JDRF REQUESTS LETTERS OF INTENT FOR:

GENERATING IMPROVED BETA/ISLET CELL SOURCES THROUGH GENETIC MODIFICATIONS

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 and the insufficient human islet supply from cadaveric pancreata. 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.

Two alternatives to human cadaveric islets have shown the most promise as clinically applicable commercial beta cell replacement products. 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 exogenously generated cells will encounter robust allo-, xeno-, and/or auto-immune responses upon transplantation into a T1D patient. Furthermore, the inflammatory transplant environment, metabolic demand, and the lack of immediate vascular access all contribute toward increased stress on implanted insulin-producing cells. An improved beta/islet cell preparation might benefit from genetic engineering to acquire immune privilege and resistance to cell stress. Meanwhile, recent improvements on gene editing techniques, such as the CRISPR-Cas system, offer an unprecedented efficiency and precision in the quest to modify the properties of therapeutic cell products. This RFA wishes to take advantage of these technical advances toward developing improved beta/islet cell products for beta cell replacement therapies for T1D patients.

OBJECTIVES

The objective of this RFA is to support applications to use state-of-the-art gene modification techniques to develop and test improved beta/islet cell preparations, with a pathway toward therapeutic use in beta cell replacement for T1D patients. At a minimum, the cell preparations must demonstrate safety and functional competence. These should be established through in vitro and in vivo assays that can assess the lack of uncontrolled growth, appropriate insulin production/secretion, and diabetes correction. Off-target editing errors should also be characterized, identified, and minimized. The improved properties of the cell preparations must then be tested in appropriate

models to ascertain whether the cells can provide a functional cure in diabetes models with minimal or no chronic immune suppression.

Applications selected for funding will foster multidisciplinary collaborations that are required for translational research to develop a safe and effective cell based therapy for beta cell replacement for treating T1D. A successful team will ideally draw upon expertise from investigators established in stem cell biology, beta cell biology, immunology, transplantation, and/or diabetology.

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

- Gene modifications to enhance beta/islet cell preparations:
  - Imparting protection from allo- or xeno-geneic rejection or autoimmune destruction
  - Increasing the cell's resistance to stress
  - Enhancing cell preparation's safety profile with suicide switches
- Development of in vitro tools and in vivo models that can have predictive values on whether the modified cells can withstand human immune responses in the clinical setting
- Demonstration of the intended effects by the modifications in vitro and in vivo while balancing minimal number of modifications with efficacy and minimizing off-target mutations

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

- Refinement of stem cell differentiation protocols to produce terminally differentiated beta cells
- Studies using cells that are not intended for clinical use, or cannot be used in a clinical setting

BETA CELL FUNCTION ANALYSIS FACILITY

Investigators whose proposed plan includes stem cell-derived beta/islet cell preparations must submit their cell of choice to the Beta Cell Function Analysis Lab at the University of Illinois in Chicago for beta cell phenotype verification. For detailed information please visit our website: http://grantcenter.jdrf.org/wp-content/uploads/2012/12/Pamphlet_JDRF.pdf

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A

JDRF will hold an announcement introduction meeting via teleconference on March 9, 2016 at 11:00AM 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 grant application portal (RMS360) will also be given.

Teleconference Information:
US dial in: 877-261-5012
International dial in: 678-373-4776.
Conference code 7025171343.

View international toll-free or local dial-in numbers:
https://www.intercallonline.com/listNumbersByCode.action?confCode=2255387797

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 $350,000 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).

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. Interested applicants are encouraged to join the announcement introduction teleconference on March 9, 2016 at 11:00AM US Eastern time and to contact the JDRF Programmatic Contact to discuss the responsiveness of their proposal to this program. Inquiries in this area should be referred to Andrew Rakeman, Ph.D., arakeman@jdrf.org, +1-212-479-7664.

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:…….. February 2, 2016
Teleconference Introduction and Public Q&A:…… March 9, 2016
LOI Submission Deadline:……..April 28, 2016
LOI Decision Notification:……..……..May 16, 2016
Full Application Submission Deadline: …… July 14, 2016
Funding Notification:…….……October 2016
Earliest Anticipated Start Date:……..November 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 April 28, 2016.

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.