IMMUNOTHERAPIES RFA WEBINAR

13 November 2015

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Request for LETTERS OF INTENT for selection to FULL PROPOSALS

OVERCOMING OBSTACLES TO ACHIEVING IMMUNE TOLERANCE IN TYPE 1 DIABETES PORTFOLIO REVIEW

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Agenda

- Goal/Objectives of RFA
- A therapeutic rationale for achieving tolerance
- Examples of investigation topics
- Proposal submission process

Long-Term Goal

To treat T1D by *restoring and then maintaining* immune tolerance to halt or reverse disease progression in prediabetes with islet autoimmunity and dysglycemia (i.e., Stage 2*), new-onset, established disease

- via potent antigen-specific immunotherapy (ASI) in combination with immunomodulatory agents

** Insel, R.A. (2015) Diabetes Care 38:1964*

Objectives

To improve our understanding of how immunoregulatory mechanisms develop and function so that optimal physiological conditions can be created for ASIs to restore immune tolerance to β cells.

Such knowledge creation includes investigation of:

- disease-associated immunological changes in T1D that are barriers to the optimal performance/selection of ASIs
- mechanisms of establishing durable (vs. transient) tolerance using IM, ASI, and a rational combination of both
- rationally justified combinations of IM therapies with ASIs in preclinical models to achieve tolerance
- preclinical studies with candidate combinations to determine optimal dosing and timing of administration for modeling combination therapies in clinical trials

Therapeutic Rationale

1. Clinical Observations
   - ASI (mainly "naked antigen") or immunomodulatory (IM) therapies have not shown robust or durable metabolic outcomes in disease prevention or treatment trials.
   - However, ASI and IM therapies, when administered individually, can lead to the desired but "transient" immune regulatory outcomes (increases in Treg/decrease in Teff cells) and sometimes slowing of metabolic decay.

2. Challenge: These observations of immune mechanistic outcomes suggest that the desired metabolic outcomes could be achieved with improvements in therapeutic approaches that include ASIs.

3. Solutions
   - Create conditions better suited for ASIs to induce a robust Treg development and function that will lead to durable immune tolerance that prevents re-occurrence of autoreactivity.
   - Develop more potent ASIs with Tolerance Delivery Systems (i.e., tolerance adjuvant) – *covered in another RFA (webinar on Monday, 16 Nov 2015)*

Examples of pertinent topics include, but are not limited to:

- Use of relevant preclinical models to evaluate IM therapies to enhance ASI-induced immune tolerance at different disease stages
- Does pathogenic cell-mediated pancreatic inflammation and beta cell destruction negatively influence the performance of ASIs
- Functional status of Treg cell populations in T1D subjects (or appropriate mouse models); i.e., are there any functional defects that are cell-intrinsic and/or a consequence of disease activity affecting ASIs?
- Therapeutic benefit of achieving immunoregulation/tolerance via a single- vs. multiple-antigen ASI that may be linked to a T1D disease stage?
- Elucidation of the degree and mechanism-of-action of autoantigen-specific Treg cell by-stander suppression that leads to restoration of immune tolerance upon ASI treatment (use of inducible autoimmune models is appropriate)
- Addressing the relative roles of cell ablative vs. immunomodulatory therapies as necessary prerequisites for success with ASI (use of inducible autoimmune models is appropriate)
- Establishing a mechanistic rationale for ‘when’ beta cell therapies are best combined with ASI or IM therapies.

This RFA is NOT intended to support:

- efficacy readouts only in preclinical models of disease
- development of cellular therapies or gene therapy approaches
- studies without potential for translation or informing future clinical approaches

Collaborations during and after funding

- Collaborative efforts with complementary expertise are highly encouraged

- Depending on progress, JDRF may identify synergistic projects and approach Investigators for non-confidential discussions about their projects. These discussions have in the past led to fruitful collaborations.

Funding Mechanism and Eligibility

Funding Mechanism

- Up to a maximum of $250,000 USD per year including 10% indirect costs for up to 2 years
- Level of funding will vary depending on the scope and overall objectives of the proposal.
- Pilot proposals may be identified from LOIs that do not move forward to full SRA applications – applicants will be notified if so
- Projects would be funded as:

  Strategic Research Agreements (SRA) (http://grantcenter.jdrf.org/grant-center/information-for-applicants/grant-mechanism-descriptions/strategic-research-agreements/)

Eligibility

- 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
- Applications from for-profit entities or industry collaborations accepted

PROPOSAL SUBMISSION PROCESS

RFA Timeline:

- **Letter of Intent Release:** Wednesday October 21, 2015
- **Letter of Intent Submission Deadline:** Thursday December 3, 2015
  - Applicants should register and submit their completed letter of intent application in RMS360 (http://jdrf.smartsimple.us).
- **Notification of Full Application Request:** Tuesday January 19, 2016
- **Full Application Submission Deadline**: Wednesday March 2, 2016
- **Earliest Response to Applicants:** July 2016
- **Earliest Anticipated Start Date:** September 2016

Letter of Intent/Full Proposal Application

Letters of intent and full proposal applications should be submitted via the RMS360 system (jdrf.smartsimple.us) using the research plan template provided and including the following information:

- Background /Rationale and Specific Aims of overall project
- Overview of hypotheses, goals, deliverables and collaborative framework as applicable
- Title, lead investigator and a description and specific aims of individual projects (if collaborative/network)
- Expected deliverables and impact of the proposed study with potential next steps
- Intellectual Property or commercial efforts associated with the current application
- Total budget / budget by year by project
- Biosketches for all Principal Investigators and Key Personnel

RMS360

- JDRF is using a grants management system to collect online application submissions called RMS360. The RMS360 link is as follows: https://jdrf.smartsimple.us/s_Login.jsp.
  - Please note that if you are new to the system, you must register and log in details will be generated.
- Call details and deadlines can be found in the "Funding Opportunities" tab of RMS360.
- All materials and templates pertaining to the application can be found once you've initiated an application in RMS360.
- It is recommended to use Google Chrome or Firefox when using RMS360, as these browsers are most compatible with the system.

Where should questions be directed?

- Questions on, scientific suitability of proposals:
  - David Alleva (dalleva@jdrf.org)
  - Simi Ahmed (sahmed@jdrf.org)
- Questions on eligibility, logistics, deadlines or submission problems:
  - Christine Dredger (cdredger@jdrf.org)
- 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.

THANK YOU

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