JDRF Request for Applications: Translation of Hypoimmunogenic Beta/Islet Cell Sources into Late Preclinical/Clinical Testing for Cell Therapies in T1D

July 2023

Summary

- The goal of this funding opportunity is to support the advancement of hypoimmunogenic pluripotent stem cell sources into late preclinical or pilot clinical testing.
- Applicants to this RFA should have demonstrated expertise developing discovery and early preclinical stage beta/islet cell sources with the potential for translation of these technologies for T1D beta cell replacement therapies.
- This program will award grants to non-profit and for-profit entities such as academic institutions and industry partners of up to $1,000,000.00 over 3 years. JDRF will consider applications with increased scope (time and/or budget) where there is a strong justification and interested applicants should discuss with the JDRF scientific contact.

Funding Opportunity Description

JDRF aims to support the advancement of early preclinical stage hypoimmunogenic pluripotent stem cells (PSCs) for beta cell replacement in type 1 diabetes (T1D) into late preclinical or pilot clinical testing. Here late preclinical testing refers to experiments in relevant preclinical models (pre-IND) and/or IND-enabling studies. Prior investments in genetic engineering of renewable PSC sources of beta/islet cells has resulted in the development and validation of modifications which impart cells with immune-evasive properties. However, these technologies are still relatively new and require further validation and development. This funding opportunity aims to support the further development of such cell sources. Therefore, JDRF is soliciting Letters of Intent (LOI) from investigators who have an early- to late-stage preclinical beta/islet cell source fitting these criteria.

Proposed experiments may use preclinical animal models such as porcine, NHP, or humanized mouse models to demonstrate immune evasive properties with a focus on long term survival and protection from allo- and/or auto-rejection. Simple immune protection experiments (e.g., teratoma formation, *in vitro* assays, and/or allogeneic transplant in mice) should have previously demonstrated success and be included as preliminary data. PSC sources must be able to demonstrate functional competence in beta cell/islet differentiation and insulin production before and after genetic modification. The scaling and manufacturing of previously validated hypoimmunogenic cell sources for beta cell replacement are also of interest. The discovery of new genes to evade the immune system that require extensive *in vitro* and *in vivo* testing are **NOT** of interest. Our primary objective is to further develop established genetically modified beta/islet cell derived from PSCs with immune evasive properties through late preclinical validation, scaling, and clinical testing which will ultimately lead to T1D therapies.

Prioritization will be given to proposals testing hypoimmunogenic properties of a GMP/clinical grade parental cell source with previously demonstrated safety and efficacy in a T1D model.

Examples of topics pertinent to this call include but are not limited to:

- Validating genetic modifications of PSCs for long term immune protection against allo-, and/or auto-immune rejection in relevant preclinical animal models
- Transplantation studies in late preclinical animal models or pilot clinical studies demonstrating immune protection and/or enhanced survival and function when combined with previously validated complementary therapies:
    - Immune therapies
    - Beta cell stress reagents
    - Strategies to improve engraftment and minimize cell death
- Improvements in hypoimmunogenic PSC source safety for pre-IND/IND-enabling studies:
    - Defining optimal combination of genetic edits that are sufficient for immune protection
    - Characterization of genetic stability, integration, and/or off target effects
- Pilot clinical studies demonstrating safety and function of immune protected stem cell-derived beta cells

Requirements of successful proposals for this call:

- Demonstration of maintained differentiation potential for beta/islet cell fate and function after genetic engineering
- Preliminary data demonstrating immune protection in early preclinical models (teratoma formation, in vitro assays, etc.)

This RFA is not intended to support:

- Development or further characterization of cell sources not intended for clinical use – unless there is a clear, feasible, and swift pathway to move validated gene edits to a clinical grade source.
- Discovery of new genetic modifications
- Development of new *in vitro* or animal models
- *In vitro* or early preclinical *in vivo* validation of genetic modifications

Background

One of JDRF's goals is to accelerate the development of therapies capable of restoring glycemic control in type 1 diabetes (T1D) through the replacement/transplantation of insulin-producing beta cells/islets. (Link to Strategy Document Here).

