Opportunity for Cooperative Research and Development Agreements (CRADAs)

Prospective, randomized, controlled multicenter clinical trial of vitamin E versus an insulin-sensitizing agent versus placebo in patients with well characterized nonalcoholic steatohepatitis (NASH), including both children and adults

INTRODUCTION: A retrospective and prospective database of adult and pediatric cases of nonalcoholic fatty liver disease will also be created by the newly formulated NIDDK-funded NASH Clinical Research Network that will allow prospective evaluation and follow-up of a large group of patients. Ancillary studies to evaluate the natural history, pathogenesis, genetic factors, and determinants of progression and severity of nonalcoholic fatty liver disease also pose opportunities for CRADAs.

SUMMARY: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) of the Public Health Service of the Department of Health and Human Services is seeking proposals in the form of capability statements from companies for a Cooperative Research and Development Agreement (CRADA) to provide insulin-sensitizing agents, Vitamin E and placebo to perform a prospective randomized controlled trial of therapy of NASH. The NIDDK is also seeking proposals from companies for a CRADA to evaluate the natural history, pathogenesis, diagnosis, genetic factors, and determinants of progression and severity of nonalcoholic fatty liver disease (NAFLD) and/or NASH.

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), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) of the Public Health Service (PHS) of the Department of Health and Human Services (DHHS) seeks a Cooperative Research and Development Agreement (CRADA) with a pharmaceutical or biotechnology company to provide insulin sensitizing agent(s) such as biguanides or thiazolidinediones, Vitamin E and placebo to study important issues regarding possible treatment options and disease progression in NASH. The potential Collaborator(s) capability statement should provide proof of expertise in the design and implementation of studies of NASH and should include the scientific rationale for the study proposed, proposed dosing regimes, possible strategies for assessing compliance, proposed methods for assessing levels of the vitamin E and/or insulin sensitizing agent (s), pharmacokinetics, and drug distribution methodology. In addition, CRADA partners are being sought for ancillary studies. Examples of potential studies include:

The identification of host genetic factors associated with the development of NASH and with the risk of fibrosis progression. This will involve the analysis of genomic DNA from individuals with NASH as well as NAFLD for functional single nucleotide polymorphisms in prioritized candidate genes, which have been identified using a combination of literature search and informatic algorithms including biologic mechanisms, pathogenesis, linkage analysis and biochemical studies.

Exploration of serum markers for fibrosis to predict hepatic histology either by themselves or in combination with other clinical and laboratory variables. Also, the utility of these serum markers as surrogate markers of therapeutic response in study subjects participating in treatment trials.

Evaluation of the role of lipid peroxidation in the pathogenesis of NAFLD and analysis of the effect of various therapies on the levels of serum and urine peroxides in patients with NAFLD participating in treatment trials.

Develop gene expression arrays that are diagnostic of fatty liver disease and would provide staging and grading of the degree of cell injury, steatosis and fibrosis in the liver as well as insights into the pathogenesis of this disease.

Use of cytokine assays for analyses of serum/plasma cytokine levels as markers of necro-inflammatory or fibrotic activity in NASH and as surrogate markers of histologic improvement in therapeutic trials of NASH.

DATES: Only written CRADA capability statements received by the NIDDK on or before **April 11, 2003** will be considered. Applicants meeting the criteria as set forth in this announcement will be invited at the Applicants' own expense to discuss with the Study Steering Committee their plans, capabilities, and research findings pertinent to the study at a meeting of the Study's Steering Committee, date to be determined.

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: rochelleb@intra.niddk.nih.gov

SUPPLEMENTARY INFORMATION: A CRADA is an agreement designed to enable certain collaborations between Government laboratories and non-Government laboratories. It is not a grant, and is not a contract 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 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 in a pre-determined field of use and may contributions that qualify one or more of its employees as a co-inventor(s) of new technology developed under the CRADA.

Study Goal: The overall goal of this study is to perform clinical, epidemiological and therapeutic research in patients with NASH using a standardized and coordinated approach to the evaluation and therapy of NASH and to provide sufficient numbers of patients for the research. This will be done by development of a database on adult and pediatric patients with NASH and NAFLD including clinical information as well as serum and tissue samples. In addition, the NASH Clinical Research Network will conduct a prospective, randomized, double-blind controlled trial of promising therapies for NASH, including use of an insulin-sensitizing agent (such as a biguanide or thiazolidinedione) and/or an anti-oxidant (such as vitamin E) compared to placebo. Applicants for a CRADA to support this clinical trial must include a description of investigators and staff with experience and expertise to collaborate in multicenter clinical studies to assess patients with NAFLD and NASH. Applicants should provide a detailed description of the pharmacokinetics of the proposed drugs to be used including how and when the drugs should be taken. The process for biologic sample collection, storage and handling needs must be included. A description of the laboratory tests that are needed including assays to determine specific drug levels along with appropriate methods for performing them should be provided, as well as other core facilities and interactions with core facilities that are needed. Also included should be the methods that would be used to assure privacy and maintain confidentiality of data. How the drug or product will be sent to each participating center as well as packaging, storing, and accountability issues must be presented.

Capability Statements: A Selection Committee will utilize 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 Capability Statement should not exceed 10 pages and should address the following selection criteria:

The statement should provide specific details of the methods to be utilized in the investigation of an insulin-sensitizing agent or vitamin E in patients with NASH and clearly describe important issues surrounding the evaluation of disease progression in these patients.
The statement should include a detailed plan demonstrating the ability to provide sufficient quantities of the therapeutic agents in a timely manner for the duration of the study.
The statement may include outcome measures of interest to the Collaborator. The specifics of the proposed outcome measures and the proposed support should include but not be limited to therapeutic treatment and evaluation of NAFLD or NASH, specific funding commitment to support the advancement of scientific research, personnel, services, facilities, equipment, or other resources that would contribute to the conduct of the commercial development.
The statement must address willingness to promptly publish research results and ability to be bound by PHS intellectual property policies (see CRADA: http://ott.od.nih.gov/newpages/crada.pdf).