

# National Health and Medical Research Council of Australia/ Juvenile Diabetes Research Foundation International

## Special Program Grants in Type 1 Diabetes

### Request for Applications

#### Background

**National Health and Medical Research Council of Australia (NHMRC)** is the major agency responsible for funding health research at universities, their affiliated teaching hospitals and research institutes in Australia. NHMRC wishes to facilitate the development of international links with other national and international funding agencies to mutual benefit.

**The Juvenile Diabetes Research Foundation's (JDRF)** mission is to find a cure for diabetes and its complications through the support of research. JDRF was founded in 1970 by parents of children with diabetes who were convinced that the disease and its complications could be cured through research. With chapters from coast to coast and affiliates around the world, JDRF gives more money to diabetes research than any other non-profit, non-governmental health agency in the world. In 2006, JDRF will award more than US\$125 million to diabetes research worldwide.

#### Purpose

NHMRC and JDRF intend to award jointly up to five Special Research Program Grants in Australia to further research in Type 1 diabetes. The research should emphasize the clinical application and translation of basic research findings. The establishment of potential frameworks and infrastructures in the form of a Special Program is expected to stimulate meritorious scientific investigations, as well as provide a critical mass of scientists to provide places for training and stimulation of talented young scientists and clinical investigators. Each Special Program should be supported by a strong research foundation in basic medical sciences. Interactions and partnering with other research entities, including appropriate biotech industries, is encouraged.

#### Research Objectives

Diabetes has been identified as one of the Australia's national health priorities.

The general concept of the proposed NHMRC/JDRF partnership is to support research to find a cure for Type 1 diabetes and its complications. The three general research objectives of the JDRF are:

- Restoration and maintenance of normal blood sugar levels

- Prevention and improved treatment of complications
- Prevention of Type 1 diabetes

Specific research areas of emphasis are presented in detail in Appendix 1.

### **Mechanism of Support**

Support will be provided in the form of a Special Program Grant, awarded to a group of investigators, to pursue broadly based collaborative research. Grants supported by this partnership will have a maximum budget of \$600,000 per year (including all costs) for up to 5 years. The duration of projects will be as the research requires, but will not exceed five years.

The first named Chief Investigator will be the point of contact with NHMRC and JDRF; and will normally take the lead role in the conduct of the research program. This Chief Investigator must be an Australian citizen or hold permanent residency in Australia and must be based in Australia for the duration of the grant. Investigators are eligible to apply regardless of previous funding by the program.

Each grant will be for the support of a broadly based multidisciplinary or multifaceted research program which has a specific central theme relevant to one or more of the three general research objectives. The support provided for successful applicants is for the research team, to support the team's broad research theme. The team will be expected to:

- contribute new knowledge in Type 1 diabetes at a leading international level;
- develop novel ideas and approaches;
- tackle problems for which longer term stable funding is essential;
- develop training and career development opportunities within the team; and
- facilitate collaborative use of specialized facilities or expertise.

The award may support research components and core activities. Collectively, the components should demonstrate essential elements of unity and interdependence, and result in a greater contribution to the objectives than if each activity were pursued individually.

Interactions and partnering among research entities is strongly encouraged. Special Programs receiving support may be located at more than one Australian institution and may be a 'virtual' Program, involving more than one institution.

The responsibility for the planning, direction, coordination, execution and reporting of the overall Special Program Grant will be that of the Chief Investigator, with each research component within the program under the direction of one or more project investigators. The current policies and requirements that govern "program grants" of NHMRC will apply, except that holding of a Diabetes Special Program Grant will not restrict access by the Chief Investigators to other NHMRC funding (although time commitments to this Grant will be taken into account during consideration of other applications).

### **Availability of Funds**

Up to \$2.9 million per annum will be allocated to this program over the next five years. It is anticipated that up to five Special Program Grants will be awarded, subject to receipt of sufficiently meritorious applications, relevance to the research objectives and direction of the RFA, and the availability of funds.

Grants supported by this partnership will have a maximum budget of \$600,000 per year (including all costs) for up to 5 years. The duration of projects will be as the research requires, but will not exceed five years.

