SPECIAL REQUEST FOR EXPRESSIONS OF INTEREST FOR:

SMALL MOLECULE SCREENS FOR 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, 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 type 1 diabetes (T1D). 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 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 for T1D. T1D is characterized by the declining function and loss of the insulin-producing beta cells of the islet resulting in a 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 T1D. 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.

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 T1D 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 selected on a competitive basis by a review panel comprised of JDRF scientific staff 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:

- Reducing beta cell stress and improving beta cell survival and function
- Promoting beta cell replication and regulation of beta cell mass
- Reprogramming of non-beta cells (e.g. alpha cells) towards a beta cell phenotype
- Dedifferentiating/redifferentiating beta cells

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.

This mechanism is not intended to support:

- Screens against targets without relevance to beta cell expansion, survival, or T1D
- Approaches to expand beta cells ex vivo for transplantation or to improve transplant outcomes without relevance to enhancing endogenous beta cell mass or function
- Approaches to generate beta cells for transplant from other sources (e.g. stem cells)
- Pathways and targets whose modulation is expected to cause side effects incompatible with T1D
- 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. Applicants who are selected for further participation 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 joint inventions and specify equal sharing of future revenue generation between Calibr and the investigator. Calibr’s established relationships with the pharmaceutical industry will 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. Applicants will be notified approximately six weeks after the EOI deadline date if their EOI will be considered for further development.

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<tr>
<th>Therapeutic Approach</th>
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<tr>
<td><strong>TARGET</strong></td>
<td>List the target, pathway, or cellular phenotype</td>
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<td>What target, pathway, or cellular phenotype would you like to modulate?</td>
<td><em>(e.g. “GLP1R” or “the NFkB pathway” or “oxidative stress”)</em></td>
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<td><strong>VALIDATION</strong></td>
<td>Provide a brief description of published work with appropriate reference(s). If appropriate, organize key supplemental data into one attached page.</td>
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<td>What biological findings support modulation of this target, pathway, or cellular phenotype in T1D therapy?</td>
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<td><strong>THERAPEUTIC PARADIGM</strong></td>
<td>Describe in simple terms the ideal profile of a therapeutic discovered from the proposed work. Address the following questions:</td>
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<td>How do you imagine these modulators being used as T1D therapeutics?</td>
<td><em>(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)) Speculation is encouraged.</em></td>
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<td>CATEGORY</td>
<td>Choose one that best fits your proposal</td>
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| | • Reducing beta cell stress and improving beta cell survival and function  
| | • Promoting beta cell replication and regulation of beta cell mass  
| | • Reprogramming of non-beta cells (e.g. alpha cells) towards a beta cell phenotype  
| | • Dedifferentiating/redifferentiating beta cells  
| | • Or other categories to be described |

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<td><strong>BIOLOGICAL ASSAY</strong></td>
<td>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.</td>
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<td><strong>REFERENCES &amp; CONTROLS</strong></td>
<td>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).</td>
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<tr>
<td><strong>PREVIOUS DISCOVERY WORK</strong></td>
<td>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).</td>
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**REVIEW CRITERIA**
EOIs will be reviewed by JDRF and Calibr scientists to assess innovation, programmatic fit, suitability for screen development and target validation. Reviews will be competitive and it is expected that only a limited number of EOIs will be developed as full collaborations.

**ELIGIBILITY**
Applications may be submitted by non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments. 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: ........................................10/28/2013
- Expression of Interest Deadline: ..............12/18/2013
- Response to Applicants: ..................................1/13/2014
- Earliest Anticipated Start Date: ....................3/1/2014

**SUBMISSION**
EOIs should be completed using the template provided here and should be submitted via email to EOIs@jdrf.org no later than December 18, 2013.

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 external peer review and will be conducted under appropriate non-disclosure and conflict-of-interest agreements.

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