JDRF REQUESTS LETTERS OF INTENT FOR:
Novel Pathways and Targets for Beta Cell Regenerating Therapies in Diabetes

PURPOSE

JDRF invites letters of intent (LOI) from single investigators or groups of investigators to develop and conduct studies aimed at the discovery and validation of novel pathways and targets to promote the regeneration of functional human beta cell mass. Both T1D (type 1 diabetes) and T2D (type 2 diabetes) are characterized by declining function and loss of insulin-producing beta cells of the pancreatic islet; all T1D and the majority of T2D patients ultimately depend on insulin therapy due to the loss of adequate functional beta cell mass. Disease modifying regenerating therapies to restore functional beta cells mass are needed for both forms of diabetes.

BACKGROUND

Beta cell regenerating therapies will be needed to induce an increase in functional beta cell mass in order to achieve a cure for both major forms of diabetes. Recent major scientific developments provide a range of potential strategies for the discovery of beta cell regenerating therapies. At the same time, it is desirable to discover other novel pathways and targets to safely and specifically promote functional human beta cell replication.

In addition, some evidence suggests that beta cell regeneration may be achieved by promoting neogenesis of mature beta cells from a pancreatic progenitor cell. However, more work needs to be done to characterize these putative progenitor cells, and establish that this could represent a viable strategy to induce regeneration of mature, functional human beta cells. Alternatively, transdifferentiation of other cell types in the islet, such as alpha cells, to become functional beta cells has been described – at least in animal models. Better understanding of the pathways involved in these processes may enable discovery of regenerating therapies to increase functional beta cell mass and function in diabetes. The ability to establish the relevance of these pathways to the human islet/beta cell is crucially needed.

Recent data suggest that human beta cells exhibit cellular plasticity as a result of pathophysiological conditions. De-differentiation can be found after immune and metabolic stress resulting in a cell type with greatly reduced insulin secretory capabilities and some level of immune protection. Further understanding of the pathways controlling these processes could lead to therapies to “reawaken” or restore sub-functional beta cell mass. Such therapies could be disease modifying in the diabetic state and result in reversion to normoglycemia.

Other recent findings surprisingly suggest that the healthy human pancreas exhibits functional and phenotypic beta cell heterogeneity. This aspect of human beta cell biology has been described by several groups, but the pathways and targets contributing to this process are not understood. The relevance to the diabetic pancreas also needs to be established. Discovery of pathways and targets that contribute to beta cell heterogeneity may provide insights for regenerating therapies to modulate islet cell fate in diabetes to increase functional beta cell mass.

In summary, there are several avenues to explore for the discovery of therapies to promote beta cell regeneration by promoting beta cell replication, inducing neogenesis to convert precursors in the

pancreas to become functionally mature beta cells, converting other islet cells type to become functional beta cells by transdifferentiation, or by redifferentiation of beta cells to gain lost functionality, as well as other novel strategies to achieve the long term therapeutic goal of increasing functional beta cell mass and curing both major forms of diabetes. Each of these approaches hinges on the discovery and validation of targets and pathways to enable future efforts to discover and develop novel beta cell regenerating therapies for diabetes.

SCOPE

We invite the submission of Letters of Intent for projects that will identify and characterize novel drug targets or pathways in the beta cell that will selectively enhance regeneration of functional human beta cell mass.

In the context of this RFA Beta cell Regeneration is defined as any process that increases functional beta cell mass such as but not restricted to:

- Replication of existing mature, beta cells
- Neogenesis of fully functional beta cells
- Conversion of endocrine or non-endocrine pancreatic cell types into beta cells (transdifferentiation)
- Recovery of functional capacity of dedifferentiated beta cells (reversion of beta cell dysfunction)

It is required that major findings be validated with primary human islets/beta cells. Priority will be given to hypotheses driven proposals and screens using relevant human cell types.

Examples of pertinent topics include, but are not limited to:

- Discovery of novel, druggable pathways and targets to promote functional human beta cell regeneration based on biologic or mechanistic insights
- Characterization and validation of druggable pathways identified in other model systems and targets to promote regeneration of functional beta cell mass in primary human islets ex vivo and in relevant transplant models
- Studies should incorporate readouts or biomarkers of functional beta cell maturity as well as metabolic signatures
- Establishment of screens to promote increased functional beta cell mass (small molecule or biologic factors). Screens may be based on validated functional humanized systems such as human cell lines, ES/iPS derived beta cells, etc. If the screen does not include primary human cells for screening purposes, projects must incorporate validation of major findings in human beta cells/islets.
- Development of novel lineage tracing methodologies to monitor or read-out transdifferentiation of alternative human islet cell types to become functional beta cells; coupled with development of reporter cell lines for drug screening purposes ex vivo and in vivo
- Characterization of human pancreatic progenitor cells coupled with demonstration of feasibility for generation of new functional beta cells; establishment of novel drug screens based on these findings
- Validation of targets to promote human beta cell regeneration by anti-sense RNA or other novel therapeutic methodologies (CRISPR, etc...) coupled with strategies to selectively target such moieties to the human beta cell