In the event of a large number of meritorious applications, JDRF will consider providing additional funding support.

### **Required Ethical Approvals**

JDRF and NHMRC reaffirm their commitment to research within the framework of the highest scientific and ethical standards. All required ethical approval documents and licences (such as a license for the use of excess human embryos) must be received by NHMRC and JDRF before funding can begin.

Further information regarding research using excess human embryos can be found on the NHMRC Web site at:  
<http://www.nhmrc.gov.au/embryos/index.htm>

For research involving pluripotent human embryonic stem cells, JDRF's Stem Cell Oversight Committee will provide a separate ethical review for applications in this area. Approval from this committee is required for funding.

### **Intellectual Property**

All intellectual property forthcoming from the NHMRC/JDRFI Special Program grants will be owned by the administering institution(s) and will be managed in line with the policy of the institution(s) and in accordance with the Australian Government *National Principles of Intellectual Property Management for Publicly Funded Research*.

### **Sharing of Research Data**

JDRF and NHMRC recognize the principle that all resources developed using funds provided by this Program will be available in the public interest. JDRF and NHMRC are committed to the timely release and sharing of research data and reagents from supported studies for use by other researchers. All funded investigators must agree to this principle, and must take steps in order to facilitate availability of data and reagents. A detailed statement in this spirit must appear in the body of the grant application. Failure to share resources may lead to discontinuation of funding.

The distribution of human material, including human pluripotent stem cell lines, derived from this program will be covered by the relevant Australian legislation in force.

## Reporting Requirements

The Chief Investigators of each funded Special Program Grant are required to submit an annual progress report to NHMRC and JDRF, as well as to participate in other appropriate evaluation measures, such as periodic site visits.

Renewal of funding in year two and thereafter will be contingent on the availability of funds, and on satisfactory scientific progress as assessed by NHMRC and JDRF. Based on the evaluation of research progress each year, funding may be revised as determined by NHMRC and JDRF. A joint decision will be made on the continuation of each project within each Special Program.

Financial reporting will be in accordance with the rules and regulations of NHMRC and JDRF. NHMRC will be responsible for the distribution of funds to the grantee(s).

## Expressions of Interest

Prospective applicants are asked to submit, by 5 p.m., on October 4, 2006 an Expression of Interest letter that includes:

- i. a descriptive title of the proposed research;
- ii. the name, address, telephone number, fax number and e-mail address of the Chief Investigator of the Special Program and of the project investigator of each component project;
- iii. the identities of other key personnel and participating institutions/industry; and
- iv. a brief description of the overall Special Program Grant proposal, and of each project and core (maximum two pages per project/core), including a brief description of plans for fostering interactions among personnel involved to achieve program synergy.

The first named Chief Investigator will be the point of contact for the Special Program.

Expressions of Interest will be independently reviewed by a committee of scientists established for this purpose by the NHMRC and by a JDRF committee consisting of scientists and JDRF Lay Review Committee members. For those selected for further consideration, the proposed Chief Investigator will be notified by December 1, 2006, and invited to submit a full application.

The Expressions of Interest should make clear reference to the NHMRC/JDRF Program and should be sent to:

Ms Tracey Cross  
Director, Enabling Research and International Collaborations Section  
Centre for Research Management and Policy  
National Health and Medical Research Council Australia  
GPO Box 1421  
Canberra ACT 2601

Address for Courier:

Ms Tracey Cross  
Director, Enabling Research and International Collaborations Section  
National Health and Medical Research Council  
Level 5, 20 Allara St  
Civic ACT 2601

An electronic copy of the Expressions of Interest should also be submitted to:  
[research@nhmrc.gov.au](mailto:research@nhmrc.gov.au)

### **Full Applications**

Applications that are considered sufficiently meritorious and that fulfill the general aims of the combined NHMRC/JDRF Program will be invited to proceed to the next stage of Full Application.

Chief Investigators of each potential Special Program will be advised of the outcome of the initial proposal by December 1, 2006. Full Applications will follow the form of a standard NHMRC Program Grant application.

