JDRF REQUESTS LETTERS OF INTENT FOR: NOVEL IMMUNE STRATEGIES TO ENHANCE BETA CELL REPLACEMENT THERAPIES FOR T1D

BACKGROUND & PURPOSE

JDRF is committed to advancing the development of beta cell replacement therapies that are able to restore glycemic control and eliminate the need for exogenous insulin administration in people with T1D. It has been shown that pancreatic islet transplantation is efficacious in improving metabolic control, preventing severe hypoglycemia, reducing exogenous insulin requirements, 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 in overcoming recurring autoimmunity and allogeneic immune rejection remain which must be addressed before beta cell replacement can be widely implemented as a cure for established T1D. The reliance on systemic administration of immunosuppressive drugs to protect the cell graft from the recipient's immune response is one key limitation which calls for the development of safer and better alternatives capable of ensuring long-term graft survival and function.

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 achieving insulin independence, stable glycemia, reduction in hemoglobin A1c (HbA1c), and elimination of hypoglycemia for several years. Although some of these patients (<10%) are able to maintain insulin independence for 5 years or more, the use of immunosuppressive drugs is associated with serious adverse side effects, can impair beta cell function, and severely limits the population of patients eligible for this type of therapy. Alternative approaches being explored for providing immune protection include encapsulation of cells using permselective physical barriers that allow exchange of nutrients, glucose, and insulin but block immune cells and other immune effectors from recognizing and attacking the graft. Although progress has been promising, limitations on mass transfer and nutrient delivery to the cells as well as the foreign body reaction to implanted materials remain a challenge.

The field of immunology has made significant advances thanks to efforts in the fight against cancer and other autoimmune diseases as well as organ transplantation. These include a better understanding of mechanisms of activation and regulation of the immune system and the development of novel biologics and immunotherapies targeting immune checkpoint, co-stimulation, and immunometabolic pathways. Similarly, the field of biomedical engineering has made significant progress in the development of novel materials and systems for targeted and controlled drug delivery. These systems enable delivery of signals or drugs to specific tissues, cells, or cell compartments in a manner that results in therapeutic efficacy while evading the unwanted side effects encountered when delivering drugs systemically. At the intersection of these two fields lies the more recently established discipline of immunoengineering which seeks to integrate engineering tools and principles with those from immunology to develop novel therapeutic strategies to modulate the immune system in a highly specific, targeted, and controlled manner. In the context of beta cell replacement therapy and T1D, these approaches could be employed to target and exploit mechanisms of immune cell recruitment or homing, antigen presentation and recognition, and immune cell activation and regulation to effectively subvert and/or modulate undesired immune reactivity against implanted cell products towards more tolerogenic responses in vivo.

Immunoengineering offers several advantages over other approaches under investigation and holds great potential for addressing the challenge of providing immune protection to transplanted cells without the use of burdensome chronic systemic immune suppression. However, certain barriers must be surmounted before this technology delivers long-term protection to transplanted insulin-producing cells. These include knowledge gaps in the roles of various components of the immune system and their crosstalk in mechanisms of graft rejection, the need to target multiple compartments of the immune system simultaneously in a complementary and synergistic fashion, and evaluation of these approaches in the context of cell transplantation and existing autoimmunity and immunological memory. JDRF wishes to mobilize the research community and promote the interdisciplinary collaborations necessary to effectively address the unique challenges encountered in this space. Therefore, JDRF

seeks applications to support research into novel immune modulation and engineering strategies aiming to protect transplanted insulin-producing cells from immune rejection and achieve long-term graft survival and function without the use of systemic immune suppression.

OBJECTIVES

Letters of intent (LOI's) are sought for preclinical and/or clinical studies from academic or industry applicants with innovative and incremental immune modulation and engineering approaches aiming to effectively subvert and/or modulate undesired immune reactivity against implanted cells products towards more tolerogenic responses in vivo. Collaborations including complementary expertise i.e. bioengineers, immunologists, cell biologists, transplant researchers, are highly encouraged and will be prioritized. Only projects with relevance to T1D will be considered.

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

- Research on the roles of various components of the immune system (i.e. innate and adaptive immunity, cellular and humoral immunity) and their crosstalk in mechanisms of graft rejection in the context of T1D, autoimmunity or immune memory, and clinically translatable alternative sites of transplantation.
- The development of combinatorial approaches that employ controlled localized drug delivery systems targeting multiple compartments of the immune system (i.e. innate and adaptive, cellular and humoral) at the graft site and/or secondary lymphoid organs in a complementary and synergistic fashion with the goal of achieving operational tolerance towards the cell graft in transplantation settings.
- The use of biomaterials and controlled delivery systems to recruit immune cells and modulate their function with the goal of achieving operational tolerance towards the cell graft in transplantation settings.
- The development of biomimetic technologies or controlled drug delivery approaches for eliminating or disabling undesirable effector cells and/or inducing tolerogenic or regulatory immune cell phenotypes in an antigen-specific manner (i.e. killer aAPCs, TolAPCs, tolerogenic vaccines, functionalized microgels) with the goal of achieving operational tolerance towards the cell graft in transplantation settings.
- Testing of novel immunotherapies, preferably in combination with controlled localized drug delivery systems, which obviates the need for toxic immunosuppressive regimens while maintaining or enhancing graft longevity and may lead to operational tolerance towards the cell graft in transplantation settings.

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

- Technologies or interventions to arrest or delay the autoimmune process and the progression of T1D (stages 1-3).
- Genetic modification or engineering of immune cells for adoptive transfer (i.e. CAR Tregs).
- Genetic modification of islets or other insulin-producing cells for immune-cloaking and/or secretion of immunomodulatory factors/molecules.
- Hematopoietic stem cell transplantation to induce mixed chimerism.
- Co-transplantation of islets with mesenchymal stem cells (MSC's).
- Macro and microencapsulation of islets.

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)** funding mechanism. 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.

For more information on the Strategic Research Agreement (SRA) grant mechanism please refer to our website: https://grantcenter.jdrf.org/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/

For more information on the Industry Discovery and Development Partnership (IDDP) grant mechanism please refer to our website https://grantcenter.jdrf.org/industry-discovery-development-partnerships/). If you plan to submit and IDDP LOI you must contact Dr. Jaime Giraldo (jgiraldo@jdrf.org) to discuss prior to submitting an LOI.

Each application may request up to total $350,000 USD per year (including up to 10% indirect costs) for up to 2 years. The level and length of funding will vary depending on the scope, stage of development, 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).

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) 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 eight weeks 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 of 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

DEADLINES

- **RFA Release Date** **September 27, 2021**
- **Letter of Interest (LOI) Deadline** **October 25, 2021**
- **Notification of Full Application Request** **November 8, 2021**
- **Application Deadline** **December 20, 2021**
- **Response to Applicants** **April 2022**
- **Earliest Anticipated Start Date** **July 2022**

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

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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.