JDRF REQUESTS LETTERS OF INTENT FOR:
LOCALIZED IMMUNOMODULATION IN BETA CELL REPLACEMENT

BACKGROUND & PURPOSE

JDRF is committed to the development of beta cell replacement therapies to restore glycemic control and eliminate the need for exogenous insulin administration in people with T1D. Pancreatic islet transplantation has been efficacious in improving metabolic control, preventing severe hypoglycemia, and improving quality of life in patients with medically unstable T1D. Despite significant progress in the development of alternative renewable sources of insulin producing cells to overcome the shortage of donor tissue, major scientific and technical challenges remain that must be addressed before beta cell replacement is widely incorporated into the clinical management of established T1D. One key limitation is the need for systemic administration of immunosuppressive drugs to protect the cell graft from the recipient’s immune response.

The advent of the Edmonton protocol signified a major breakthrough in clinical islet transplantation by significantly improving outcomes in patients that underwent the procedure as reflected by stable glycemia, reduction in hemoglobin A1c (HbA1c), and elimination of hypoglycemia for several years.¹ ² However, most of these patients still failed to maintain insulin independence for more than 5 years due to graft failure. Moreover, the use of immunosuppressive drugs is associated with serious adverse side effects and can impair beta cell function.³ ⁵ Alternative approaches being explored for providing immune protection include encapsulation of cells in permselective membranes that allow exchange of nutrients, glucose, and insulin but block immune cells and other immune effectors from recognizing the graft.⁶-¹³ Although progress has been promising, the foreign body reaction and ensuing fibrotic encapsulation of implanted materials paired with limitations on mass transfer and nutrient delivery remain a challenge.

More recently, the emerging field of immuno-engineering has come to the forefront of efforts to develop technologies to control the patient's innate and adaptive immune responses.¹⁴-²⁴ These approaches employ various strategies targeting mechanisms of immune cell recognition and activation which could be exploited to direct the host response to implanted materials and/or cells towards a wound healing and/or tolerogenic response, as opposed to an inflammatory and/or effector response. Local immunomodulation at the graft site is highly desirable, as it could obviate the need for harsh and burdensome systemic immunosuppression regimens and perhaps even encapsulation barriers. Therefore, JDRF wishes to support research into novel strategies for localized modulation of the host response to implanted materials and development of immunomodulatory therapeutics to provide graft protection at the transplant site leading to long-term graft function.

OBJECTIVES

Letters of intent (LOI’s) are sought for preclinical and/or clinical studies from academic or industry applicants with innovative approaches to modulate the immune response of the host to reduce or eliminate (1) the fibrotic response to implanted materials and (2) the immune response to implanted cells. Only projects with relevance to T1D will be considered.

Examples of research appropriate for this RFA include, but are not limited to:

- Bioactive coatings and surface treatments of implant surfaces to reduce the fibrotic response and induce graft tolerance (e.g. extracellular matrix or basement membrane mimetic coatings, tethering of immune cell signaling ligands).
- The use of nanocomposite materials for controlled combinatorial localized delivery of drugs and tolerogenic factors.
- Technologies for in vivo reprogramming of immune cells for induction of tolerogenic phenotypes to achieve antigen-specific tolerance (e.g. novel tolerogenic nanoparticle formulations, artificial antigen-presenting cells (aAPC)).
- Technologies for eliminating antigen-specific effector cells or rendering them unreactive (e.g. killer aAPCs)
• Testing of candidate immunotherapies in low burden regimens to enhance graft longevity and survival.

This RFA will **not** support applications focused on:

- Standard macro and microencapsulation of islets
- Genetic modification of islets for secretion of immunomodulatory factors/molecules.
- Co-transplantation of islets with mesenchymal stem cells (MSC’s).
- Adoptive transfer or infusion of regulatory T cells (T-regs) in conjunction with islet/beta cell transplantation.

Applicants are encouraged to consult with JDRF Scientific Staff to discuss the alignment of their proposal to this RFA and to develop the project concept.