### **Review Considerations for Full Applications**

Completed applications will be evaluated by an appropriate scientific and lay review group convened by NHMRC and JDRF, in accordance with the criteria stated below for scientific/technical merit. At the time of review, each Chief Investigator may be invited to present the Special Program proposal to the Program review committee.

Review criteria for this program are generally the same as those for unsolicited program grant applications.

#### *Research*

- Relevance to the objectives of the program – i.e., research to find a cure for Type 1 diabetes and its complications;
- Scientific validity, merit, quality
- Technical feasibility - appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research
- Significance - impact on accelerating discovery, development of therapeutics, potential translation to human type 1 diabetes, addressing a critical research gap
- Innovation of proposed research - potential for change in a paradigm or for a seminal discovery;
- Synergy among component projects;
- Sharing plan for data and resources derived from funded research

#### *Personnel*

- Qualifications and research experience of the Chief Investigator, other investigators and collaborators;

#### *Environment*

- Availability of resources and facilities necessary to perform the research;

- Synergy of individual components to achieve the goals of the Special Program; and
- Appropriateness of the proposed budget and duration in relation to the proposed research.

The earliest anticipated date of announcement is May 1, 2007, with funding to commence May 1, 2007, or at a mutually acceptable date.

Inquiries concerning this program are encouraged and should be directed to:

Ms Tracey Cross  
 Director, Enabling Research and International Collaborations  
 Centre for Research Management and Policy  
 National Health and Medical Research Council Australia  
 GPO Box 1421  
 Canberra ACT 2601  
 Tel: +61 2 6217 9430; Fax: +61 2 6217 9045; e-mail: [tracey.cross@nhmrc.gov.au](mailto:tracey.cross@nhmrc.gov.au)

and/or

Robert A. Goldstein, M.D., Ph.D.  
 Chief Scientific Officer  
 Juvenile Diabetes Foundation International  
 120 Wall Street, 19th Floor  
 New York, NY 10005-4001  
 Tel: (212) 785-9500; Fax: (212) 785-9609; e-mail: [rgoldstein@jdrf.org](mailto:rgoldstein@jdrf.org)

and/or

Concepcion R. Nierras, Ph.D.  
 Director, Partnerships and Consortia  
 Juvenile Diabetes Foundation International  
 120 Wall Street, 19th Floor  
 New York, NY 10005-4001  
 Tel: +1212 479-7589; Fax: +1212 479-7692; e-mail: [cnieras@jdrf.org](mailto:cnieras@jdrf.org)

### **Schedule**

Deadline for Expressions of Interest: October 4, 2006

Invitation to Apply: December 1, 2006

Application Deadline: February 1, 2007

Review: April 2007

Anticipated Award: May, 2007

## Appendix 1. Research Areas of Emphasis

Type 1 or “juvenile” diabetes is an autoimmune disease in which the insulin secreting beta cells in the islets of Langerhans of the pancreas are destroyed by targeted immune attack. Beta cells are essential for glucose homeostasis. By the time of clinical diagnosis, patients have lost sufficient functional beta cell mass for glucose homeostasis and are dependent on exogenous insulin to survive. Insulin is not a cure for the disease, however, because it cannot prevent the chronic and devastating complications of kidney failure, blindness, nerve damage, amputation, heart attack and stroke.

A cure for type 1 diabetes will require restoring functional beta cell mass by activation of endogenous regeneration of beta cells or by exogenous replacement of a source of glucose responsive insulin secreting cells. Restoration of functional beta cells either by regeneration or transplantation will need to be coupled with the prevention of their immune-mediated destruction.

