

JDRF Request for Applications: Development of Interventions to Modulate Immune Cell Trafficking in T1D

December 2023

Summary

- The goal of this funding opportunity is to accelerate the identification and validation of reagents that promote immune rebalance and the protection of beta cell function through modulating the trafficking of immune cells to the pancreatic islets.
- Proposals submitted for this opportunity should describe the preclinical or clinical development of therapeutic strategies targeting the trafficking of disease-relevant immune cell populations.
- This program will award grants of up to \$900k over 3 years.

Funding Opportunity Description

JDRF, the world's leading non-profit organization with the mission to improve the lives of people with T1D by accelerating breakthroughs for T1D, aims to catalyze and support innovative studies that enhance beta cell health and function. A potential therapeutic strategy to stop the immune mediated destruction of beta cells is to limit immune trafficking to the islets, however this approach has not been extensively evaluated in human-relevant models. The identification and validation of novel strategies to target islet homing pathways while avoiding broad immunosuppression is of high interest for this funding opportunity.

Background

The JDRF Disease Modifying Therapies Program aims to develop therapies that can prevent, halt or reverse T1D at any stage of disease. JDRF's research strategy can be found [here](#).

T1D is characterized by an aberrant immune response towards pancreatic beta cells, resulting in damaged and dysfunctional islets, and subsequent loss of insulin production (1). What initiates T1D is unknown; however, it is thought that impaired immunoregulation and a loss of self-tolerance allows for the survival and propagation of autoreactive cells that infiltrate pancreatic islets and attack insulin-producing beta cells. Extravasation, the process by which lymphocytes exit circulation and enter tissue in the body, involves a series of steps including selectin-mediated rolling, chemoattractant signaling, and adhesion to vessel walls through integrins. Each of these fundamental steps serves as a potential target for intervention, and a blockade at any step could inhibit the extravasation process. One potential strategy for preventing the autoimmune attack on beta cells is to inhibit immune trafficking to the pancreas and islets.

Multiple pathways that affect immune migration have been assessed in T1D. T1D patients have increased levels of cleaved L-selectin in their serum, and preclinical mouse models of T1D show that a blockade of selectins leads to reduced disease (2,3,4). Additionally, T1D mouse models show that several chemokines, including CCL3 and CXCL10, are elevated

and neutralization or knockouts of these chemokines lead to reduced insulinitis and progression of disease (4,5,6). Interestingly, serum from children with T1D have elevated chemokines which may precede onset of disease (7,8,9). Moreover, inhibition of sphingosine phosphate receptors, shown to play a crucial role in the egress of T cells from the thymus to peripheral organs, is clinically successful for treating Multiple Sclerosis and Ulcerative Colitis, and has demonstrated efficacy in preclinical models of T1D (10-14).

Despite their therapeutic potential, chemokines and their receptors are highly redundant, making avoiding broad immunosuppression difficult (4). It is unclear whether the redundancy seen in diabetic mice reflects the chemokine landscape in humans, representing a gap in our knowledge. Importantly, inhibition of immune trafficking via targeting adhesion molecules has led to approved therapies for Multiple Sclerosis, Crohn's disease, and psoriasis (15). Further investigation of how we can effectively target mechanisms of immune migration in T1D is necessary to enable the development of targeted therapeutic interventions that prevent or delay beta cell destruction. This RFA will support grants that identify therapies that can modulate the trafficking of proinflammatory or autoreactive cells to pancreatic islets.

Applicant Eligibility

- We welcome Letters of Intent (LOI) from investigators, established teams, organizations, and industry with demonstrated expertise appropriate to the tasks above, paying attention to the criteria listed below.
- Examples of demonstrated expertise desired: immunology, molecular biology, bioinformatics, human beta cell biology, targeting reagent generation (antibodies, oligonucleotides, nanomedicines, small molecule inhibitors, etc.), expertise with animal models to assess migratory inhibition with an emphasis on drug metabolism and pharmacokinetics.
- Applications may be submitted by domestic and foreign non-profit organizations, public and private entities, 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.

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.

Project Eligibility

Examples of proposals that would be considered under this call include, but are not limited to:

- Development or validation of reagents that target receptors (e.g., chemokines receptors, sphingolipids receptors, etc.) or adhesion molecules involved in the trafficking of pro-inflammatory and/or autoreactive immune cells to the pancreas. Approaches that have been previously tested in T1D must be incremental and evaluated at the next stage of development.
- Realignment of mechanisms and clinical grade reagents involved in cell trafficking validated in other diseases for assessment in T1D.

Priority will be given to approaches that:

- Propose methods of targeting cell trafficking while avoiding broad immunosuppression.
- Validation of reagents in T1D that have been clinically evaluated in other disease indications.
- Projects that include research protocols utilizing human samples or human relevant model systems.

Out of Scope for this request:

- Studies focused solely on broad phenotyping of knockout or transgenic models that do not directly measure T1D outcomes, or onset.
- Studies focused solely on the broad characterization of trafficking targets from large datasets.
- Projects seeking to test reagents that target pathways not involved in immune cell migration.

Funding Mechanism

In response to this announcement, LOI's can be submitted to JDRF's **Strategic Research Agreement (SRA)** or **Industry Discovery and Development Program (IDDP)** grant mechanisms. For more information on these mechanisms, please refer to our website:

- Strategic Research Agreements
 - <http://grantcenter.jdrf.org/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/>
 - SRA application may include up to 10% indirect costs as part of the \$900K.

Industry Development and Discovery Program

- <https://grantcenter.jdrf.org/industry-discovery-development-partnerships/>
- For IDDP applications, applicants are required to contact the JDRF scientific contact below prior to submitting a LOI.
- IDDP applications do not permit indirect costs.
- This program will award grants of up to \$900k over 3 years. The level of funding will vary depending on the scope and overall objectives of the proposal. JDRF may 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 below.

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.

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](#).

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 **December 13th** at 4-5 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 for Webinar (please register by December 12th):

https://jdrf.zoom.us/webinar/register/WN_5AjclKJkQpgFrs6cBSFOQg

Projected Timeline

Milestone	Date
Information Webinar and Q&A	December 13 th 2023
LOI deadline	January 17 th 2024
Notification of LOI Outcome	January 31 st 2024
Full proposal deadline	February 28 th 2024
Award notification	August 2024
Earliest anticipated start	October 2024

Program Contacts

Strategic Fit and Scientific Inquires

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