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/ 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) 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: fEYxpjc7

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1-866-469-3239 Call-in toll-free number (US/Canada)
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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

1. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000 Jul 27;343(4):230-8.
2. Barton FB1, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, Oberholzer J, Odorico JS, Garfinkel MR, Levy M, Pattou F, Berney T, Secchi A, Messinger S, Senior PA, Maffi P, Posselt A, Stock PG, Kaufman DB, Luo X, Kandeel F, Cagliero E, Turgeon NA, Witkowski P, Naji A, O'Connell PJ, Greenbaum C, Kudva YC, Brayman KL, Aull MJ, Larsen C, Kay TW, Fernandez LA, Vantyghem MC, Bellin M, Shapiro AM. Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care. 2012 Jul;35(7):1436-45.
3. Hirshberg B1, Rother KI, Digon BJ 3rd, Lee J, Gaglia JL, Hines K, Read EJ, Chang R, Wood BJ, Harlan DM. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. Diabetes Care. 2003 Dec;26(12):3288-95.
4. Zhang N1, Su D, Qu S, Tse T, Bottino R, Balamurugan AN, Xu J, Bromberg JS, Dong HH. Sirolimus is associated with reduced islet engraftment and impaired beta-cell function. Diabetes. 2006 Sep;55(9):2429-36.
5. Lombardi A, Gambardella J, Du XL, Sorriento D, Mauro M, Iaccarino G, Trimarco B, Santulli G. Sirolimus induces depletion of intracellular calcium stores and mitochondrial dysfunction in pancreatic beta cells. Sci Rep. 2017 Nov 20;7(1):15823.
6. Borg DJ, Bonifacio E. The use of biomaterials in islet transplantation. Curr Diab Rep. 2011 Oct;11(5):434-44.
7. Olabisi RM. Cell microencapsulation with synthetic polymers. J Biomed Mater Res A. 2015 Feb;103(2):846-59.
8. de Vos P, Lazarjani HA, Poncelet D, Faas MM. Polymers in cell encapsulation from an enveloped cell perspective. Adv Drug Deliv Rev. 2014 Apr;67-68:15-34.
9. Scharp DW, Marchetti P. Encapsulated islets for diabetes therapy: history, current progress, and critical issues requiring solution. Adv Drug Deliv Rev. 2014 Apr;67-68:35-73.
10. Orive G, Santos E, Poncelet D, Hernández RM, Pedraz JL, Wahlberg LU, De Vos P, Emerich D. Cell encapsulation: technical and clinical advances. Trends Pharmacol Sci. 2015 Aug;36(8):537-46.
11. Desai T, Shea LD. Advances in islet encapsulation technologies. Nat Rev Drug Discov. 2017 May;16(5):338-350.
12. de Vos P. Historical Perspectives and Current Challenges in Cell Microencapsulation. Methods Mol Biol. 2017;1479:3-21.
13. Farina M, Alexander JF, Thekkedath U, Ferrari M, Grattoni A. Cell encapsulation: Overcoming barriers in cell transplantation in diabetes and beyond. Adv Drug Deliv Rev. 2018 Apr 30. [Epub ahead of print]
14. Hubbell JA, Thomas SN, Swartz MA. Materials engineering for immunomodulation. Nature. 2009 Nov 26;462(7272):449-60
15. Swartz MA, Hirosue S, Hubbell JA. Engineering approaches to immunotherapy. Sci Transl Med. 2012 Aug 22;4(148):148rv9.
16. Purwada A, Roy K, Singh A. Engineering vaccines and niches for immune modulation. Acta Biomater. 2014 Apr;10(4):1728-40.
17. Hotaling NA, Tang L, Irvine DJ, Babensee JE. Biomaterial Strategies for Immunomodulation. Annu Rev Biomed Eng. 2015;17:317-49.
18. Tostanoski LH, Gosselin EA, Jewell CM. Engineering tolerance using biomaterials to target and control antigen presenting cells. Discov Med. 2016 May;21(117):403-10.
19. Farhadi SA, Hudalla GA. Engineering galectin-glycan interactions for immunotherapy and immunomodulation. Exp Biol Med (Maywood). 2016 May;241(10):1074-83.
20. Foster GA, García AJ. Bio-synthetic materials for immunomodulation of islet transplants. Adv Drug Deliv Rev. 2017 May 15;114:266-271.
21. Ben-Akiva E, Meyer RA, Wilson DR, Green JJ. Surface engineering for lymphocyte programming. Adv Drug Deliv Rev. 2017 May 15;114:102-115
22. Stewart JM, Keselowsky BG. Combinatorial drug delivery approaches for immunomodulation. Adv Drug Deliv Rev. 2017 May 15;114:161-174.
23. Pearson RM, Casey LM, Hughes KR, Miller SD, Shea LD. In vivo reprogramming of immune cells: Technologies for induction of antigen-specific tolerance. Adv Drug Deliv Rev. 2017 May 15;114:240-255.
24. Kishimoto TK, Maldonado RA. Nanoparticles for the Induction of Antigen-Specific Immunological Tolerance. Front Immunol. 2018 Feb 20;9:230.