### General Research Goals:

Restoration and maintenance of normal blood sugar levels

- Activating endogenous beta cell regeneration
- Developing a replenishable source of glucose-responsive, insulin-secreting cells
- Abrogating immune-mediated destruction of beta cells to preserve regenerated beta cells or transplanted insulin-secreting cells in established type 1 diabetes and to preserve residual beta cell function in recent onset type 1 diabetes and at-risk individuals

Prevention and improved treatment of complications

Prevention of Type 1 diabetes

### Specific Research Goals

#### ***Activating endogenous beta cell regeneration***

In experimental animal models of diabetes, new islet cells are regenerated by either replication of pre-existent beta cells or by differentiation from precursor cells. There is evidence for physiological beta cell turnover in healthy individuals and for an increase in beta cell mass in obesity and pregnancy. The mechanisms of physiologic generation of new human beta cells, however, have not been defined. In human type 1 diabetes, it is not clear whether attempts at beta cell regeneration are ongoing but are aborted by the autoimmune response, but the detection of residual beta cells in many patients with long-standing disease suggests ongoing regeneration. It is likely, however, that control of the autoimmune response alone would not prove sufficient to restore normal glucose regulation in most individuals with type 1 diabetes.

A goal of this program is to develop therapeutics that activate endogenous regeneration of functional beta cells with simultaneous prevention of their autoimmune destruction. Development of innovative approaches to quantify residual and new beta cell mass and function will aid in the assessment of regeneration and preservation of beta cells.

Examples of pertinent areas targeted by this partnership include (not intended to be exclusive or all-encompassing):

- Identification of factors, extracellular signals, and intracellular signaling pathways and transcription factors to develop new therapeutics that activate:
    - Beta cell proliferation and functional differentiation;
    - Beta cell neogenesis from precursors;
    - Prevention of apoptosis of beta cells;
    - Reprogramming of non-beta cells to beta cells;
  - Identification of the role and mechanisms of non-beta cells in regeneration;
  - Identification of the mechanisms and pathways of *ex vivo* expansion of functional cadaveric islets;
  - Characterization of the mechanisms of beta cell regeneration in established human type 1 diabetes and in healthy subjects;
  - Proof of principle trials of regeneration therapeutics in animal models and humans
  - Development of novel approaches for imaging of islet mass, function, and inflammation
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#### ***Developing a replenishable source of glucose-responsive, insulin-secreting cells***

A major limitation of islet transplantation is the restricted number of donated human cadaver pancreata available for transplantation. Potential solutions to the limited cell source for transplantation include: *ex vivo* expansion of cadaveric islets, use of foreign specie or xeno sources of islets or beta cells, generation of glucose-responsive, insulin-secreting cells from alternative sources such as human embryonic or adult stem cells, precursor cells, or reprogramming human non-beta cells to glucose-responsive, insulin-secreting cells.

**Important Note:** The Department of Health and Aging and JDRF have recently implemented a joint initiative Australian Islet Transplant Program (ITP). Therefore, clinical human islet transplantation is not part of this Special Program in Type 1 Diabetes, and will not be supported.

Examples of pertinent areas targeted by this partnership include (not intended to be exclusive or all-encompassing):

- 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 insulin-secreting cell lines suitable for therapeutic use in humans
- Development of novel approaches for imaging of islet mass, function, and inflammation

**Important Note:** NHMRC and JDRF reaffirm their commitment to research within the

framework of the highest scientific and ethical standards. The relevant Australian legislation on ethical review requirements for human pluripotent stem cells applies to all projects to be funded by this Program. In addition, JDRF has convened a Stem Cell Oversight Committee, which will provide independent ethical review for all applications in this area. Approval from both committees is required for funding.

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***Abrogating immune-mediated destruction of beta cells to preserve regenerated beta cells or transplanted insulin secreting cells in established type 1 diabetes and to preserve residual beta cell function in recent onset type 1 diabetes and at-risk individuals***

Type 1 diabetes is an autoimmune disease in which the immune system destroys the insulin-producing beta cells in the pancreas. As a result of this process, there is a complete dependence upon exogenous insulin in order to regulate blood glucose levels. At clinical onset of type 1 diabetes, it is estimated that patients have some residual beta cell mass. Development of approaches to preserve this residual beta cell mass could help modulate the course of the disease and prevent, delay, or ameliorate complications. Control of the autoimmune response may allow preservation of beta cells in recent onset type 1 diabetes, may prevent the onset of type 1 diabetes, and in conjunction with ancillary interventions to regenerate beta cells, may permit restoration of beta cell function in established type 1 diabetes. As described above, control of the autoimmune response is required in the setting of islet transplantation.