This call is not intended to support:

- Studies characterizing embryonic development of beta cells
- Focusing on pathways without relevance to functional beta cell loss associated with clinical diabetes

- Development of β-cell-specific targeting technologies
- Efforts aimed at discovery of targets for beta cell glycemic control without direct beneficial effects on human beta cell regeneration and functional beta cell mass
- Pathways specific to liver, fat, muscle, immune, and other non-islet tissues unless they directly provide the ability to identify factors promoting human beta cell regeneration
- Studies on insulin action and sensitivity in peripheral tissues, such as muscle, fat, or liver without any known or hypothesized effects on β cells (since β cells have the capacity to respond to insulin or growth factors).

ELIGIBILITY

Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent academic degree and hold a faculty position or equivalent at a college, university, medical school, or comparable institution.

Applications may be submitted by domestic or foreign non-profit organizations, public or private, such as colleges, universities, hospitals, laboratories, units of state or local governments, eligible agencies of the federal government, or for-profit organizations.

There are no citizenship requirements. 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 [2 pages maximum] online via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application. Applicants will be notified approximately four weeks after the LOI deadline date if they have been approved to submit a full application.

POTENTIAL FOR CO-FUNDING

JDRF may consider the suitability of the LOIs for co-funding by partners (other non-profit and for-profit institutions). The LOI template will include a field by which the principal investigator may opt-out of sharing the LOI with JDRF's partners for co-funding opportunities. All proposals, regardless of the presence or absence of co-funding, will undergo the same JDRF-managed review process.

In case of any questions or concerns, please contact JDRF staff via email to the contacts listed in this RFA.

MECHANISMS OF SUPPORT

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 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.

JDRF intends to direct funds to support suitable SRA proposals for 1-2 years with funding ranging between $100,000-$500,000 USD per award total including indirect costs (10%). The level of funding may vary depending on the scope and overall objectives of the proposal.

Under the terms of the SRA grant application, regular written reports will be required from the funded investigator with evidence of progress toward achieving research milestones as a basis for continued support. Reports will be reviewed by JDRF staff with the investigator, and will provide the opportunity for investigators to highlight progress towards research milestones as well as identify bottlenecks or impediments to progress – allowing JDRF the opportunity to identify ways to help address issues.

Investigators (and Institutions) selected for SRA grant funding will be required to agree to JDRF standard terms and conditions (a sample of the most recent version can be found here: http://grantcenter.jdrf.org/wp-content/uploads/2018/10/JDRF-Terms-and-Conditions-10.18.2018.pdf). The awards may also be administered by contract agreements.

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

Timelines for proposals that will require contracts will be discussed with the PI at the time of invitation to full proposal.

Applicants who wish to consult with JDRF Program Staff to discuss the responsiveness of their proposal to this program or to discuss ideas or resources that might benefit this initiative may do so via email to the contacts listed in this RFA.

PROPOSAL

An approved Letter of Intent 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 in RMS360 (http://jdrf.smartsimple.us). Proposal section templates in MS Word, **[10 pages 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-Aug2015.pdf

SCIENTIFIC REVIEW CRITERIA

Applications will be subjected to confidential external scientific review and evaluated on the following:

- Significance
- Relevance
- Approach

- Innovation
- Investigator Experience
- Environment

Significance: Does this study address an important problem?

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

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? Are resources and knowledge based on prior experience and know-how?

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? If the investigator does not have diabetes experience, are there appropriate collaborative arrangements with experts in diabetes? For collaborative projects, is the project well led and coordinated?

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?

PROJECTED DEADLINES

- **RFA Release Date**..... October 23, 2018
- **Letter of Intent Deadline**.....November 20, 2018
- **Notification of LOI Outcome**.....December 18, 2018
- **Full Proposal Deadline** .....January 31, 2019
- **Earliest Response to Applicants**.....July 1, 2019
- **Earliest Anticipated Start Date**.....September 1, 2019

CONTACTS

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RMS360 (http://jdrf.smartsimple.us)
If you have any grant-specific questions as you work within RMS360, please contact the administrative contact listed above.