JDRF AND ELI LILLY AND COMPANY JOINTLY REQUEST FULL PROPOSAL APPLICATIONS FOR RESEARCH TOWARD GLUCOSE-RESPONSIVE GLUCOSE-MODULATING THERAPIES

PURPOSE

JDRF, the world's leading non-profit organization with the mission to cure, treat and prevent type 1 diabetes (T1D) and Eli Lilly and Company, a global healthcare company working to make life better for people around the world, invite full proposal applications for the discovery of novel glucose responsive glucose modulating drugs for better treatment of insulin-dependent diabetes mellitus (IDDM) and reducing the burden of daily management of the disease, particularly T1D.

BACKGROUND

Since its discovery in 1921, insulin has been the lifeline for people with insulin-dependent diabetes mellitus, as well as playing a key role in the treatment of patients with insulin-independent diabetes mellitus. Yet almost 100 years later, truly adequate control of blood glucose concentration via therapeutic treatment has not been achieved. Despite the advent of better insulins, automated devices and diligent self-care, the disease remains challenging to manage, and is a huge burden on both the affected individual and the caregiver. Current treatment options do not provide adequate glycemic control, as evidenced by results from numerous clinical and epidemiological studies demonstrating prevailing high HbA1c levels, frequency of hypoglycemia and ketoacidosis, more than 70% time spent outside of target glucose values, as well as long term complications of the disease mostly arising from years of dysglycemia.

The efficacy of insulin-centered treatment in preventing hyperglycemia is limited by the risk of insulin-induced hypoglycemia due to the glucose concentration-independent nature of insulin action. Additionally, maintaining glycemic control requires diligence and orchestration of several lifestyle factors throughout the day and lifetime of individuals with type 1 diabetes (T1D). In an effort to achieve tighter glucose control and reduce the burden of living with insulin dependent diabetes mellitus, JDRF has prioritized the development of insulin-based therapies whose actions are glucose-dependent. Such therapies may modulate the activity and/or the concentration of insulin as a function of glucose concentration, and consist of novel insulin analogs or other insulin receptor agonists. One may also consider glucagon analogs, glucagon receptor agonists, or insulin receptor antagonists engineered to reverse the effects of non-glucose-dependent insulins in a glucose concentration-dependent manner. Used in combination with insulins, such agents would also be expected to decrease the risk of insulin-induced hypoglycemia and afford greater glycemic control than currently available insulins alone. Mechanisms that modulate the systemic concentrations of agents such as insulin and glucagon in a glucose-dependent manner are also of interest provided they do not require an infusion pump or entail the large hysteresis associated with the current generation of controlled release approaches.

OBJECTIVES

Full proposal applications are sought from academic or industry applicants with innovative approaches toward the development of therapies that can be expected ultimately to modulate the activity and/or the concentration of a freely-circulating insulin analog or other insulin receptor agonist as a function of changes in glucose concentration over the physiologically relevant range. Alternatively, proposals for systems in which the activity and/or the concentration of a freely-circulating glucagon, glucagon receptor agonist or insulin receptor antagonist are made dependent on changes in glucose concentration will be considered. A preferred proposal will define what the researcher feels are the key technological challenges toward glucose responsive systems, and the steps necessary to resolve them. Innovative concepts without prior data but have the potential to lead to a change in the current paradigm or conventional wisdom and/or lead to a groundbreaking discovery will be considered for initial validation of hypothesis and supported accordingly.

The means by which the activity and/or the concentration of the freely circulating glucose-concentration modulating agent are modified are not prescribed. Initial systems may be made responsive to changes in concentration of solutes other than glucose, but a path toward glucose dependence must be clear. Furthermore, the responsiveness of initial systems need not be applicable to use over the physiologically relevant glucose concentration range, but a path toward such responsiveness must be clear. Such an end product should be expected to find utility in the treatment of patients with either insulin-dependent or -independent diabetes mellitus, and as such applicants are expected to consider compatibility of the components of their systems with therapeutic use.

