
New JDRF Beta Cell Replacement Initiative in Australia
Request for Application

Release Date:	August 11th, 2008
Expression of Interest Receipt Date	October 15th, 2008
Application Receipt Date:	December 30th, 2008

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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 toxicity associated with current regimens of immunosuppression and islet administration and 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 for transplantation; to improve methods for harvesting pancreata and isolating islets; to improve techniques for the administration of transplanted islets; to enhance the engraftment and vascularization of transplanted islets; to develop approaches to prolong and enhance transplanted islets' function; and to monitor the functional mass of transplanted 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.

The ITP was established to develop multi-centre clinical studies, accompanied by mechanistic studies, which implement a single clinical islet transplantation protocol. ITP groups share information and resources to advance the field of islet transplantation. The exchange of

information among this group will be an important part of all proposals to improve the current techniques of islet transplantation.

This RFA is not a program being run in isolation. It is created specifically as a supplement to the ITP clinical program underway to address and support the need for improved clinical outcomes. This RFA will fund projects that will ultimately assist in the development of improved clinical islet transplantation outcomes.

Purpose and Objectives of this RFA

JDRF's role is to facilitate the scientific community in addressing the remaining 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 pre-clinical proposals addressing:

Restoring euglycemia and insulin independence by transplanting a replenishable source of glucose-responsive, insulin-secreting cells in the absence of chronic immunosuppression

- Development of methods for *ex vivo* expansion of cadaveric islets and identification of relevant mechanisms and pathways
- Robust and reproducible *in vitro* methods for differentiation of human stem cells to functional islets or beta cells
- Identification, characterization, and differentiation of pancreatic stem cells and beta cell progenitors
- Reprogramming of non-beta cells to glucose-responsive, insulin-secreting beta cells
- Development of glucose-responsive, insulin-secreting cell lines suitable for therapeutic use in humans
- Prevention of rejection of insulin-secreting cells
- Approaches to maintain long-term beta cell viability and function after transplantation, including interventions to regenerate beta cells *in-vivo* post-transplantation
 - Discovery of biologic factors for potential use as therapeutics to promote beta cell regeneration and for target isolation
 - Discovery of New Molecular Entities (NME) for activating the regeneration of endogenous beta cells
 - Proof-of-principle investigations of potential regeneration therapeutics in animal models and clinical studies
- Development of assays that detect and quantify human alloimmune versus autoimmune beta cell rejection and protection
- Preclinical strategies to prevent islet graft rejection without long-term immunosuppression
- Develop clinically relevant, non-invasive beta cell-specific imaging methods that can quantify functional beta cell mass of the endogenous islets and/or in the transplanted grafts
- Develop biomarkers that can quantitatively reflect functional graft mass.
- Studies to develop, evaluate, and validate biomarkers for the induction, maintenance and/or loss of immune tolerance and/or for the onset of acute or chronic graft rejection
- Studies to improve the consistency, yield, and viability of human pancreatic islets during the islet isolation process

Advances are needed in the application of tissue engineering to improve islet transplantation outcomes and to generate renewable beta cell sources. The design must be directed at satisfying the cell and molecular requirements for long-term functional success while considering the clinical requirements of beta cell replacement therapy. Determining the fate and function of implanted devices/materials is also of critical importance. These materials and their degradation products (if any) must be non-toxic and non-immunogenic, as well as possess other properties specific for beta cells/pancreatic islets and the site of implantation. Topics of interest includes:

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- Encapsulation and immunoisolation technology that can protect pancreatic islets/beta cells from immune attacks with proof of concept tested in an in vivo animal model; meanwhile cell viability and function must be maintained
 - Novel materials and encapsulation methods for uniform micro- or macro-encapsulation of islets/beta cells to provide immunoisolation
 - Coupling additional benefit of easy readout (e.g. imaging) of surviving and functional islet mass
- Novel biomaterial, encapsulation, or scaffold designs that may
 - Achieve innate and/or adaptive immunological isolation/ignorance for engineered devices;
 - Enhance islet engraftment, survival, and vascularization;
 - Meanwhile remain conducive to mass transfer of nutrients, oxygen, and other biological products necessary for islet survival and proper blood glucose regulation
- Development of strategies to promote vascularization and/or innervation within engineered tissue
- Promoting human stem/progenitor cell differentiation toward a physiologically-responsive insulin-producing cell
- Long-term maintenance of physiological beta cell phenotypes in an in vitro culture system for better characterization and understanding of the physical, chemical, and biomechanical aspects of beta cell biology

