JDRF REQUESTS LETTERS OF INTENT FOR: SAFE AND EFFECTIVE USE OF SGLT INHIBITORS FOR TYPE 1 DIABETES

PURPOSE

JDRF is committed to improving outcomes in people with type 1 diabetes (T1D) through the use of adjunctive drugs that complement insulin therapy. Drugs in the sodium-glucose linked transporter inhibitor class, i.e. SGLT2 and SGLT1/2 inhibitors, have demonstrated efficacy in T1D. However, clinical trials have shown an increased risk of diabetic ketoacidosis (DKA) in people with T1D taking these drugs at the most efficacious doses. We invite applications for research projects that will increase safe and effective use of SGLT inhibitors for T1D.

BACKGROUND

SGLT2 inhibitors, which block SGLT2-mediated glucose reabsorption in the kidney, lower blood glucose by inducing beneficial glycosuria; the SGLT1/2 inhibitor also transiently blocks SGLT1 activity in the intestine, slowing the rate of glucose absorption into the bloodstream as well. SGLT inhibitors lower HbA1c, increase time-in-target glucose ranges, and reduce postprandial glucose excursions and glycemic variability in people with T1D. SGLT inhibitors have also demonstrated non-glycemic metabolic benefits in the form of beneficial weight loss and blood pressure reduction. Emerging evidence indicates that SGLT2 inhibitors also offer renal and cardiac protection in type 2 diabetes, long-term benefits that may be expected *a priori* to translate to T1D but have yet to be tested in that population.

The largest hurdle to safe, effective use of SGLT inhibitors in T1D is the risk of DKA. People with T1D are at heightened risk for DKA relative to people with T2D or the nondiabetic population, and numerous clinical trials have shown increased rates of DKA, including euglycemic DKA, in people with T1D taking SGLT inhibitors compared to placebo. While several SGLT inhibitors are approved for T1D in Europe and Japan as insulin adjuncts, none are yet approved for T1D in the United States. JDRF recognizes the potential benefits of SGLT inhibitors for T1D and the urgent need to mitigate their associated risk of DKA to support the successful use of these effective therapies in T1D worldwide.

OBJECTIVES

Letters of intent (LOI's) are sought from academic or industry applicants with innovative research projects to advance safe, effective use of SGLT inhibitors for T1D.

Examples of research appropriate for this RFA include but are not limited to:

- Development and testing of education/safety/monitoring tools or protocols to prevent DKA
- Physiology studies to better understand ketosis and DKA
- Development of pharmacological or other interventions to prevent DKA
- Development and/or testing of novel and user-friendly ketone monitoring technologies
- Assessment of real world efficacy and safety outcomes for SGLT inhibitors in T1D
- Data analysis to determine T1D patient characteristics (demographic, clinical, biological, behavioral, T1D management regimen, other) that predict efficacy and/or safety of SGLT inhibitors
- Additional analysis of data from pivotal phase 3 clinical studies

This RFA will not support applications primarily focused on the following areas:

- Investigation of SGLT inhibitors for indications other than T1D (e.g. T2D)
- Basic research on SGLT inhibitors unlikely to influence care of people with T1D

Deliverables

- Successful grants will deliver findings that can be translated into increased safe and effective use of SGLT inhibitors for T1D in the near- and middle-term.

CRITICAL CONSIDERATIONS

- Applicants are required to procure SGLT inhibitors and/or other drugs required for their study
- User burden should be considered when proposing protocols or interventions
- Applicants should consider practical aspects of how their proposed studies will lead to improved efficacy and/or safety of SGLT inhibitors for people with T1D (e.g., how new technologies will move from proof-of-concept to commercialization; how improved safety protocols will be communicated and adopted; how results can lead to clear conclusions by the T1D stakeholder community, including regulators and payers; etc.)

Applicants are encouraged to consult with JDRF Scientific Staff to discuss the alignment of their proposal to this RFA as they develop the projected study concept.

CLINICAL STUDIES

- JDRF follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the common rule changes: https://nexus.od.nih.gov/all/2019/01/07/nih-implementation-of-the-final-rule-on-the-federal-policy-for-the-protection-of-human-subjects-common-rule/
- JDRF endorses the use of outcomes beyond A1c. Please review Section 6.3 of JDRF's Award Terms & Conditions: http://grantcenter.jdrf.org/wp-content/uploads/2019/07/JDRF-Terms-and-Conditions-7.2.2019.pdf

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/
- Industry Development and Discovery Program*:* http://grantcenter.jdrf.org/industry-discovery-development-partnerships/

Each application may request up to $400,000 (including up to 10% indirect costs) for a project lasting up to two years. Substantially shorter projects are welcome. Applicants should discuss with JDRF Staff (see below) when proposing projects with increased scope (time, budget).

Applications that are not funded through this RFA may be resubmitted to other JDRF grant mechanisms according to the deadlines and guidelines described on the JDRF website: http://grantcenter.jdrf.org/rfa/

ELIGIBILITY

Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants must hold a faculty position or equivalent at a college, university, medical school, industry setting or other research facility. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this RFA; however, additional information will be requested from for-profit entities if a full application is invited. Submissions from for-profit entities or collaborations involving for-profit entities will be reviewed by the JDRF T1D Fund (t1dfund.org) in addition to JDRF 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.

LETTER OF INTENT

Prospective applicants should submit a LOI online via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal request. The LOI template provided on the RMS360 website must be used to complete the application. Applicants will be notified if they have been approved to submit a full application according to the timeline below.

Please see below for complete instructions. Letters of intent should use the template provided and include the following information:

- Background/rationale, published or preliminary data, hypotheses, specific aims, deliverables of project, collaborative framework if applicable
- Description of how proposed research will lead to of safe, effective SGLT inhibitor use for type 1 diabetes
- Plan for acquiring drugs used in the study, if applicable
- Intellectual property or commercial efforts associated with the current application
- Estimated budget (total and yearly)
- Indication of whether research will include human subjects

PROPOSAL

An approved LOI is required prior to submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided on RMS360 (http://jdrf.smartsimple.us). Proposal section templates in MS Word [**10 page 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 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:
http://grantcenter.jdrf.org/wp-content/uploads/2012/12/JDRF_Scientific_Guidelines_final-Aug20151.pdf

DEADLINES

- **RFA release date** September 18, 2019
- **LOI deadline** October 28, 2019
- **Notification of full application request** November 20, 2019
- **Application deadline** January 8, 2020
- **Response to applicants** May 2020
- **Earliest anticipated start date** August 2020

SUBMISSION INSTRUCTIONS

Applicants should register and submit their completed LOI 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 to RFA purpose
- 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.