JDRF nPOD (Network for Pancreatic Organ donors with Diabetes) Research Projects

Request for Applications

Release Date: November 19, 2009
Letter of Intent Receipt Date: December 28, 2009
Application Receipt Date: February 8, 2010

This RFA contains the following information:

Purpose of this RFA

The Juvenile Diabetes Research Foundation International (JDRF) invites applications from individual investigators or groups of investigators wishing to conduct an in-depth analysis of organs/tissues obtained from cadaveric organ donors with type 1 diabetes, as well as donors who are islet autoantibody positive. These organs/tissues will be provided by JDRF nPOD program (www.jdrfnopod.org). **The goal of the nPOD initiative is to utilize pancreata and related tissues from cadaveric organ donors with type 1 diabetes and from islet autoantibody-positive donors to address key immunological, histological, viral, and metabolic questions related to how type 1 diabetes develops. Specifically, applications addressing and focusing**

on the natural history of type 1 diabetes in humans are of interest. This should include studies in stages of pre-diabetes, early diabetes, and late/long-term diabetics, as well as non-type 1 diabetic comparators (e.g., healthy controls, type 2 diabetes).

Data collection and sharing

Investigators who receive funding through this RFA will become members of the nPOD Consortium. While an investigator will perform independent studies, the overall goal of nPOD is to characterize tissues from donors in multiple ways and gain a comprehensive understanding of the physiological abnormalities associated with T1D. Therefore, as members, investigators are required to share reagents, methods, strategies, samples, knowledge and data with other members of the Consortium. Thus, nPOD studies will be coordinated to promote sharing of information and to reach the best possible understanding of type 1 diabetes from the collective study of human tissues. Posting of final research data for use by other nPOD members will be accomplished through a secured online database. While publication rights will be preserved for consortium members, all awardees must acknowledge their willingness to make available and share their data.

BACKGROUND

nPOD MISSION: Type 1 diabetes, also known as 'juvenile diabetes', results from a self-destructive immune response against the insulin producing pancreatic beta cells. As a result of this so-called 'autoimmune' disease, patients with type 1 diabetes develop a life long dependence on insulin replacement therapy. Unfortunately, this form of treatment is often insufficient for preventing a number of debilitating complications including heart disease, blindness, and kidney disease, among others. As a result, the JDRF is committed to find a method for preventing or permanently reversing this disorder; an effort that would undoubtedly benefit from an improved understanding of how type 1 diabetes develops.

JDRF has helped to organize and develop *nPOD*; the Network for Pancreatic Organ donors with Diabetes, in order to provide a research resource for investigators to examine questions of type 1 diabetes in humans.

nPOD OPERATING STRUCTURE: nPOD is governed by an executive committee, comprised of leading diabetes investigators, representatives from JDRF, and members of the JDRF Lay Review Committee. nPOD also receives oversight from an independent External Scientific Advisory Board (SAB), as well as having its operations submitted to an annual voluntary scientific audit of policies/procedures/holdings. nPOD data and tissue samples are processed through two different cores. The Administrative Core is located at the University of Florida. The Organ Procurement and Pathology Core, also located at the University of Florida, receives tissue directly from Organ Procurement Organizations (OPOs) and ships these tissues directly to investigators. In addition, the Barbara Davis Center (Denver, CO) provides quality control and assurance for nPOD's islet autoantibody screening laboratories and provides secondary testing of nPOD samples for diabetes-related autoantibodies. The City of Hope (Duarte, CA) handles many data related aspects of nPOD, serves as the project's interface with the United Network of Organ Sharing (UNOS) and manages the autoantibody database. Other governing bodies include the Tissue Prioritization Committee and the Publications Policies Committee.

nPOD PARTNERS: nPOD's success is dependent on its many partner organizations. These organizations assist nPOD with organ recovery and delivery and ensure that research consent is obtained from donor families. Current nPOD partner organizations include: Donor Alliance,

Joslin Diabetes Center, Lifesharing, Lifequest, One Legacy, NDRI, the National Institute of Transplantation, IIAM, Gift of Life, LABS, Inc., KRONUS, Golden State Donor Services, DCIDS, CHORI, and the University of Washington, Northwest Lipid Metabolism and Diabetes Research Laboratories . This impressive list of partners is continuously growing.

Research Objectives and Scope

The successful applications solicited through the current RFA participate in the design, conduct and analyses of immunological, histological, viral or molecular studies on the procured organs/tissues.

All requests for JDRF nPOD samples are reviewed by JDRF nPOD's Tissue Prioritization Committee. When completing your application, please consider that JDRF nPOD's tissue samples are a precious and finite resource. Meritorious applications will be given access to tissue in a prioritized fashion and collaborations (where appropriate) among existing projects are strongly encouraged, including data sharing to help interpret findings on samples that are examined by multiple investigators. Before filling out your application, please review the list of current JDRF nPOD research projects (http://www.jdrfnpod.org/current-projects.php). If your project duplicates work already underway by an approved JDRF nPOD investigator, you should justify how your proposed study will provide additional insights above and beyond what will be gained from ongoing projects.

