JDRF REQUESTS LETTERS OF INTENT FOR:

DEVELOPING AND TESTING RETRIEVABLE DEVICES AND SCAFFOLDS FOR BETA CELL REPLACEMENT THERAPIES

BACKGROUND & PURPOSE

One of JDRF's therapeutic goals is to restore beta cell function in type 1 diabetes (T1D) by replacement/transplantation of beta cells/islets. Pancreatic islet transplantation has been efficacious in selected patients in improving metabolic control and quality of life, and in preventing severe hypoglycemia in patients with medically unstable T1D. Despite improvements in cadaveric pancreas procurement, islet isolation, and islet purification, major scientific and technical challenges remain that must be addressed before beta cell replacement could be widely incorporated into the clinical management of established T1D; examples include: serious side effects from chronic immunosuppression, islet sensitivity to certain immunosuppressants, the insufficient human islet supply from cadaveric pancreata, and the desire for an alternative transplantation site. JDRF's role is to enable the scientific community to address these challenges with the ultimate goal of developing safe and effective beta cell replacement approaches available to large numbers of individuals with T1D.

The yield and quality of cadaveric human islets remain variable, and the number of cadaveric pancreata cannot meet the demand of T1D patients. Porcine islets represent a readily available, scalable and better quality-controlled cell source. At the same time, many researchers and commercial entities have begun to position human embryonic stem cell (hESC) and human induced pluripotent stem cell (hiPSC) derived pancreatic progenitors or beta/islet cell preparations as potential cellular therapeutics for T1D. It is therefore expected that more than one clinically applicable, manufactured, replenishable beta/islet cell preparation will become a reality in the near future.

Despite great progress made in generating replenishable beta cell sources, the delivery method practiced by clinical islet transplantation today – intra-portal infusion – is not considered the most promising route of implantation for these new beta/islet cell preparations. It has been widely accepted that infusion of islets into the portal circulation significantly lowers the effective islet mass peri-transplant and in long-term follow up[1,2,3]. Many alternative transplantation sites have been studied, including the omentum, intra-muscle, subcutaneous space, spleen, bone marrow, kidney capsule, etc. with varying degrees of success. But some of these choices have practical limitations in the clinical setting, such as using the kidney subcapsule or the eye as a potential site. An ideal implantation method should accommodate the characteristics of these replenishable beta cell preparations for a safe and effective clinical treatment. Considerations for explant/re-implant needs and for the risks posed by potential teratoma formation suggest an implantation design that is retrievable. Additionally, future beta/islet cell preparations might be genetically engineered to impart immune privilege, resistance to cell stress, and suicide switches. The yet unknown consequences of genetic engineering on the cells may also demand an implantation design that is retrievable. Therefore JDRF is prioritizing

[1] Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges. *DiabetesMetab Syndr Obes.* 2014 Jun 23;7:211-23.
[2] Revascularization of transplanted pancreatic islets and role of the transplantation site. *Clin Dev Immunol.* 2013;2013:352315.
[3] Alternative transplantation sites for pancreatic islet grafts. *Curr Diab Rep.* 2011 Oct;11(5):364-74.

development of a cell delivery vehicle that permits a clinically impactful cell dose and allows full retrieval of the implanted cells.

OBJECTIVES

JDRF is soliciting applications to encourage collaborations among bioengineers, chemists, immunologists, transplant researchers, and pancreatic beta cell biologists to develop and test retrievable scaffolds and devices as a key component of beta cell replacement therapy for T1D. A scaffold is defined as a three-dimensional porous construct that allows cell loading and attachment and guides tissue development. At a minimum, it should provide mechanical support and spatial distribution for the cells and is non-degradable for future explantation. The proposed designs should be tailored for the intended implantation site and allow physiological integration of the implanted islet/beta cells with the host tissue – i.e., vascularization and potentially innervation of the implanted cells/tissue. Full retrievability of the implanted cells should be demonstrated after a substantially long period of engraftment. Ultimately, the funded projects should have specific milestones and make progress towards establishing scaffold or device prototypes in clinical proof-of-principle testing. Applicants should include in their proposals the envisioned product concept – the scaffold/device design, intended site of implantation, surgical procedure, and cell delivery method.

