance, gap-filling nature and potential impact of the proposed studies for type 1 diabetes, milestones and timelines, and how this proposal differentiates from other work being done in the field;
- Description of the synergism among any projects/cores within the PPG

The Letter of Intent template is available on the proposalCentral website, under [Beta Cell Replacement Initiative in Australia: Program Project Grant](#), and should be submitted electronically by **11:59 p.m., on December 8<sup>th</sup>, 2008, EST**. Letter of Intent will be reviewed for programmatic fit, scientific merits, and relevance to beta cell replacement therapy. If selected for further consideration, the proposed Principal Investigator will be notified by **January 16<sup>th</sup>, 2009**, and invited to submit a full application.

### Full Application Submission (if invited)

A template for the full application is available through JDRF on-line application system (<http://proposalcentral.altum.com/default.asp?GMID=16>), which must be used to complete the application by **March 2<sup>nd</sup>, 2009**.

### Application Review

#### Peer Review Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by JDRF in accordance with the review criteria stated below. As part of the review, all applications will undergo a process in which only those applications deemed to have the highest scientific merit will be discussed and assigned a priority score.

### Review Criteria

The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

- Approach
- Innovation
- Investigator
- Environment
- Budget

**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?

**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 this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

**ENVIRONMENT:** Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

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**BUDGET:** The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

### **Required Ethical Approvals**

JDRF reaffirms its commitment to research within the framework of the highest scientific and ethical standards. The relevant regional legislation on ethical review requirements for human pluripotent stem cells applies to all projects to be funded by this Program. For research utilizing human pluripotent stem cells, all applicants are required to provide evidence of appropriate ethical review by the Regional Ethical Committee. In addition, JDRF has convened its own Oversight Committee, which will provide a separate ethical review for all applications utilizing human embryonic stem cells, human embryonic germ cells/tissues, and human fetal tissues. Approval from both committees is required for funding.

All required ethical approval document(s) must be received by the JDRF before funding can begin. The Funded Applicant will provide certification, in English, as to the content of all ethical approval documents provided in other languages.

### **Contractual Agreement with JDRF Australia**

All applicants who are ultimately selected for funding through this RFA will also be required to enter a contractual agreement with JDRF Australia, from whom funding will be provided through support from the Department of Health and Ageing.

Should your Letter of Intent result in an invitation for a full application, the proposed contract with JDRFA will also be provided at the time that this invitation is made. Anything of concern the contract terms that is not raised by the applicant prior to submission of their full application or in their application response may not be raised at a later stage

### ***Receipt and Review Schedule***

Release Date: October 6th, 2008

Letter of Intent Receipt Date: December 8<sup>th</sup>, 2008

Notification of Letter of Intent Approval Date: January 16<sup>th</sup>, 2009

Full Application Receipt Date: March 2<sup>nd</sup>, 2009

Anticipated Award Date: May, 2009

### ***Inquiries***

**Inquiries concerning this program are encouraged and should be directed to JDRF staff.**

### **Scientific Inquiries:**

Albert Hwa, Ph.D.

Scientific Program Manager, Beta Cell Replacement

Juvenile Diabetes Research Foundation International

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### **Administrative Inquiries:**

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### **Other Inquiries:**

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### **proposalCENTRAL Inquiries:**

- <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.