The RFA will support investigators to characterize organs/tissues from cadavers with type 1 diabetes as well as those who are islet autoantibody positive. The focus of the research projects may include but not be limited to: 1) elucidation of the cellular composition and antigen specificity of insulitic lesions and pancreatic draining lymph nodes; 2) examination of the presence of viral infection(s) in pancreas of type 1 diabetes associated autoantibody positive donors; 3) characterization of pancreatic histology, with special emphasis on islet regeneration. Beyond studies of pancreas, nPOD also affords investigators analysis of a variety of additional tissues (e.g., spleen, peripheral blood, serum, non-pancreatic lymph nodes); hence, efforts proposing studies of these related tissues are also welcome. In addition, nPOD, through its design, seeks to provide investigators with any organs/tissues deemed relevant to the mission of the JDRF. As such, the JDRF, as well as nPOD, is open to applications from investigators seeking to recover tissues not currently subject to procurement, but which may provide valuable scientific insights (e.g., skin, bone marrow, thymus, thyroid).

Examples of research questions may include, but are not limited to the following:

- What is the composition of leukocytes/lymphocytes in the insulitis lesion in autoantibody positive organ donors? What degree of variability exists between subjects as well as between islets of the same donor, and what parameters (e.g., age, autoantibody titer or number, etc.) influence the cellular composition?

- How diverse are the T- or B-lymphocyte populations found in the pancreas, pancreatic lymph nodes, and peripheral blood? What are their antigenic specificities and receptor usage? Does this differ in the pancreatic lesion versus other tissues and are they present in peripheral blood?

- What is/are the antigen(s) responsible for breaking tolerance in diabetes? Are there differences in the autoreactive T cell population depending on the disease stage?

- Is there any evidence for pancreatic infection with particular microbes in autoantibody positive individuals or those with recent onset T1D? This could include evaluation of candidate viruses (e.g., enteroviruses) and broad microbe screenings for other infectious agents using newer genomic or proteomic approaches.

- Is there evidence of activation of the innate immune system? Are there indicators of stress, whether it is microbial, metabolic or other?

- What role do chemokines play in immunoregulation of disease? Does the chemokine profile differ depending on the stage of disease?

- What role does the intestinal microbiota play in the etiology of disease, particularly in the early stages?

- Is evidence for beta cell regeneration or replication detectable?

- Do the beta cells respond to the infiltrate by metabolic adjustments or by changes in their patterns of gene or protein expression?

- What are the immune parameters and pancreatic histology in patients who have had type 1 diabetes for 50 years or longer?

Tissues available for study:

Fresh, frozen, or fixed tissues/cells will be made available from the following organs:

- Pancreas
- Pancreatic lymph nodes
- Lymph nodes from non-pancreatic regions
- Spleen
- Peripheral blood
- Serum

The following samples may be made available in the future, depending on need and availability from the following organs:

- Small intestine
- Bone Marrow (BM)
- Skin
- Thymus
- Thyroid
- Bile duct
- Others

However, based on the needs of the successful RFA applicants, this list could be subject to modification, based on a series of logistical, financial, and practical limitation. The applicants are requested to state the types of tissues they want to use.

The following donor groups are currently available (as of November 4, 2009) in the nPOD collection:

Donor Type	Count	Age Range
No Type 1 Diabetes, Autoantibody Positive	2	18 to 41
Type 1 Diabetes Medalist (donors with T1D for over 50 years)	7	59 to 82
Type 1 diabetes	26	4 to 50
Other	6	18 to 76
No diabetes (Type 1 or Type 2), Autoantibody Negative	35	1 to 75

For a current list of JDRF nPOD donor groups, see http://www.jdrfnpod.org/donor-groups.php.

IMPORTANTLY, with recent modifications to the strategic priorities of nPOD, it is anticipated that the following donor groups will be obtained annually:

Group	Number	Organs/Tissues Recovered
Autoantibody Positive T1D patients**	10	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*
T1D patients (<7 yr from Dx)	8	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*
Long-term T1D "Medalists"	4-6	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*, Kidney, Eye
Healthy controls	10	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*
T2D patients	2-3	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*
Pregnancy	1-2	Pancreas, PLN, LN, Spleen, Peripheral Blood, Serum, BM*, Skin*
Estimated recovery total	**35**	

- = Currently under SAB consideration; ** = Will be single or double AA positive depending on ongoing interpretation of data and SAB advisement.

Actual, and future tissue availability, should be taken in to consideration by applicants when forming their research proposals.

Funding Mechanism

A. Fixed Total Budget, Variable Project Duration
Grant applications will have a fixed budget of up to $55,000 (including 10 percent indirect costs), for one year or $110,000 per year (including 10 percent indirect costs) for two years. *The research plan will determine the length and terms of the award and the investigators should submit their proposals accordingly.* Note, higher budgets may be requested with strong justification and prior JDRF staff approval.

Successful applicants will have priority access to organs, as determined by the Initiative's Scientific Advisory Board and Tissue Prioritization Committees, but this access may be intermittent. Thus, the budget requests must reflect these intricacies.