To achieve this, JDRF is soliciting proposals addressing aspects of the following (not intended to be exclusive or all-encompassing):

- Advances are needed in the development of novel engineered scaffolds and devices that promote beta/islet cell engraftment and long-term survival and function in an extra-hepatic site, with retrievability as a key feature to allow complete removal of implanted cells
- Implantation of retrievable scaffolds/devices without cells to create a pre-vascularized site, followed by cell implantation
- Scale-up of the scaffold/device for clinical implementation to allow enough beta/islet cell delivery to reverse diabetes in humans
- Large animal and/or clinical testing of mature prototypes
    - Proposals including clinical components must provide either regulatory approval or well-developed plans to obtain such

This RFA is **not** intended to support:

- Encapsulation technologies that use physical barrier to provide immune protection

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A

JDRF will hold an announcement introduction meeting via web and teleconference on August 17, 2015 at 11AM-12PM US Eastern time, to which all interested prospective applicants are invited. JDRF scientists will give an overview of the goals of this initiative, explain the application process and answer initial questions on applications. A brief introduction on JDRF's new grant application portal (RMS360) will also be given. Please click here to for the call information.

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 or for-profit organizations. There are no citizenship requirements.

LEVELS OF FUNDING AND GRANT MECHANISM

Each project may request up to total $300,000 USD per year (including 10 % indirect costs), for up to three years. Proposals containing clinical study components may request up to total of $660,000 USD per year (including 10% indirect costs), for up to three years. Applicants should discuss with JDRF Programmatic Contact (see below) when proposing large projects involving multiple components with higher budget figures, to determine the suitability of such a proposal. Projects with a three-year research plan will be held to a strict review of the milestones at the end of year 2 before year 3 funding is approved.

Pilot and feasibility studies without significant preliminary data may request up to total $150,000 USD per year for one year (including 10 % indirect costs).

Indirect costs may not exceed 10% of the direct costs.

Under the terms of the final grant award, written quarterly reports will be required from the funded investigator as a basis for continued support.

In the full application applicants must provide:

- Projected timelines on a quarterly basis for each specific aim
- Projected deliverables for each year

These will be reviewed and may be modified as work progresses during the course of the research program in discussion with the JDRF Program Scientist.

TO APPLY:

Both academic and industry researchers are welcome to apply (please see the above eligibility criteria). The indirect costs cannot exceed 10% of the total direct costs. Applicants are strongly advised to consult with JDRF Programmatic Contact by September 15, 2015 to discuss the responsiveness of their proposal to this program. Inquiries in this area should be referred to Albert Hwa, Ph.D., ahwa@jdrf.org, +1-212-479-7663.

LETTER OF INTENT

An approved LOI is required prior to submission of a full proposal. Please see below for complete instructions. Letters of intent should use the template provided and include the following information:

- Background /Rationale and Specific Aims of overall project
- Overview of hypotheses, goals and deliverables
- Expected deliverables and impact of the proposed study Title, lead investigator and brief description and specific aims of individual projects
- Intellectual Property or commercial efforts associated with the current application
- Total budget / budget by year by project
- Biosketches for all Principal Investigators

DEADLINES

Request for LOI Release Date:…… July 27, 2015
Announcement Introduction and Public Q&A:…… August 17, 2015
LOI Submission Deadline:……..October 15, 2015
LOI Decision Notification:……..November 16, 2015
Full Application Submission Deadline: …… January 8, 2016
Funding Notification:……May 2016
Earliest Anticipated Start Date:……..June 1, 2016

SUBMISSION INSTRUCTIONS

Applicants should register and submit their completed LOI in RMS360 (http://jdrf.smartsimple.us). The deadline to submit a completed LOI is October 15, 2015.

REVIEW CONSIDERATIONS

Applications will be evaluated in accordance with the criteria described below. Evaluations will be competitive and performed by an appropriate peer review group convened by the JDRF. Reviewers will be asked to evaluate applications based on the likelihood that the proposed research will have a substantial impact on the mission of JDRF. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighing them as appropriate for each application.

Relevance: Is the proposed research relevant to the objectives of this RFA? What will be the expected impact of these studies on JDRF's mission to develop beta cell replacement therapies?

Significance: Does this study address and important problem? What will be the expected effect of these studies on the concepts or methods that drive the beta cell replacement field?

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?

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 Experience: Is the investigator appropriately trained and well suited to carry out the planned studies? Is the work proposed appropriate to the experience level of the principal investigator? Due to the nature of the RFA objectives, it is expected that multiple investigators might be required to contribute the expertise required for a project to succeed – e.g., bioengineering, transplantation, chemistry, etc. If the investigator does not have T1D experience, are there appropriate collaborative arrangements with experts in T1D?

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

PROGRAMMATIC CONTACT

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ADMINISTRATIVE CONTACT

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If you have any grant-specific questions as you work within RMS360, please contact the administrative contact listed above.

For any **non grant-specific** inquiries or issues, please contact SmartSimple Support Services via email support@smartsimple.com or phone (866) 239-0991. Support hours are Monday through Friday between 5:00am and 9:00pm US Eastern Standard Time.