**The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) seeks Cooperative Research and Development Agreement (CRADA) collaborators for NAFLD, NASH & cryptogenic cirrhosis clinical trials**

**DESCRIPTION:**
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) seeks collaborators for Cooperative Research and Development Agreements (CRADAs) to (1) evaluate a panel of serological assays that reflect hepatic fibrosis, inflammation, insulin resistance, and oxidative stress to differentiate among NAFLD, NASH, or cryptogenic cirrhosis, (2) identify protein alterations in patients with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cryptogenic cirrhosis, (3) evaluate noninvasive imaging methods for assessing fat, inflammation, disease activity and/or fibrosis in NASH including but not limited to the use of elastrography, nuclear magnetic resonance, molecular imaging, and (4) provide S-Adenosylmethionine (SAMe) to perform a randomized controlled trial of therapy of NASH and/or cryptogenic cirrhosis.

**The NAFLD Database study** – A prospective database of adult and pediatric cases of nonalcoholic fatty liver disease or cryptogenic cirrhosis was created by the NIDDK-funded NASH Clinical Research Network (CRN), which is currently accruing patients, and will ultimately allow prospective evaluation and follow-up of approximately 1,500 patients for 3 years on average.

In addition to the NAFLD Database study, the NASH CRN has developed two treatment trials: **(1) PIVENS** – to evaluate whether 96 weeks of treatment with either pioglitazone or vitamin E lowers NASH activity as determined from hepatic histology in nondiabetic adults with NASH compared to treatment with placebo, **(2) TONIC** – to determine whether 96 weeks of treatment with either metformin or vitamin E leads to sustained reduction in serum alanine transferase in nondiabetic children with NAFLD compared to treatment with placebo. PIVENS is currently recruiting patients and TONIC will begin recruitment by June, 2005.

Ancillary studies to evaluate the natural history, pathogenesis, genetic factors, proteomics, metabolomics, lipidomics, imaging studies, and determinants of progression and severity of nonalcoholic fatty liver disease present a variety of opportunities for CRADAs.

**SUMMARY:** The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) is seeking proposals in the form of capability statements from companies for a Cooperative Research and Development Agreement (CRADA) to provide s-adenosylmethionine (SAM-e) to perform a randomized controlled trial of therapy of cryptogenic cirrhosis. The NIDDK is also seeking proposals from companies for a CRADA to evaluate the natural history, pathogenesis, diagnosis, genetic factors, proteomics, metabolomics, lipidomics, imaging studies, 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 for ancillary studies. Examples of potential studies include: 1) Exploration of serum markers for fibrosis and serum markers for disease activity to predict hepatic histology either by themselves or in combination with other clinical, laboratory, proteomic, metabolomic, and lipidomic variables in the NAFLD Database study. 2) Exploration of the utility of these serum markers as surrogate markers of therapeutic response in study subjects participating in adult (PIVENS) and pediatric (TONIC) treatment trials. 3) Evaluation of the role of lipid peroxidation in the pathogenesis of NASH or NAFLD and analysis of the effect of various therapies on the levels of serum peroxides in patients with NASH or NAFLD participating in treatment trials. 4) Develop serum/plasma proteomic, metabolomic, and lipidomic expression arrays that are diagnostic of fatty liver disease or NASH or cryptogenic cirrhosis and that 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. 5) Use of cytokine assays for analyses of serum/plasma cytokine levels as markers of necro-inflammatory or fibrotic activity in NAFLD or NASH and as surrogate markers of histologic improvement in therapeutic trials of NAFLD or NASH. (6) Evaluation of the role of noninvasive imaging methods for assessing fat, inflammation, disease activity and/or fibrosis in NASH. (7) Investigation of S-Adenosylmethionine (SAMe) as an antioxidant and therapeutic agent for NASH and/or cryptogenic cirrhosis.

**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 make 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 the NASH Clinical Research Network is to perform clinical, epidemiological and therapeutic research in patients with NAFLD or NASH using a standardized and coordinated approach to the evaluation and therapy of NAFLD or NASH and to provide sufficient numbers of patients for the research. This will be done by the NAFLD Database on adult and pediatric patients with NAFLD or cryptogenic cirrhosis including clinical information as well as serum, plasma, liver tissue, and DNA samples. A description of laboratory tests that are needed including assays and required amount of specimens, to determine specific biomarker 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.