The overall purpose of this RFA, to be funded by the JDRF Islet Transplantation Program in Australia, is to assist in the delivery of improved human clinical islet transplantation outcomes. This will complement and not replace other funding available through:

- ITP clinical program grants (initial commitments already made)
- Joint JDRF / NHMRC Program Grants
- 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 will also be considered. Collaboration of engineering/chemistry and beta cell/islet transplantation/immunology expertise is required for proposals involving tissue engineering concepts.

Funding Mechanism

JDRF Australia intends to direct up to AUD\$2.2 million over two years to fund Pilot and Feasibility Studies and Collaborative Research Grants addressing the basic science surrounding pre-clinical approaches to improve current state-of-the-art islet transplantation techniques.

The initial stage of review will require the submission of a brief Expression of Interest.

Applicants who are invited to submit a full application must adhere to the following guidelines:

- For Pilot and Feasibility Studies, the budget may not exceed AUD\$150,000 per year total costs, including 10% indirect costs.
- Collaborative Research Grants involving multi-group collaborations may budget up to AUD\$300,000 per year, including 10% indirect costs.
- The total project budget period may not exceed two years.
- The research plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 10 pages, excluding figures, tables and legends.
- An annual progress report is required

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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

Expression of Interest

Expressions of Interest should include, where applicable, the following information:

- Name, title, institution, and contact information of principal investigator, co-investigators and / or key collaborators
- (If it is a resubmission of a previously rejected Australian ITP application) a one-page summary of previous criticisms and current response;
- Brief details of approach proposed, including rationale and references to published or preliminary data (preliminary data need not exist), limited to two pages
- Biosketches of PI, co-PI, and key collaborators (not included in two-page limitation)
- Total estimated budget and project duration (up to 2 years)

Prospective applicants are asked to submit an Expression of Interest letter.

Expressions of Interest will be reviewed for programmatic fit by JDRF staff members. For those selected for further consideration, the proposed Principal Investigator will be notified by October 31st, 2008, and invited to submit a full application.

The Expressions of Interest template is available on the proposalCentral website, under [ITP-Research](#), and should be submitted electronically by **11:59 p.m., on October 15th, 2008, EST.**

Full Application Submission (if invited)

A template for the full application is available through JDRF on-line application system (<https://proposalcentral.altum.com/>), which must be used to complete the application by **December 30th, 2008.**

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

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- 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?

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 Expression of Interest 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: August 11th, 2008

Expression of Interest Receipt Date: October 15th, 2008

Notification of Expression of Interest Approval Date: October 31st, 2008

Full Application Receipt Date: December 30th, 2008

Anticipated Award Date: March, 2009

Inquiries

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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
120 Wall Street, 19th Floor
New York, NY 10005, USA
Tel: +1 (212) 479-7663
Email: ahwa@jdrf.org

Robert Goldstein, M.D., Ph.D.
Chief Scientific Officer
Juvenile Diabetes Research Foundation International
120 Wall Street, 19th Floor
New York, NY 10005, USA
Tel: +1 (212) 479-7523
Email: rgoldstein@jdrf.org

Proposal Central Inquiries

Nicholas A. Roose
Grant Coordinator
Juvenile Diabetes Research Foundation International
120 Wall Street, 19th Floor
New York, NY 10005
Tel: +1 (212) 479-7694
E-Mail: nroose@jdrf.org

Other Inquiries:

Mike Wilson
Chief Executive Officer
Juvenile Diabetes Research Foundation Australia
Level 4 / 80 Chandos Street
St Leonards NSW 2065
Tel: 02-9966-0400
Email: mwilson@jdrf.org.au

Dorota Pawlak
Research Development Manager
Juvenile Diabetes Research Foundation Australia
Level 4 / 80 Chandos Street

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St Leonards NSW 2065

Tel: 02-9966-0400

Email: dpawlak@jdrf.org.au