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
Amended to Extend Deadline

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health of the Department of Health and Human Services (DHHS) seeks Industry collaborators for Cooperative Research and Development Agreements (CRADAs) to provide novel therapeutic agents, diagnostic markers and devices for use in NIH-sponsored multi-center clinical trials and studies in patients with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cryptogenic cirrhosis.

BACKGROUND:
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 has accrued over 1,500 adults and pediatric subjects over the past 3 years. 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 aminotransferase in nondiabetic children with NAFLD compared to treatment with placebo. PIVENS and TONIC have completed recruitment and these studies are expected to be completed in 2009. 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.

STUDY GOALS:
The overall goal of the NASH Clinical Research Network sponsored by the NIDDK is to focus on the etiology, contributing factors, natural history, complications, and therapy of nonalcoholic steatohepatitis. The NASH CRN studies currently comprise a large and well characterized population of individuals with various stages of nonalcoholic fatty liver disease, including steatosis, steatohepatitis, and cirrhosis.

The NASH CRN is interested in conducting research that will lead to improved clinical outcomes in patients with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and cryptogenic cirrhosis patients with industry collaborators to:

- Evaluate the natural history, pathogenesis, diagnosis, genetic factors, proteomics, metabolomics, lipidomics, epigenomics, imaging studies, and determinants of progression and severity of nonalcoholic fatty liver disease (NAFLD) and/or NASH as well as clinical trials to assess optimal treatment of adult and pediatric patients with NAFLD, NASH and/or cryptogenic cirrhosis.

- Develop serum/plasma proteomic, metabolomic, lipidomic, microbiomic and 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.
- Explore use 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.
- Explore the utility of these serum markers as surrogate markers of therapeutic response in study subjects participating in adult (PIVENS) and pediatric (TONIC) treatment trials.
- Evaluate a panel of serological assays that reflect hepatic fibrosis, inflammation, insulin resistance, and oxidative stress to differentiate among NAFLD, NASH, or cryptogenic cirrhosis.
- Investigate proprietary drugs, reagents, or devices in controlled randomized clinical trials as potential therapy for NASH, NAFLD and/or cryptogenic cirrhosis in children and/or adults.
- Evaluate noninvasive imaging methods for assessing fat, inflammation, disease activity and/or fibrosis in NAFLD/NASH including but not limited to the use of elastrography, nuclear magnetic resonance imaging, and molecular imaging.
- Identify protein alterations in patients with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or cryptogenic cirrhosis.
- Evaluate 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.
- Evaluate the use of cytokine assays for analyses of serum/plasma cytokine levels as markers of necroinflammatory or fibrotic activity in NAFLD or NASH and as surrogate markers of histologic improvement in therapeutic trials of NAFLD or NASH.

SUPPLEMENTARY INFORMATION: 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 Industry for the described ancillary studies. A CRADA is an agreement designed to enable certain collaborations between Government laboratories and non-Government laboratories. It is not a grant, and it 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 predetermined

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.

CAPABILITY STATEMENTS: The Steering Committee will utilize the information provided in the Collaborator Capability Statements received in response to this announcement to aid 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 of narrative (not including appendices) and should address the following selection criteria:

1. The statement should provide specific details of the methods to be utilized in the investigation of the pharmacologic, surgical or device intervention in patients with NAFLD or NASH and clearly describe important issues surrounding the evaluation of disease progression in these patients.
2. The statement should provide a detailed plan demonstrating the ability to provide sufficient quantities of the laboratory test agent or device in a timely manner for the duration of the study.
3. Must include 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 such tests.
4. A description of other core facilities and interactions with core facilities that are needed.
5. A description of the methods that would be used to assure patient privacy and maintain confidentiality of data.
6. If appropriate, include specific funding commitment to support the advancement of research directed to NAFLD, NASH, and/or cryptogenic cirrhosis clinical trials.
7. Must agree to have their preparation used in NASH CRN-developed protocols which will be conducted by the NASH CRN and will have data collection and analysis performed by the NASH Data Coordinating Center.
8. Must provide a letter of cross reference to the sponsor of the NASH studies to be included with any US FDA filing that contains the chemistry, manufacturing and control information for the drug substance and drug product or device Master File.
9. Dosing and Pharmacokinetic data from human studies must be provided for novel agents**.** The proposed preparation or device must have been tested in Phase I trials in humans.
10**.** Adverse event profile from human studies must be provided.
11. Must agree to share (with NASH CRN) all safety data from other studies involving their preparation or device as well as relevant efficacy data from other studies (updated Investigator Brochure, etc).
12. 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 directed to NAFLD, NASH, and/or cryptogenic cirrhosis clinical trials, personnel, services, facilities, equipment, or other resources that would contribute to the conduct of the commercial development.

13. 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).

DATES: Only written CRADA capability statements received by the NIDDK on or before May 30, 2008 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 NASH Steering Committee their plans, capabilities, and research findings pertinent to the study at a meeting of the NASH Steering Committee to be held later in 2008 in the Baltimore-Washington, DC area..

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

For Scientific Inquiries contact:
Patricia R. Robuck, Ph.D., M.P.H.
Director, Clinical Trials Program
Division of Digestive Diseases and Nutrition, NIDDK
6707 Democracy Blvd., Room 659
Bethesda, MD 20892-5450
Telephone: (301) 594-8879
FAX: (301) 480-8300

A formatted version of the original, unmodified Notice of Opportunity is posted at: http://techdev.niddk.nih.gov/collabs.shtml.