Prospective, placebo-controlled clinical trial of Peroxisome Proliferator-Activated Receptor Agonist (PPAR) versus placebo to prevent further beta cell loss in young patients with recently-diagnosed, autoimmune-mediated type 1 diabetes

SUMMARY: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS) is seeking proposals in the form of capability statements from companies for collaborative arrangements to provide active agent (PPAR agonists such as thiazolidinediones) and placebo to study the safety and possible protective effect of the agent on pancreatic beta cell function in young individuals with new onset autoimmune mediated type 1 diabetes.

INTRODUCTION: The NIDDK is developing a prospective, placebo-controlled study of the safety and efficacy of peroxisome proliferator-activated receptor agonist therapy for the treatment of members of the pediatric population between the ages of 8 and 18 who have been diagnosed with type 1 diabetes within the previous 6 weeks. The trial will be conducted at the Clinical Center on the Bethesda campus of the National Institutes of Health by the National Institute of Diabetes and Digestive and Kidney Diseases. It is anticipated that 30 subjects will be enrolled in each arm of the trial (30 on study agent, 30 on placebo). Treatment is expected to last 12 months from the time of enrollment. Repeated C-peptide stimulation tests will be conducted. Serial immunological assays will be performed to monitor the anti-beta cell immune response. Additional factors will be monitored including blood glucose control, blood pressure, lipid levels, and inflammatory markers. Subjects will be guided in diabetes management in order to assure that optimal blood glucose control is achieved and maintained during the research study.

STUDY GOAL: The overall goal of this study is to determine whether peroxisome proliferator-activated receptor (PPAR) agonist therapy (such as thiazolidinediones) is a safe and effective therapy to prevent further loss of beta cell function in a pediatric patient population.

SUPPLEMENTAL INFORMATION: Type 1 diabetes mellitus (T1DM) is caused by T cell mediated, autoimmune destruction of pancreatic beta cells resulting in nearly absolute insulin deficiency. It affects more than 1 million people in the US and typically presents during childhood

or young adulthood. During the first year after diagnosis, patients frequently experience several months during which they require very little insulin and glucose management is easy. However, further destruction of beta cells leads to worsening of the condition such that blood glucose control becomes increasingly difficult, and if patients fail to keep their blood sugar values near normal, they are at increased risk for micro- and macrovascular complications. Since the 1980s, several clinical trials have shown that immunosuppression can hold or slow down this destructive process, but the safety of such an approach remains much debated. No other treatment except excellent insulin therapy has demonstrated both safety and efficacy.

PPAR agonists, specifically ligands for the PPAR-γ subtype, such as thiazolidinediones (TZDs), have well known effects on insulin sensitivity and lipid metabolism, playing an important role in the management of type 2 diabetes. However, they also have anti-inflammatory and immunomodulatory characteristics, e.g. in vitro studies have shown that TZDs can suppress nuclear factor-κB (NF-κB) which in turn serves to reduce interleukin-2 (IL-2) secretion by T cells, thereby inducing T cell apoptosis. Furthermore, in vivo studies have demonstrated beneficial effects of TZDs in several autoimmune animal models, including prevention of diabetes in the NOD mouse, and reducing disease activity in mice/rats with experimental autoimmune encephalomyelitis, and inflammatory bowel disease (IBD). Supportive data are also available in human clinical trials. One small study in patients with latent autoimmune diabetes in adults (LADA) showed that 7 patients treated with Rosiglitazone and insulin maintained their endogenous insulin secretion over 18 months, whereas 7 individuals treated with insulin alone had significantly less residual insulin secretion. TZD treatment of patients with IBD has also been shown to ameliorate their disease, and promising preliminary results have been reported following TZD treatment of patients with multiple sclerosis.

Capability Statements: A Selection Committee will use the information provided in the "Collaborator Capability Statements" received in response to this announcement to help in its deliberations. It is the intention of the NIDDK that all qualified Collaborators have the opportunity

to provide information to the Selection Committee through their capability statements. The narrative portion of the Capability Statement should not exceed 10 pages.

The capability statement should include details on the PPAR agonist's availability to be administered to a population from 8 to 18 years, including options for administering the agent in a dose adjusted for body weight; details on provision of placebo; detailed plans demonstrating the ability to provide sufficient quantities of the therapeutic agent and placebo in a timely manner for the duration of the study; as well as the ability to provide technical and/or financial support to facilitate the scientific goals, including support for a study nurse. Additional information such as proposed dosing regimes, possible strategies for assessing compliance, proposed methods for assessing levels and/or biological effects of the PPAR agonist, proof of expertise in the design and implementation of studies involving pharmacologic therapy of young patients will be considered. The statement must address a willingness to publish research results promptly and the ability to be bound by a Cooperative Research and Development Agreement (CRADA) pursuant to the Federal Technology Transfer Act of 1986 (FTTA, 15 U.S.C. 3710; and Executive Order 12591 of April 10, 1987, as amended by the National Technology Transfer and Advancement Act of 1995), and substantially as found at http://techdev.niddk.nih.gov/ICTCRADA2005.pdf .

CRADAs are agreements designed to enable certain collaborations between Government laboratories and non-Government entities. They are not grants, and not contracts for the procurement of goods/services. The NIDDK is prohibited from transferring funds to a CRADA Collaborator. Under a CRADA, NIDDK can contribute facilities, staff, materials, and expertise to the effort. The Collaborator typically contributes facilities, staff, materials, expertise, and occasionally funding to the collaboration. The CRADA collaborator receives an exclusive option to negotiate an exclusive or non-exclusive license to Government intellectual property rights arising under the CRADA and makes contributions that may qualify one or more of its employees as a co-inventor(s) of new technology developed under the CRADA.

DATES: Only written capability statements received by the NIDDK on or before October 11, 2005, will be considered. Applicants meeting the criteria as set forth in this announcement may be invited at the Applicants' own expense to discuss with the Collaborator Selection Committee their plans, capabilities, and research findings pertinent to the study.

FOR ADDITIONAL INFORMATION AND QUESTIONS: Capability statements should be submitted to Rochelle S. Blaustein, J.D., Director, Technology Transfer and Development, National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, MSC 5632, Bethesda, MD 20892-5632, phone: (301) 451-3636, fax: (301) 402-7461, e-mail: Rochelle.Blaustein@nih.gov. For scientific inquiries contact Kristina Rother, M.D., Senior Staff Clinician, at kr58q@nih.gov or Tel: 301-402-3905. Capability Statements may be submitted by e-mail with attachments, by facsimile at the number above, by mail, or by overnight courier so long as they are received by the posted deadline.

A formatted copy of this announcement is available at
http://TechDev.NIDDK.NIH.gov/PPARpub.pdf