JDRF REQUESTS LETTERS OF INTENT FOR: DEVELOPING COMBINATION THERAPIES IN TYPE 1 DIABETES

BACKGROUND & PURPOSE

JDRF, the world's leading non-profit organization with the mission to cure type 1 diabetes (T1D), invites letters of intent (LOI's) for the preclinical and clinical development of combination therapies to improve on the previous evidence of safety and efficacy of monotherapy approaches in the setting of T1D.

Successes across multiple aspects of autoimmune disease modifying therapies have brought the field to a unique place that will benefit from coordination, integration, and harmonization of efforts both in the preclinical and clinical settings for drug development. JDRF has an unprecedented opportunity to achieve progress in assessment of increased therapeutic effectiveness and reduced toxicity offered by pairing of single agents as combination therapies. T1D is a complex disease, suggesting that multipronged therapeutic approaches might be needed to improve clinical outcomes. To that end, proposals will be considered that combine agents with different modes of action and targets, such as those that modulate immune responses, improve metabolic status, and/or improve/protect beta cell function. To be considered, projects proposed should have goals that align with the JDRF Cures Program aims of delaying, halting, or reversing the onset of T1D, as outlined in the JDRF Research Strategy for Disease Modifying Therapies (available for review **here**).

RESEARCH OBJECTIVES

LOI's are sought for preclinical and/or clinical studies with novel approaches toward the development of combination therapies which utilize multiple therapeutic agents targeting mechanisms involved in the following biological pathways: immune modulation (including antigen specific targeting), beta cell function and regeneration/replication, and/or metabolic control. Only projects with relevance to T1D will be considered. In addition, proposals must align with one of the following 3 research objectives:

Objective 1: Identification of novel combination therapy for T1D through predictive modeling.
In silico approaches have been used successfully in other indications, such as oncology and transplant immunology, to predict combination approaches that are optimized for safety and efficacy. These approaches allow the generation of a combination index, a measure of the synergy for a given drug combination. For this research objective, we seek proposals to use similar in silico and bioinformatics approaches to derive combination indices that would address the key mechanisms contributing to human T1D pathogenesis – namely T cell mediated autoimmunity, beta cell stress and dysfunction, loss of functional beta cell mass, systemic insulin resistance, and metabolic dysregulation. Identification of appropriate combinations for therapy is a critical step in the advancement of the treatment of T1D.

Project aims can include the identification of healthy- and disease-specific signaling networks for therapeutic intervention but should also include the assessment of drug combinations that can revert signaling to a healthy state. Bioinformatics approaches to identify combination therapy strategies or targets will be considered, as will *ex vivo* interrogation of combination therapy agents to identify mechanisms of action of the combined drugs versus single agents. Stated goals of projects submitted for this research objective should include proposed combination therapy strategies with the potential for future preclinical testing, inclusive of combination index assessment or similar approaches that report on the potential synergy, efficacy, and safety considerations. Projects utilizing retrospective analysis of EMR or other data with machine learning and artificial intelligence tools to develop predictive algorithms for combinatorial therapies may also be considered.

Objective 2: Preclinical testing of novel combination therapy approaches for T1D.
Research proposed should focus on drug combinations aimed at preventing or reversing T1D. *In vivo* models are requisite steps to determine the pharmacokinetic properties of drug combinations and the safety and

efficacy associated with the unique mechanism of action (MOA) associated with these approaches. Using specific animal models of T1D, the combination therapy approaches are expected to demonstrate improved efficacy, durability, and or decrease toxicology over monotherapy approaches.

Rationale for the combination of the agents being tested is required, with research design including pharmacokinetic assessment in relevant models currently available, as development of new animal models will not be considered for funding. Proposals should have clear aims to demonstrate the safety, biological effect, and efficacy of the combination therapy, and include comparative analysis of the risk-benefit ratio of the proposed combination vs. each single agent. Priority will be given to studies that propose the delivery of a final data set sufficient to initiate Phase 1/2 clinical testing of the combined therapy. To this end, non-GLP toxicology studies may be included in study proposal.

Objective 3: Clinical testing of novel combination therapy approaches for T1D.
Proposals submitted for this objective will test a proposed combination therapy in a Phase 1/2 clinical trial. Agents to be tested must have previously demonstrated safety as monotherapies in T1D or other diseases (or as combination therapies in other diseases) and be available prior to funding with a statement of drug commitment provided at application. Measurement of HbA1C, C-peptide, and CGM as clinical outcomes are strongly encouraged to be included in the trial design, as appropriate. Stated goals of trials submitted for this research objective must include either expanded clinical studies based upon the results or pursuit of regulatory approval. For studies with efficacy endpoints, choice of intended patient population must be well supported by prospect of direct benefit, such as but not limited to stage of disease, age of intervention, duration of intervention, and patient reported outcomes (if applicable).