Multiple factors appear to play a role in the activation of diabetogenic T cells, including antigen presentation, cytokines, co-stimulation, and loss or absence of central and peripheral tolerance. Promising approaches to induce tolerance or immunoregulation via immune modulation are emerging, including blocking co-stimulatory pathways involved in T-cell activation, deleting pathogenic T cells, inducing immunoregulation, increasing regulatory T cells, deviating the Th1 response, and inducing tolerance using donor bone marrow.

Examples of pertinent areas targeted by this partnership include (not intended to be exclusive or all-encompassing):

- Characterization of the roles of the innate and adaptive immune systems in the pathogenesis of human type 1 diabetes
- Identification of the beta cell epitopes recognized by autoimmune T-cells in human type 1 diabetes
- Development and standardization of assays that reproducibly detect, quantify, and characterize the function of human beta cell-specific T cells
- Discovery and development of new therapeutics that induce beta cell-specific immunoregulation
- Mechanistic research studies using samples from human clinical trials of immunomodulatory interventions for T1D. Such studies are not part of the parent clinical trial, and the parent clinical trial must have independent financial support. Proposed mechanistic studies associated with clinical trials supported by industry are encouraged, but clinical trials supported by any source, public or private, are eligible.
- Pre-clinical evaluation of immune therapies previously used in other autoimmune diseases or inflammatory conditions;

- Phase I and phase II clinical trials of novel immunoregulatory therapeutics in recent onset type 1 diabetes with or without ancillary interventions to regenerate beta cells

**Important Note:** Applicants for support for research in this area are reminded that the JDRF research program is intended to complement, and not to replace, funding available from national research funding organizations, including the Diabetes Vaccine Development Center ([www.dvdc.org.au](http://www.dvdc.org.au)), NIH-sponsored consortia such as the International Type 1 Diabetes Genetics Consortium ([www.t1dgc.org](http://www.t1dgc.org)), the Type 1 Diabetes TrialNet ([www.diabetestrialnet.org](http://www.diabetestrialnet.org)), the Immune Tolerance Network (ITN) ([www.immunetolerance.org](http://www.immunetolerance.org)), and the Autoimmune Disease Prevention Centers ([www.niddk.nih.gov/fund/diabetesspecialfunds/consortia/Prevention\\_Centers.pdf](http://www.niddk.nih.gov/fund/diabetesspecialfunds/consortia/Prevention_Centers.pdf)).

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### ***Prevention and improved treatment of short-term and long-term complications of diabetes***

The fundamental goal in this area is to discover, develop, and deliver to the clinic therapeutics needed to prevent, treat and cure the complications of diabetes and new methods to predict the risk, onset, and progression of complications. There is especially strong interest in: 1) translating findings from basic research in complications into new therapies, and 2) developing biomarkers that predict risk of complications or detect the earliest signs and progression of complications to allow clinical trials to be performed efficiently.

The chronic complications of diabetes are associated with a variety of factors, including poorly controlled diabetes, hypertension, hyperlipidemia, inflammation and anemia, but the precise causative mechanism(s) remain unknown. The Diabetes Control and Complications Trial (DCCT) showed that intensive metabolic control reduces the risk of complications onset and progression in Type 1 diabetes. Uncontrolled diabetes, associated with hyperglycemia, hyperlipidemia and insulin deficiency is thought to result in the activation of detrimental cellular signaling pathways that damage various organs and their blood vessels.

Research is currently focused on understanding the biochemical events induced by diabetes and developing and testing therapeutics to block this damage. Identifying the genes responsible for susceptibility and resistance to complications will help to understand the molecular and cellular pathogenesis of complications. A fundamental understanding of the genetic and molecular basis of diabetes complications will prove important to identify targets for complications therapeutics and will aid in the development of biomarkers to predict the risk of developing complications or detect the onset and progression of complications.