**CAPABILITY STATEMENTS:** The Steering 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 Steering Committee through their capability statements. The Capability Statement should not exceed 10 pages and should address the following selection criteria: 1. The statement should provide specific details of the methods to be utilized in the investigation of pioglitazone or metformin or vitamin E in patients with NAFLD or NASH and clearly describe important issues surrounding the evaluation of disease progression in these patients. 2. The statement should include a detailed plan demonstrating the ability to provide sufficient quantities of the laboratory test agents in a timely manner for the duration of the study. 3. 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 treatment and evaluation of NAFLD or NASH or cryptogenic cirrhosis, 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. 4. 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).

**OTHER RELEVANT INFORMATION:** Whole blood will be collected from all participants enrolled into the NASH CRN main studies.

1) In the NAFLD Database study, 15 mL fasting blood will be drawn at screening visit 2 and then annually at weeks 48, 96, 144, and 192 of the study.

2) In the PIVENS Trial, 15 mL fasting blood will be drawn at screening visit 2 and then annually at weeks 48 and 96 after randomization.

3) In the TONIC Trial, 15 mL fasting blood will be drawn at screening visit 2 and then annually at weeks 48 and 96 after randomization.

Whole blood will be processed into serum and plasma locally at each NASH CRN clinical center according to the study standard operating procedures summarized below.

1) Collect whole blood from patients of all ages

2) Separate plasma and serum at clinical center: four 0.5 mL aliquots of plasma and ten 0.5 mL aliquots of serum are to be obtained in 2.0 mL cryogenic vials

3) Store plasma and serum aliquots at -70° C prior to batch shipping to the NIDDK Biosample Repository at McKesson BioServices

CRADA partners will transfer assay results to the NASH CRN Data Coordinating Center quarterly after receipt of the first batched shipment of serum and plasma specimens from the NIDDK Biosample Repository at McKesson Bioservices.

The NASH CRN Data Coordinating Center will accept electronic data sets provided by the CRADA partners and may request data audits and queries if deemed necessary.

Masked NASH CRN data collected at baseline and follow-up study visits will be provided to CRADA partners after receipt of the assay results on at least 200 patients at the Data Coordinating Center. Updates will occur as appropriate but not more often than at 6 months intervals.

The NASH CRN data that will be provided to the CRADA partners will consist of data collected from participants enrolled in the following main NASH CRN studies:

(1) NAFLD Database (sample size: 1500 adult and pediatric NAFLD or NASH patients)
(2) PIVENS Trial (sample size: 240 adult nondiabetic NASH patients)
(3) TONIC Trial (sample size: 180 pediatric nondiabetic NAFLD patients)

Unmasked PIVENS and TONIC treatment trial follow-up visit data will be provided to CRADA partners after completion of the trials.

According to the NASH CRN guidelines, the data collected in the proposed studies are considered part of the NASH CRN database. All study proposals must be reviewed and approved by the NASH CRN Steering Committee prior to initiation.

Utilization of assay results and NASH CRN data must follow all applicable NASH CRN guidelines including the Ancillary Studies Policy and Presentations and Publications Policy both of which can be viewed at the links below:

http://www.jhucct.com/nash/open/ancillary/ancpolicy040628.pdf

http://www.jhucct.com/nash/closed/cpub/pubpolicyJul04.pdf

Publications or presentations arising from the proposed studies must be approved by the NASH CRN Presentations and Publications Committee prior to initiation, and the resulting manuscript or abstract must be approved by the NASH CRN Presentations and Publications Committee prior to journal submission. Authorship format for primary papers arising from the proposed studies will usually be of the modified conventional type (i.e., J Smith, E Brown, and the NASH CRN Research Group). Where allowed by the journal, a full credit roster will be included with the paper. Authorship format for secondary papers arising from the proposed studies will be of the conventional type.

**DATES:** Only written CRADA capability statements received by the NIDDK on or before January 31, 2006 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 on or about May 30, 2006.

**SUBMIT CAPABILITY STATEMENTS** to Patricia Lake, Deputy Director, Extramural Technology Transfer, National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike Building 12A, Suite 3011, MSC 5632, Bethesda, MD 20892-5632, phone: (301) 594-6762, fax: (301) 480-7546, e-mail: lakep@niddk.nih.gov

A formatted version of the original, unmodified Notice of
Opportunity is posted at: http://TechDev.NIDDK.NIH.GOV/