

JDRF requests Expressions of Interest for:

[Discovery and development of strategies for targeted drug delivery to human islets for T1D](#)

PURPOSE

JDRF aims to catalyze and support innovative studies for the selective delivery of therapeutics (bioactive molecules) to human beta cells, or other major pancreatic cell types, to promote the survival and recover functional beta-cell mass in type 1 diabetes (T1D). Expressions of Interest (EOI) from investigators who would be interested in collaborating with a cross-functional team to help achieve this goal are being solicited. Both validation of existing drug-delivery systems and the discovery of novel drug-delivery systems are of interest.

BACKGROUND

The JDRF Beta Cell Regeneration Program aims to halt the progression of T1D and ultimately achieve a cure through the development of disease-modifying therapies (small molecules and/or biologics) that promote the survival, function, and regeneration of endogenous insulin-producing beta cells ([Specific program details can be found here](#)).

Novel targets and pathways have recently been described that are able to promote beta-cell regeneration and survival. However, it has been empirically determined that many of these targets and pathways are not sufficiently specific or unique to the islet/beta cell and may present safety concerns if delivered systemically, when non-pancreatic cellular targets could become deleteriously affected. Targeted drug delivery presents an opportunity to restrict a regenerative or survival therapy to the islet/beta cell and avoid or reduce on target but deleterious effects on tissues or cells outside the pancreas.

Targeted drug delivery, also known as smart drug delivery, has most notably been successful in the cancer setting. It is likely that active drug targeting, utilizing small molecule or biological (e.g., antibodies or aptamers) drug conjugates to selectively bind to the target, could mitigate potential non-islet/beta-cell activities. Specific interactions with surface receptors or other cellular addresses (e.g., transporters) could restrict specific drug uptake, internalization, and activation within the islet to achieve desired drug effects. This is of high interest to this call. Passive drug targeting refers to the accumulation of a drug around certain sites in the body and relies on distribution by blood circulation. Passive drug targeting is unlikely to convey enough islet specificity to prevent undesirable on-target effects elsewhere in the body and is therefore excluded from this program.

To date, limited data exist demonstrating successful active drug targeting to the beta or islet cells. Respondents to this EOI will be prepared to build a multi-disciplinary team that brings together the skills needed to develop and validate innovative bioactive drug-delivery systems for human islet cells. It must be noted that, at this time, novel therapeutic payload development (such as chemical campaigns to optimize hit or lead molecules to drug target) will not be considered. Rather the goal is to discover and develop “modular” systems with broad applicability to a range of known drug/biologic candidates that promote human beta-cell survival, function, and/or regeneration. Proposed studies must, therefore, be based on existing knowledge of available drug targets, candidates, and tool compounds.

OBJECTIVE

To safely increase functional beta-cell mass, we need to develop ways to deliver drugs/biologics specifically to the human beta cell (or other major pancreatic cell types) to safely induce their survival, proliferation, or hormone-type

reprogramming. Few beta cell –specific bioactive molecules have been identified and even fewer have been tested in drug-delivery platforms. Our primary objective is the creation of a first-generation model system (or systems) for the delivery of therapeutic payloads to islet cells, especially for beneficial effects on functional beta-cell mass.

We wish to form a milestone/deliverable-oriented research team that will provide expertise, data, reagents, and benchmarks for the following:

- Discovery and validation of new addresses with characteristics appropriate for active drug delivery to human islet endocrine cells;
- Validation, for the purposes of drug delivery, of existing human islet-cell–specific surface molecules;
- Testing their ability to deliver a model payload into a human islet cell, both in vitro and in vivo.

SCOPE

We welcome EOIs from investigators, pre-formed teams, and organizations with demonstrated expertise appropriate to these tasks above, paying attention to the criteria listed below. Applicants do not need to have expertise in all these areas however must be willing and able to participate in a larger working group founded on the principles of shared expertise and free interchange of data, techniques and concepts .

Demonstrated expertise desired:

- Quantitative proteomics
- Bioinformatics
- Human beta-cell biology
- Targeting reagent generation (antibodies, aptamers, etc.)
- Humanized animal models for beta cell regeneration and survival with an emphasis on drug metabolism and pharmacokinetics
- Intracellular activity, trafficking, and endosomal release of therapeutic payloads
- Quantitative pharmacology in drug-conjugate development

Examples of pertinent topics:

- Develop and validate methods for targeted drug delivery (small molecule, peptide, or oligonucleotide based) to pancreatic beta cells using known beta-cell–selective receptors (e.g., GLP1R); demonstrate proof of concept of drug delivery in human islets with ex vivo and in vivo models
- Identify novel surface receptors or other surface addresses for targeting drug cargo payloads to human beta, alpha or other islet endocrine cell types; develop assays or models to demonstrate the ability of the receptor to internalize and deliver a payload to the cell target in diabetic conditions
- Discover and validate methods for targeted delivery of model cargo payloads (e.g. antibody, aptamer, genetic material) to islet endocrine/beta cells; demonstrate proof of concept in ex vivo and in vivo models of diabetes and selectivity for islets over other tissues or cell types in the body
- Discover and validate methods for islet cell-specific prodrug cleavage of small molecule therapeutics (beta cell regeneration or survival molecular targets)
- Validate existing transporters in beta cells or other islet cell types for targeted delivery of therapies to human beta, alpha or other islet endocrine types; demonstrate the selectivity of the transporter to islet cells over other tissues or cells
- Discover and develop novel methods for targeted delivery of payloads to alpha cells for the purpose of reprogramming alpha to beta cells by receptor internalization, transporter or other targeted delivery mechanisms
- Bioinformatics-based studies of existing data sets to identify novel islet cell addresses followed by validation of specificity versus other cell types

- Development of human endocrine-cell-specific viral delivery systems with efficient uptake into islet cells for targeted drug delivery, including consideration of safety requirements for application in T1D

This EOI and eventual mechanism are not intended to support:

- Optimization of therapeutic payloads
- Animal-model development such as transgenic mice for target validation or other purposes
- Targeting to cells other than those of the endocrine pancreas
- Passive drug delivery systems
- Development of particulate carriers (nanoparticles, etc.)
- Development of systems reliant on cellular payloads (i.e. CAR-T cells)
- Development of systems dependent on surgical intervention
- Target identification or validation regarding pathways that control regeneration or survival

MECHANISM

The program will establish a core team of investigators to drive the discovery, development, and validation of first-generation active drug delivery systems for the endocrine cell types of the pancreas. JDRF will select and fund an Islet Targeting Group to share resources, data, and expertise with each other with the near-term goal, using a deliverable/milestone-oriented program, of generating a first-generation active drug-delivery system for islet endocrine cells. Applicants may be investigators, pre-formed teams, companies, or industry-academic partnerships.

As core goals of this initiative include the formation of a working group and encouraging collaborations between investigators, **awardees of this program will be expected to 1) sign confidentiality agreements to enable data sharing (including unpublished data) between members of the working group, and 2) facilitate sharing of reagents and technologies for potential collaboration with other members of the working group.**

The level of funding for individual projects will vary depending on the scope and overall objectives of a project, and EOIs from strong cross functional teams will be given highest priority. The level of funding may vary depending on the scope and overall objectives of the proposal. Budgets proposed should be commensurate with project scope. Pilot and feasibility studies may also be proposed.

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. 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.

For-profit entities may apply under JDRF's Industry Discovery & Development Partnership (**IDDP**) funding mechanism, which entails additional requirements including matching funds from the company. IDDP awards will be administered by contract agreements. Timelines for awards administered by contracts are typically longer than those listed at the end of this call document and will be determined ad hoc.

ELIGIBILITY

This call is open to academic investigators, biotechnology and pharmaceutical companies, or industry-academia partnerships. Please note that additional information will be requested of applicants from for-profit entities or industry collaborations with academia if a full application is invited.

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

of the federal government. Applicants 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 submissions from for-profit entities or collaborations involving for-profit entities will also be reviewed by the JDRF T1D Fund (<http://www.jdrf.org/about/t1dfund/>) in addition to JDRF 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.

EXPRESSION OF INTEREST

Prospective applicants should submit an expression of interest online via RMS360 (<https://jdrf.smartsimple.us>) to be considered for a full proposal request. The EOI template and associated questionnaire provided on the RMS360 website must be used to complete the application. Not all criteria within the questionnaire need to be met. It is important to concisely describe what expertise and resources are currently available or what may be required to complement available know-how and resources. EOIs will be competitively reviewed based on strategic fit with JDRF’s mission and portfolio, and scientific merit/feasibility.

PROPOSAL

An approved Expression of Interest is required prior to the submission of a full proposal. JDRF staff will contact applicants of successful EOIs regarding next steps.

SCHEDULE

- o **Release Date**.....January 2020
- o **Expression of Intent Due**.....**Friday, February 7, 2020**
- o **Full Proposal Notification**Friday, February 21, 2020
- o **Full Proposal Due**.....**Friday, March 20, 2020**
- o **Response to Applicants**.....July 2020
- o **Earliest Start Date**.....September 2020

JDRF STAFF CONTACTS

Frank Martin, Ph.D.
Director, Research
fmartin@jdrf.org
212-479-7554

Karen Ng, BBA
Senior Program Administrator, Research
kng@jdrf.org
212-479-7563

If you have any grant-specific questions as you work within **RMS360** (<http://jdrf.smartsimple.us>), 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