B. Research Plan Proposal Narrative
NOTE: A five page limit applies to research plans submitted in response to the RFA.

The research plan must:
- Present the scientific question to be addressed, and the rationale for making this a priority.
- If similar in scope to already ongoing projects, explain how this study would differ and provide additional important information. (See http://www.jdrfnpod.org/current-projects.php for a list of ongoing projects.)
- Indicate what tissues/organs will be required to conduct the research, and consider the feasibility of obtaining these tissues, given current North American procurement procedures (For U.S. policies, please see: http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp)
- The experimental questions should be addressable considering tissue availability; thus, the plan must be based on a realistic projection of the number of specimens available, including those already collected and those that are projected to be collected.
- Accommodate what will be the intermittent supply of islet autoantibody-positive organs.
- For existing projects, preliminary data will be required.
- Include a brief data sharing plan (i.e., explain in what form data will be deposited with nPOD).

Eligibility

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 domestic and foreign 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.

Instructions to Submit an Application

LETTER OF INTENT

Prospective applicants are requested to submit a letter of intent to apply to the RFA. This letter should include the name, telephone number, and mailing address of the Principal Investigator, the names of other key personnel, the name of the applicant institution, the title of this RFA, the title of the proposal and a list of the specific aims of the study. Such a letter of intent is not binding and it will not enter into the review of any application subsequently submitted. Letters of intent are requested solely for planning purposes. The JDRF staff will not provide responses to such letters. Letters of intent must be received no later than December 28, 2009 and should be submitted using JDRF's on-line application system, proposalCENTRAL:
https://proposalcentral.altum.com/default.asp?GMID=16

NOTE: When the LOI is administratively accepted, 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". When the LOI status changes to **LOI: Approved**, you may click the Edit button to gain access to the full application.

APPLICATION PROCEDURES

Applications in response to this RFA must be submitted using JDRF's on-line application system proposalCENTRAL:
https://proposalcentral.altum.com/default.asp?GMID=16

The research plan may not exceed five pages, including figures and tables. Please note that the 5-page limit includes narrative items *a* through *d* as described below. Complete information should be included to permit review of each application without reference to previous applications. The research plan must address the requirements indicated above, and may be organized as follows: A) Specific Aims; B) Background and Significance of this work to JDRF nPOD and T1D; C) Preliminary Studies (if applicable; required for existing nPOD projects); D) Research Design and Methods; E) Literature Cited (no page limit).

Review of Applications

Scientific Review Criteria

Applications will be assessed as individual projects evaluating the investigators' potential to address scientific questions that are not likely to be addressed in the absence of cadaveric tissues. The proposed projects will be evaluated for scientific merit by an external scientific review committee.

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
- Relevance to the scope of this RFA
- Investigator/environment
- Preliminary data (if applicable)

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 and using the tissues that are available or are projected to be available from nPOD?

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?

RELEVANCE TO THE SCOPE OF THIS RFA: Are the research questions addressed by the application relevant to the goals of this RFA. If the aims of the proposal are achieved, will that lead to a significant improvement in the understanding of the pathogenesis of human Type 1 diabetes as well as information concerning pancreatic and islet response to injury.

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?

PRELIMINARY DATA: preliminary data with the techniques to be used will strengthen the proposals. Especially when proposals aim at translating observations from mouse to human, preliminary data that support feasibility are helpful. For example, immunostaining in mouse tissues may not necessarily work the same in human tissues, and preliminary data showing that methods are optimized for human specimens is particularly important. This is because the nPOD samples are a valuable and as a limited resource should not be used to optimize a technique. However, nPOD may assist investigators in providing control specimens to optimize techniques.
DATA SHRING PLANS: Have appropriate plans been established for the sharing of data within nPOD.

Lay Review

There will be Lay Review Committee (LRC) members present at the review. Each of the lay reviewers will be assigned applications in a similar manner 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. All applications will be examined closely and those deemed inconsistent with the mission of the JDRF will be removed from further consideration. 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 chosen for the funding recommendations made to the JDRF International 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.

Terms of Award

The Research Projects will be supported for up to $55,000 (including 10 percent indirect costs), for a period of 1 year or $110,000 (including 10 percent indirect costs) per year for a period of two years. Indirect costs cannot exceed 10% of direct costs minus equipment costs and/or subcontract costs if indirect costs are included in the budget submitted by the subcontracting organization. Evidence of institutional commitment in the form of dollars or resources is also highly desirable.

JDRF is committed to the publication and dissemination of all information and materials developed using JDRF resources. All recipients of JDRF awards must agree to this principle, and must take steps in order to facilitate availability of data and samples.

Application Receipt and Review Schedule

Release Date: November 19, 2009
Letter of Intent Receipt Date: December 28, 2009
Application Receipt Date: February 8, 2010
Response to Applicants Date: April 1, 2010
Earliest Anticipated Start Date: May 1, 2010

Award Criteria

Criteria that will be used to make award decisions include:

- Scientific merit and relevance of the proposed project to the objectives of this RFA as determined by peer review
- Programmatic priorities
- Availability of funds

Program Contacts

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

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pcsupport@altum.com
Assistance can be obtained Monday through Friday between 8:30am and 5pm U.S. Eastern Time.