Pancreatic islet transplantation has been efficacious in improving metabolic control and quality of life, and in preventing severe hypoglycemia in a select group of patients with medically unstable T1D. Despite improvements in cadaveric pancreas procurement, islet isolation, and islet purification, major scientific and technical challenges remain that must be addressed before beta cell replacement can be widely incorporated into the clinical management of established T1D; examples include serious adverse side effects from chronic systemic immunosuppression and the scarce supply of human islets from cadaveric

donors. JDRF's role is to enable the scientific community to address these challenges with the ultimate goal of developing safe and effective beta cell replacement approaches available to all individuals living with T1D.

While considerable progress has been made in developing renewable sources of beta/islet cells for replacement therapies (e.g., human pluripotent stem cells or xeno sources), in their current generation these cells would still rely on broad immune suppression to evade destruction by the immune system. Furthermore, the inflammatory transplant environment, metabolic demand, and the lack of immediate vascular access all contribute toward increased stress on and significant loss of implanted insulin-producing cells. JDRF previously catalyzed the discovery and early development of genetically modified cell sources to impart beta/islet cells with immune evasive properties to lessen or obviate the need for broad immune suppression. Fueled by the implementation of CRISPR and other genetic engineering tools, many candidate genes for immune evasion have been identified; however, these strategies require further late testing and validation before their full potential can be realized. These engineered cell sources will need to be of high functional quality, safe, and well characterized. The goal of this funding opportunity is to further develop established genetically modified beta/islet cell sources with immune evasive properties through late preclinical validation, scaling, and clinical testing which will ultimately leading to T1D therapies.

Eligibility

Applications may be submitted by domestic and foreign non-profit organization, public and private, such as universities, colleges, hospitals and laboratories, units of state and local governments and eligible agencies of the federal government, for-profit entities, or industry collaborations with academia. 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 applications from for-profit entities or industry collaborations with academia may be submitted in response to this RFA. Additional information will be requested from for-profit entities if invited to submit a full proposal.

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.

Funding Mechanism

In response to this announcement, Letters of Intent (LOI) can be submitted under the following mechanism(s):

Strategic Research Agreements (SRAs)

Strategic Research Agreements are intended for support of research activities at non-for-profit entities such as academic institutions. For SRAs, proposed budgets for projects should not exceed $1,000,000.00 USD (including 10% indirect costs) total costs for up to three (3) years. The level of funding will vary depending on the scope and overall objectives of the proposal. If your project budget and/or timeline exceeds $1,000,000.00 and/or 3 years, please discuss with JDRF staff (contact information below). For more information on the Strategic Research Agreement (SRA) grant mechanism please refer to our website.

Industry Discovery and Development Partnerships (IDDPs)

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. If you would like to submit an Industry Discovery and Development Partnership (IDDP) project LOI to this RFA, please check our website for additional information (https://grantcenter.jdrf.org/industry-discovery-development-partnerships/) and contact Dr. Nicholas Mamrak (nmamrak@jdrf.org) to discuss prior to submitting an application. Indirect costs are not permitted on IDDP applications.

Letter of Intent

Prospective applicants should submit an LOI, [2 pages maximum] online via RMS360 to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application.

Proposal

An approved LOI is required prior to the 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. Proposal section templates in Microsoft 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 a 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.

JDRF follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the Common Rule changes.

Review Criteria

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

- Significance
- Relevance
- Approach
- Innovation
- Environment
- Resource sharing plan

Informational Webinar and Q&A

JDRF will hold an announcement introduction meeting via Zoom on **August 8, 2023, from 1-2 pm** Eastern Time to which all 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.

Registration Link for Webinar (please register by August 4, 2023):
https://jdrf.zoom.us/webinar/register/WN_SXvdMt2cRHCGnhU0IUpSkA

Projected Timeline

Milestone	Date
Information Webinar and Q&A	August 8, 2023, 1-2 pm ET
LOI deadline	September 5, 2023
Notification of LOI Outcome	September 12, 2023
Full proposal deadline	October 10, 2023
Award notification	April 2024
Earliest anticipated start	June 2024

Program Contacts

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