Expected outcomes from project proposals would demonstrate but not be limited to:

- Modulation of activity/concentration of a glucose-concentration modulating agent in response to changes in solute concentration.
- Data indicating an understanding of the mechanism by which changes in glucose concentrations result in changes in activity and/or concentration.
- The establishment of analytical techniques to assess the underlying mechanism behind the changes in activity and/or concentration.
- Data supporting a path forward toward the utility of glucose as the trigger for changes in activity/concentration over the physiologically relevant concentration range.

Applicants are encouraged to consult with JDRF Scientific Staff to discuss the alignment of their proposal to this RFA.

MECHANISM

JDRF and Lilly wish to help investigators accelerate the progress and address critical research gaps through active partnering and feedback on the research programs. In addition to co-funding the initiative, Lilly will also provide drug discovery expertise and may provide certain materials or know-how to help address impediments to research progress.

Under the terms of the grant application, written quarterly reports will be required from the funded investigator with evidence of progress toward achieving research milestones as a basis for continued support. Quarterly reports will be reviewed by both JDRF and Lilly staff with the investigator, and will

provide the opportunity for investigators to highlight progress towards research milestones as well as identify bottlenecks or impediments to progress – allowing Lilly and JDRF the opportunity to identify ways to help address issues. As noted above, Lilly may offer assistance if specific capabilities can accelerate progress. Protein expression, purification or characterization, provision of insulin for chemical modification or planning and execution of in vivo studies are areas in which Lilly scientists may be able to provide meaningful help.

Investigators (and Institutions) selected for grant funding will be required to sign a modified JDRF "Program Award Agreement." In addition to JDRF's standard terms and conditions for academic grant awards, this agreement also includes the following requirements: Patent applications, public disclosures (e.g., public seminar presentations, press releases, etc.) and publications resulting from the funded research and incorporating Project Research Results and Project Confidential Information must be provided to JDRF and Lilly at least forty-five (45) days in advance of submission or public disclosure. As part of Lilly's participation, Lilly is granted a non-exclusive research-use license and limited right of first negotiation to exclusively license IP generated during the funding period.

JDRF shall make Project funding payments directly to the Investigator (and Institution) as per the Program Award Agreement.

For Strategic Research Agreements (SRA), up to a maximum of $200,000 USD per year including 10% indirect costs for up to 2 years may be requested for strategic research agreements (SRA).

For Innovative applications, up to a maximum of $110,000 USD per year including 10% indirect costs for 1 year may be requested.

The level of funding will vary depending on the scope and overall objectives of the proposal.

ANNOUNCEMENT INTRODUCTION AND PUBLIC Q&A

JDRF will hold announcement introduction meeting via web and teleconference on **Thursday December 3rd, 2015 at 10:00AM-11:00 AM** US Eastern time, to which all interested 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. A brief introduction on JDRF's new grant application portal (RMS360) will also be given.

Please click here for the call information:

Webinar Link: Join WebEx meeting

Meeting Number: 737 920 772
Meeting Password: jdrf2015

Join By Phone:
Teleconference phone number: US: 1-877-261-5012 Conference Code: 49 47 65 08 39. All others please refer to the PDF document included in the meeting invitation

ELIGIBILITY

Applicants must hold an M.D., D.M.D., D.V.M., Ph.D., or equivalent academic degree and a faculty position or equivalent at a college, university, medical school, or comparable institution.

Applications may be submitted by for-profit entities as well as nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments.

In order to submit a full application, the PI and the Institutional Official must sign and remit the 'Letter of Institutional Support' that will be found under the "Additional Attachments' tab in the RMS360 on line

application. Such document is part of the application and must be submitted on or before the Application Deadline.

There are no citizenship requirements.

DEADLINES

- Full Application Release Date — November 17, 2015
- Application Deadline — January 14, 2016
- Earliest Response to Applicants — May 2016
- Earliest Anticipated Start Date — June 2016

SUBMISSION INSTRUCTIONS

Applicants should register and submit their completed full proposal application in RMS360 (http://jdrf.smartsimple.us).

REVIEW CRITERIA

Applications will be evaluated based on JDRF's standard confidential award policy and according to the following criteria:

- Significance
- Relevance
- Approach
- Innovation
- Investigator Experience
- Environment

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If you have any grant-specific questions as you work within RMS360, 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.