SPECIAL REQUEST FOR EXPRESSIONS OF INTEREST FOR:

SMALL MOLECULE SCREENS/EARLY DRUG DISCOVERY PROJECTS FOCUSED ON BETA CELL REGENERATION AND SURVIVAL

PURPOSE
JDRF and the California Institute for Biomedical Research (Calibr) invite Expressions of Interest from investigators to participate in the JDRF-Calibr Translational Academic Research Partnership (TARP). Researchers who have identified potential drug targets, validated pathways or screening approaches to promote beta cell regeneration and/or survival are encouraged to respond.

This program is designed to give investigators access to complete high-throughput small molecule screening capabilities and associated support, including assay development, hit identification and triaging, hit characterization, and structure-activity relationship studies. Working closely with scientists at Calibr, investigators will identify and characterize novel modulators of targets, pathways, or cellular phenotypes relevant to islet biology and the restoration or preservation of beta cell mass and function in the context of insulin-dependent diabetes. It is anticipated the newly discovered small molecule modulators will serve as research tool compounds to further dissect biological pathways, validate drug targets and provide starting points for more advanced medicinal chemistry/drug refinement.

BACKGROUND
Calibr and JDRF formed a partnership to help provide academic beta cell biology investigators access to Calibr’s expertise and infrastructure to translate their basic research findings funded by JDRF or other non-profit funding agencies toward early stage drug discovery efforts. Insulin-dependent diabetes, both type 1 and type 2 diabetes, is characterized by the declining function and loss of the insulin-producing beta cells of the pancreatic islet often resulting in the need for life-long insulin replacement therapy. Therapies to safely restore functional beta cell mass and maintain or prevent loss of beta cell function are needed for all stages of diabetes pathogenesis. Even partial restoration or maintenance of endogenous beta cell function may have benefit by reducing insulin requirements, improving glucose control, and reducing the risk of complications.

Calibr is a non-profit medical research organization established in 2012 with the mission of filling a translational gap between exploratory biological research in the academic setting and drug discovery activities in biotech and pharma. Calibr has automated, high-throughput drug screening capabilities utilizing a variety of miniaturized assay formats and readouts and a library of close to a million small molecules. In addition to standard luminescence- and fluorescence-based reporter gene and enzyme assays, Calibr’s screening platform extends to more sophisticated cell-based assay formats, such as high-content imaging, high-throughput flow cytometry, and time-resolved FRET. Calibr’s staff has expertise ranging from assay development to medicinal chemistry, allowing support and execution of activities throughout the screening campaign, such as assay design and optimization leading up to the screen, and hit triaging and structure-activity relationship studies after the screen. Specifically, key Calibr personnel involved in the TARP program have years of experience executing high-throughput screens for beta cell stress and proliferation, having carried out these studies in the context of academic research at The Scripps Research Institute and under another industrial discovery partnership with JDRF. Collaboration with the academic community and JDRF is a fundamental aspect of Calibr’s mission and is facilitated by Calibr’s non-profit status. More information about Calibr can be found at this website: www.calibr.org

OBJECTIVES/SCOPE
The objective of this call for EOs is to facilitate translation of important findings in beta cell biology into the discovery of small molecule modulators to serve as research tools for pre-clinical research and/or starting points for the development of therapeutics to restore and/or preserve beta cell mass. Responses do not need to include a specific plan for adapting biological insights into high-throughput screens. Participants will be

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selected on a competitive basis by a review panel comprised of JDRF and Calibr scientists. If selected to participate, applicants will work with Calibr and JDRF to design a workplan that includes assay development, high-throughput screening, and hit follow-up. This work would primarily be carried out at Calibr; hit compounds will be made available to investigators for additional follow-up biology and characterization in their laboratories.

Pertinent topics include, but are not limited to targets, pathways, or cellular phenotypes involved in:
- Reprogramming of pancreatic non-beta cells (e.g. alpha cells) towards a beta cell phenotype
- Dedifferentiating / redifferentiating beta cells
- Targeting autophagy to improve beta cell survival and function
- Beta cell replication and regulation of beta cell mass
- Beta cell stress, survival and function

Applicants do not need to have an assay suitable for high-throughput screening already developed or any previous knowledge or experience in high-throughput screening. Preference will be given to applicants with well validated targets.

This mechanism is **not** intended to support:
- Screens against targets without relevance to beta cells or T1D/T2D
- Approaches to expand beta cells ex vivo for transplantation, generate beta cells for transplant from other sources (e.g. stem cells) or to improve transplant outcomes without relevance to enhancing endogenous beta cell mass or function
- Pathways and targets whose modulation is expected to cause side effects incompatible with chronic diabetes therapy
- Genetic screens (e.g. siRNA, cDNA)

**MECHANISM**
The program is designed to establish research collaborations with Calibr and give investigators an opportunity to translate their fundamental research findings into the discovery of small molecules with therapeutic potential. Calibr is an independent, not-for-profit organization established to accelerate the translation of basic biomedical research to innovative new medicines and structured to facilitate collaboration with academic investigators. This mechanism supports an initial period of collaboration between Calibr and selected investigators, wherein investigators contribute their efforts in-kind. The initial activities are intended to catalyze discovery of new beta cell therapeutic agents through identification of novel compounds and generation of data. These findings, if successful, may support subsequent pursuit of joint funding for downstream activities (e.g. optimization through medicinal chemistry, rodent proof-of-concept experiments, toxicology). There is precedence for successful funding of such follow-on projects from previous efforts.