JDRF follows the U.S. National Institutes of Health (NIH) guidelines for studies including human subjects, including the common rule changes. 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 (link **here**).

Overall Criteria:

- Applicants are strongly urged to consider pilot or adaptive trial designs to maximize efficiency.
- Collaborative projects combining the expertise and/or resources of multiple research groups are highly encouraged.
- Animal models used for preclinical studies should be dictated by the stage(s) of disease being targeted.
- Combination therapy involving a drug/agent paired with a device may be considered, provided abundant evidence/rationale exists to infer that the combined therapy will enhance the efficacy of treatment.
- Should contain information regarding any industry collaborations and any provisions for obtaining the agents for the proposed trial (at no-cost or at-cost) from the relevant companies.
- Proposals may leverage or extend current studies.
- Clinical trials should provide information on source of study population.

Further Considerations:

- Industry applications and industry collaborations, where necessary, are strongly encouraged.
- International collaborations, and other partnerships that bring together distinct expertise and abilities are strongly encouraged.
- Willingness to share samples and data with the clinical and scientific community, according to JDRF standards.
- Proposals will be assessed for the validity of the proposed assays, aims and hypothesis, as well as the overall potential for impact on T1D clinical care.

Out of Scope for this request:

- Cell therapy approaches.
- Studies focused solely on biomarker identification or validation.
- Studies focused solely on glucometabolic control or treating the complications of T1D.

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

MECHANISM

Nonprofit organizations, public and private universities, colleges, hospitals, laboratories, units of state and local governments may apply under JDRF's **Strategic Research Agreement (SRA)** funding mechanism. For-profit entities may apply under JDRF's **Industry Discovery & Development Partnership (IDDP)** funding mechanism, which entails additional requirements and typically has a modest royalty payback to JDRF. For more information on the SRA's or IDDP's can be found on our website (SRA: **Link**; IDDP: **Link**).

The level and length of funding will vary depending upon the research objective targeted by the proposal:

Objective 1: Identification of novel combination therapy agents through predictive modeling.
- Up to $150,000.00/year
- Up to 2 years
- Including up to 10% indirect costs

Objective 2: Preclinical testing of novel combination therapy approaches for T1D.
- Up to $300,000.00/year
- Up to 2 years
- Including up to 10% indirect costs

Objective 3: Clinical testing of novel combination therapy approaches for T1D.
- Up to $500,000.00/year
- Up to 3 years
- Including up to 10% indirect costs

Proposals with higher cost or requiring greater time than listed for the objectives above, or that fit multiple objectives, may still be considered at the discretion of JDRF. Please consult the scientific contact listed below for guidance and approval prior to submission.

ELIGIBILITY

Applicants for SRA's 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. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this LOI; however, additional information will be requested from for-profit entities if a full application is invited.

For clinical studies, applicants must hold an appointment or joint appointment in a subspecialty of clinical medicine and conduct human clinical 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 Letter of Intent (LOI) online via RMS360 (http://jdrf.smartsimple.us) to be considered for a full proposal. The LOI template provided through RMS360 must be used to complete the application. Applicants will be notified approximately four weeks after the LOI deadline date if they have been approved to submit a full application.

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

- Background/Rationale and Specific Aims of overall project

- Uniqueness about the approach and advantages over other approaches explored in the field
- Overview of hypotheses, goals, deliverables, and collaborative framework if applicable
- Impact of the expected deliverables of the proposed study with potential next steps
- Timelines/timetable
- Intellectual Property or commercial efforts associated with the current application
- Estimated total and annual budgets
- Biosketches for all Principal Investigators

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 the RMS360 portal (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. Guidance for the preparation of proposals can be found on our website

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 (link **here**).

REVIEW CRITERIA

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

- Significance
- Relevance to T1D
- Approach
- Innovation and level of differentiation
- Investigator experience
- Environment

DEADLINES

RFA RELEASE DATE ..... October 18, 2021

LOI DEADLINE ..... November 17, 2021

NOTICE OF FULL APPLICATION REQUESTS ..... December 15, 2021

FULL APPLICATION DEADLINE ..... January 31, 2022

RESPONSE TO APPLICANTS ..... May 2022

ANTICIPATED START DATE ..... July 2022

CONTACTS

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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.