**MECHANISM**

Nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments may apply under JDRF’s **Strategic Research Agreement (SRA)** and **Pilot and Feasibility (PNF)** funding mechanisms. For-profit entities may apply under JDRF’s **Industry Discovery & Development Partnership (IDDP)** funding mechanism, which entails additional requirements and typically has a modest royalty payback to JDRF.

Strategic Research Agreement applications may request up to $200,000 USD per year (including up to 10% indirect costs) for up to 2 years. The level of funding will vary depending on the scope and overall objectives of the proposal. Project proposals of up to 36 months duration and/or higher budget may be considered. Applicants should discuss with JDRF Staff (see below) when proposing longer timelines or higher budgets to determine the suitability of the proposal.

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

For more information on the Strategic Research Agreement mechanism, please refer to the JDRF website [http://grantcenter.jdrf.org/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/](http://grantcenter.jdrf.org/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/) Pilot and Feasibility LOIs should follow the same website guidelines as the Strategic Research Agreements with the smaller budget and timeline referred to above.

If you would like to submit an Industry Development and Discovery project LOI to this RFA, please contact Dr. Jaime Giraldo (jgiraldo@jdrf.org) to discuss prior to submitting an application.

**ELIGIBILITY**

Applicants for SRA’s 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. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this LOI; however, additional information will be requested from for-profit entities if a full application is invited.

For clinical studies, applicants must hold an appointment or joint appointment in a subspecialty of clinical medicine, and conduct human clinical research.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, JDRF welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

**LETTER OF INTENT**

Prospective applicants should submit a Letter of Intent (LOI) online via RMS360 ([http://jdrf.smartsimple.us](http://jdrf.smartsimple.us)) to be considered for a full proposal. The LOI template provided through RMS360 must be used to complete the application. Applicants will be notified approximately one month after the LOI deadline date if they have been approved to submit a full application.
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
- Uniqueness about the approach and advantages over other approaches explored in the field
- Overview of hypotheses, goals, deliverables, and collaborative framework if applicable
- Impact of the expected deliverables of the proposed study with potential next steps
- Timelines/timetable
- Intellectual Property or commercial efforts associated with the current application
- Estimated total and annual budgets
- Biosketches for all Principal Investigators

**PROPOSAL**

An approved LOI is required prior to submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided on the RMS360 portal (http://jdrf.smartsimple.us). Proposal section templates in MS Word [10 page maximum] should be type-written, single-spaced and in typeface no smaller than 10-point font and have no more than six vertical lines per vertical inch. Margins, in all directions, must be at least ½ inch. Complete information should be included to permit review of each application without reference to previous applications.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design and investigational product information. More details can be found in the Human Subject Research Guidelines: http://grantcenter.jdrf.org/wp-content/uploads/2012/12/JDRF_Scientific_Guidelines_final-Aug20151.pdf

**ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A**

JDRF will hold an introductory meeting via web teleconference on **Tuesday, August 28th, 2018 from 11:00am-12:00pm US Eastern Standard 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.

**Join Webex meeting**
Meeting number (access code): 730 457 464
Host key: 116329
Meeting password: fEYxjpjc7

**Join by phone**
1-866-469-3239 Call-in toll-free number (US/Canada)
+1-650-429-3300 Call-in toll number (US/Canada)
Global call-in numbers | Toll-free calling restrictions

**DEADLINES**

RFA Release Date……………………………………………………………………August 17, 2018
Teleconference Introduction & Public Q&A:……………………………………August 28, 2018
Letter of Intent Deadline…………………………………………………………September 27, 2018
Full Proposal Invitation ……………………………………………………………October 11, 2018
Full Proposal Submission Deadline………………………………………………November 15, 2018
Earliest Anticipated Response to Applicants………………………………………May, 2019
Earliest Anticipated Start Date……………………………………………………June, 2019
REVIEW CRITERIA

Applications will be evaluated based on JDRF’s standard confidential award policy and according to the following criteria:

- Significance
- Relevance to T1D
- Approach
- Innovation and level of differentiation
- Investigator experience
- Environment

CONTACTS

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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.
Literature Cited