Applicants who are selected for participation in this EOI will be provided a template collaboration agreement covering project support through the JDRF-Calibr TARP and terms of intellectual property and revenue sharing. Briefly, these terms deem all discoveries within the scope of the collaborative project as joint inventions and specify equal sharing of potential future revenue generation between Calibr and the investigator’s institution. Calibr’s established relationships with the pharmaceutical industry may facilitate partnering of potential therapeutic small molecules resulting from screens.

**EXPRESSION OF INTEREST**
Prospective applicants should submit an Expression of Interest (EOI) using the template provided. EOIs will be competitively reviewed based on strategic fit with JDRF’s mission and portfolio and scientific merit/feasibility. JDRF and Calibr may contact applicants to solicit additional information to assist in the evaluation of the EOI. Applicants will be notified approximately six weeks after the EOI deadline date if their EOI will be considered for further development.
## Therapeutic Approach

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<tr>
<th><strong>TARGET</strong></th>
<th>Briefly describe the target, pathway, or cellular phenotype (e.g. “GLP1R” or “the NFkB pathway” or “autophagy”)</th>
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<tr>
<td><strong>RATIONALE &amp; SIGNIFICANCE</strong></td>
<td>Provide any critical background information and highlight significance and novelty of the approach.</td>
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<td><strong>TARGET VALIDATION</strong></td>
<td>Highlight validation in (1) human disease, (2) human tissues, and (3) animal models of disease. If (1)-(3) are not validated, discuss plans to do so and risk associated with lack of validation.</td>
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| **THERAPEUTIC PARADIGM** | Describe in simple terms the ideal profile of a therapeutic discovered from the proposed work. With speculation encouraged, please address the following questions:  
- Would it be applicable to patients with long-standing T1D, new-onset or at-risk patients?  
- Would it be used in concert with insulin or as a stand-alone therapy?  
- Would the drug be given chronically to manage the disease symptoms or for a short period of time to reverse or “cure” the disease?  
- What issues could arise from modulating this target, pathway, or phenotype outside of the intended purpose? (i.e. known or predicted side effects) |
| **CATEGORY** | Choose the one that best fits your proposal.  
- Reprogramming of non-beta cells (e.g. alpha cells) towards a beta cell phenotype  
- Dedifferentiating / redifferentiating beta cells  
- Targeting autophagy to improve beta cell survival and function  
- Beta cell replication and regulation of beta cell mass  
- Beta cell stress, survival and function  
- Other (identify) |

## Discovery Approach

| **BIOLOGICAL ASSAY** | List methods of which you are aware and comment on their appropriateness. These need not be applicable to high-throughput screening. Note whether these methods are used in your laboratory and if you possess specialized reagents that enable them (e.g. a reporter gene). Provide literature references only for methods not used in your laboratory. |
| **REFERENCES & CONTROLS** | List any compounds, proteins, peptides, antibodies, RNAi reagents, or mutant cell types that may serve as reference or control conditions for the proposed studies and briefly explain their relevance (list all that are applicable). |
| **PREVIOUS DISCOVERY WORK** | Describe previous screening efforts closely related to the proposed work, whether carried out by you or others. Include failed attempts to initiate screening (e.g. lack of suitable assay development, inability to execute agreements or material transfers with the collaborating institute). |
| **PRELIMINARY DATA & SUPPLEMENTAL INFORMATION** | Organize key data into one supplemental page. |
REVIEW CRITERIA
EOIs will be reviewed by JDRF and Calibr scientists on a confidential basis to assess innovation, programmatic fit, suitability for screen development and target validation, and alignment with JDRF’s mission. Reviews will be competitive and it is expected that only a limited number of EOIs will be developed as full collaborations.

Applicants with successful EOIs will be contacted by Calibr scientists to discuss any outstanding questions and develop a workplan and proposal that will be competitively reviewed for inclusion in the JDRF-Calibr TARP.

ELIGIBILITY
Applications may be submitted by non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments. There are no institutional geographic limitations. 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.

DEADLINES
Release Date: ........................................10/24/2014
Expression of Interest Deadline.............12/17/2014
Response to Applicants: ..........................2/1/2015
Earliest Anticipated Start Date: ..............3/1/2015

SUBMISSION
EOIs should be completed using the template provided here and should be submitted via RMS360 no later than December 17, 2014 at 5:00pm, Eastern Time. As per JDRF policy, all EOI and application materials will be considered as confidential information. Any communication of EOI or application materials outside of JDRF will be for review purposes only and will be conducted under appropriate non-disclosure and conflict-of-interest agreements.

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