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JDRF Requests Expressions of Interest in Projects Investigating the Mechanistic Basis of Persistent Changes in Cellular Programs Impacting Risk or Progression of Type 1 Diabetic Complications

Background and Purpose of Request

The chronic nature of diabetes results in changes to cellular physiology that may contribute to development of complications including neuropathy, nephropathy, retinopathy, and cardiovascular disease. The precise molecular mechanisms that govern these persistent changes in cellular programming are currently unknown but may include factors leading to long-term changes in gene or protein expression or long-term post-translational modification of proteins. The DCCT/EDIC studies suggest the presence of a metabolic 'memory' of early tight or poor glycemic control, but mechanisms for this phenomenon have not been elucidated. Recent literature has shown that histone modifications are altered in the diabetic state, which suggests that altered chromatin biology may contribute to the persistent cellular changes observed during diabetes. Epigenetic/chromatin regulation may offer novel therapeutic targets to treat or prevent diabetic complications. However, solid groundwork is still required to confirm a causal link between potential molecular mechanisms (chromatin biology/histone modifications or other means) and diabetic complications. JDRF therefore requests expressions of interest in projects that will investigate the mechanisms that cause persistent changes in cellular programs that impact the risk or progression of type 1 diabetic complications.

Specific Goals of the Request

This request seeks carefully designed, hypothesis-driven studies that will determine mechanisms of persistent cellular re-programming observed in the diabetic state. Phenotypic changes observed in the persistent diabetic state include various metabolic perturbations, inflammation, and fibrosis. **Priority will be given to proposals that aim to find a causal link between disease-specific cellular changes (including but not limited to chromatin biology / epigenetic factors) and the pathogenesis of type 1 diabetic complications.**

Examples of topics to be investigated under this EOI include, but are not limited to:

- Investigation of molecular changes with in vivo reversibility studies that include pancreatic transplant and reversal of diabetic complications.
- Study of molecular changes in animal models that develop diabetic complications compared to corresponding models where genetic changes protect from development of disease.
- Pharmacological intervention studies analyzing gross biological effects of currently available agents, including histone deacetylase (HDAC), histone acetyltransferase (HAT) or DNA methyltransferase (DMT) inhibitors, on in vitro and in vivo models of diabetic complications.
- Correlation of epigenome status to disease stage in animal models or in disease-progressive clinical samples.
- Study of DNA methylation patterns in diabetic cohort and control samples (fresh clinical samples, autopsy samples, or formalin-fixed tissues).

Projects focused on the human aspects of diabetic nephropathy, retinopathy, and neuropathy will receive highest priority. Mechanistic studies will also receive priority over descriptive studies. Relevant multidisciplinary collaborations are strongly encouraged between experts in diabetic complications and experts in chromatin biology, epigenetics, transcription, bioinformatics, and/or well established core facilities.

Award Information and Mechanism of Support

JDRF encourages applications involving multiple investigators (co-investigators, multiple collaborators or extensive use of well established core facilities) and will provide support for the proposal of up to \$250K plus 10% indirect costs (\$275K total) per year for a maximum duration of 2 years. For single investigator proposals JDRF will provide grant support of up to \$150K plus 10% indirect costs (\$165K total) per year for a maximum of 2 years.

Data Sharing

All applicants must provide a detailed description of how they will publically share data with other investigators. This may be submitted as a brief appendix to the research plan. Potential resources are listed as suggestions:

- Potential resource for storing Next Generation Sequencing data – the NCBI Short Reads Archive: <http://www.ncbi.nlm.nih.gov/Traces/sra/sra.cgi?cmd=show&f=concepts&m=doc&s=concepts>
- Potential resource for depositing gene expression (including arrayCGH, ChIP-chip, SNP, SAGE etc) or mass spec peptide profiling data – the NCBI Gene Expression Omnibus (GEO) <http://www.ncbi.nlm.nih.gov/geo/>

Expressions of interest should be no more than two pages in length and include the following information:

- Title of Proposed Project
- Name, title and institution of principal investigator, and any co-investigator or key collaborator(s)
- Brief Rationale
- Description of the research approach
- Primary deliverable of the project
- Approximate budget and project duration

EXPRESSION OF INTEREST (EOI)

Expressions of interest should be submitted via Proposal Central (<http://proposalcentral.altum.com/default.asp?GMID=16>), using the template provided, no later than February 26th, 2009.

KEY DATES:

EOI deadline	February 26, 2009
EOI decision by	March 6, 2009
Full application due (Regular Research Grant – RRG)	April 27, 2009
Final review	June 2009

PROGRAMMATIC CONTACT

Inquiries should be directed to:

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PROPOSALCENTRAL

<http://proposalcentral.altum.com/default.asp?GMID=16>

pcsupport@altum.com

(301)916-4557 ext. 227, or toll free in the US (800)875-2562 ext. 227

Assistance can be obtained Monday through Friday between 8:30 a.m. and 5:00 p.m. U.S. Eastern Time.