JDRF has established a Coordinating Center for the Study of the Genetics of Type 1 Diabetes and Its Complications. A current project of the Coordinating Center is the [Genetics of Kidneys in Diabetes \(GoKinD\) Study](#). The GoKinD Study has assembled a DNA resource collection for use by the research community to identify genes that contribute to the susceptibility to diabetic nephropathy. JDRF encourages applications that aim to identify genes associated with the development of type 1 diabetes complications.

Hypoglycemia is an acute complication in type 1 diabetes that arises from intensive insulin therapy to achieve optimal glucose control. Hormonal control of glucose counter-regulation fails in diabetes, the result of combined deficiencies of glucagon and epinephrine responses to falling glucose levels. Research is needed to delineate the mechanisms of glucose sensing, counter-regulation, and brain function during hypoglycemia and to develop therapeutic approaches to prevent hypoglycemia and its potential effects on brain function.

A goal of this RFA is the development, preclinical evaluation, and clinical evaluation of either new therapeutics or new approaches with established therapeutics to prevent and treat the complications of type 1 diabetes. Proposals directed to therapeutics with the potential to prevent or treat multiple complications of diabetes are especially encouraged.

Examples of pertinent areas targeted by this partnership include (not intended to be exclusive or all-encompassing):

- Discovery of the cellular and molecular basis of diabetes complications to identify drug targets and pathways
- Identification of triggers and pathways common to the development of multiple complications
- Investigation of mechanisms of glucose counter-regulation and functional defects in type 1 diabetes
- Investigation of therapeutics in development for diabetic peripheral neuropathy for their use in the treatment of diabetic autonomic neuropathy
- Investigation of mechanisms leading to accelerated cardiovascular disease in type 1 diabetes
- Investigations linking clinical and basic research findings in diabetic non-proliferative and proliferative retinopathy
- Identification and mechanisms of genes that confer susceptibility or resistance to complications
- Development of biomarkers and new approaches that predict the risk of developing complications or that detect the onset and the progression of complications. This encompasses genetics approaches and surrogate diagnostic approaches, e.g.- non-invasive imaging, biopsy analysis, and genomic and proteomic approaches
- Development of novel drug delivery strategies for complications
- Preclinical development and phase I clinical trials of new therapeutics for prevention or treatment of chronic diabetes complications
- Novel approaches to prevent hypoglycemia, or support cerebral function during hypoglycemic episodes

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### ***Prevention of Type 1 diabetes***

Both genetic and environmental factors contribute to type 1 diabetes, although the exact nature of their mechanisms have not been elucidated. Understanding the role of susceptibility and resistance genes may enable the development of new diagnostics for determining risk of developing disease, help in the design of prevention trials, lead to the identification of new therapeutic targets for the prevention or cure of type 1 diabetes, and

the potential to identify environmental risk factors.

Examples of pertinent areas targeted by this partnership include (not intended to be exclusive or all-encompassing):

- Elucidation of the mechanism by which an identified diabetes-susceptibility gene produces disease phenotypes (genotype-phenotype correlation);
- Characterization of the immunopathogenesis of human type 1 diabetes;
- Validation of candidate biomarkers with increased accuracy and precision to monitor the progression to development of type 1 diabetes, or the development of new technologies to monitor biomarkers in well-defined patient populations. A biomarker is an indicator of a disease process, and could replace hard clinical end points as a measure of the effect of new therapies.

**Important Note:** Applicants are reminded that this partnership program is intended to complement, and not to replace, support for research available from other organizations, including the International Type 1 Diabetes Genetics Consortium ([www.t1dgc.org](http://www.t1dgc.org)), the Diabetes Vaccine Development Center ([www.dvdc.org.au](http://www.dvdc.org.au)), the Autoimmune Disease Prevention Centers ([www.niddk.nih.gov/fund/diabetesspecialfunds/consortia/Prevention\\_Centers.pdf](http://www.niddk.nih.gov/fund/diabetesspecialfunds/consortia/Prevention_Centers.pdf)), the Immune Tolerance Network (ITN) ([www.immunetolerance.org](http://www.immunetolerance.org)), and Type 1 Diabetes TrialNet ([www.diabetestrialnet.org](http://www.diabetestrialnet.org)).