Prospective, randomized, placebo-controlled multicenter clinical trial of corticosteroids versus placebo in patients undergoing hepatoportoenterostomy for biliary atresia

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: Opportunity for collaborations to implement a prospective, randomized, placebo-controlled multicenter clinical trial of corticosteroids versus placebo in patients undergoing hepatoportoenterostomy for biliary atresia. A prospective database of pediatric cases of neonatal cholestasis will also be created by the newly formulated NIDDK-funded Biliary Atresia Research Consortium 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 biliary atresia also pose opportunities for collaborations.

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 corticosteroids, placebo (for corticosteroids), a liquid formulation of ursodeoxycholic acid, fat soluble vitamins and Medium chain triglyceride (MCT)-containing formula to perform a prospective randomized controlled trial of therapy of biliary atresia. The NIDDK is also seeking proposals from companies for a collaboration to evaluate the natural history, pathogenesis, diagnosis, genetic factors, and determinants of progression and severity of biliary atresia and other forms of neonatal cholestasis.**

Collaborative arrangements may be either Clinical Trial Agreements or Cooperative Research and Developments Agreements (CRADAs) 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), as appropriate. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) seeks one or more collaborations with pharmaceutical or biotechnology company(ies) to provide corticosteroids, placebo, a liquid formulation of ursodeoxycholic acid, fat soluble vitamins and MCT-containing formula to study important issues regarding possible treatment options and disease progression in biliary atresia. The potential Collaborator(s) capability statement should provide proof of expertise in the design and implementation of studies involving pharmacologic and/or nutritional therapy of newborns and infants. The statement should include the scientific rationale for the study proposed in biliary atresia, proposed dosing regimes, possible strategies for assessing compliance, proposed methods for assessing levels and/or biological effects of corticosteroids, ursodeoxycholic acid and fat soluble vitamins. In addition, collaborators are being sought for ancillary studies. Examples of potential studies include:

1) The identification of host genetic factors associated with the development of biliary atresia and neonatal cholestasis and with the risk of poor outcome after hepatoportoenterostomy. This will involve the analysis of genomic DNA from individuals with biliary atresia as well as neonatal cholestasis 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.
2) Development of methods for screening for novel or known infectious etiologies that may be associated with the development of biliary atresia.
3) Development and/or refinement of new techniques for the diagnosis of biliary atresia and/or the evaluation of neonatal cholestasis. These might include but are not limited to serum biochemical markers, radiologic/nuclear medicine imaging techniques, and liver histologic/histochemical markers.
4) Exploration of biochemical and clinical markers to predict outcome after hepatoportoenterostomy.

5) Development of gene expression arrays that are diagnostic of biliary atresia and would provide staging and grading of the degree of cell injury, cholestasis and fibrosis in the liver as well as insights into the pathogenesis of this disease.
6) Development of strategies for assessing vaccine response in infants with biliary atresia who receive either corticosteroids or placebo after hepatoportoenterostomy. This will involve but is not limited to measuring antibody titers to vaccine antigens routinely given during the first six months of life and providing a plan for revaccination if protective levels of antibodies are not found.
7) Development of a molecular footprint for biliary atresia. This can be accomplished by two independent methodologies using high throughput profiling. The first will be proteomics of circulating proteins from patients with biliary atresia or diseased-controls (other causes of intrahepatic cholestasis of infancy). The second will be expression profiling using high-density gene chips and liver samples from patients with biliary atresia and diseased controls. These complimentary approaches will provide insight into potential diagnostic tests and novel therapeutic targets for children with biliary atresia.

SUPPLEMENTARY INFORMATION: Clinical Trial Agreements and CRADAs are agreements designed to enable certain collaborations between Government laboratories and non-Government laboratories. They are not grants, and not contracts for the procurement of goods/services. The NIDDK is prohibited from transferring funds to a Clinical Trial or 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 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 this study is to perform clinical, epidemiological and therapeutic research in patients with biliary atresia using a standardized and coordinated approach to the evaluation and therapy of biliary atresia and to provide sufficient numbers of patients for the research. This will be done by development of a database of infants with neonatal cholestasis and biliary atresia including clinical information as well as serum and tissue samples. In addition, the Biliary Atresia Research Consortium will conduct a prospective, randomized, double blind controlled trial of promising therapies for biliary atresia, including use of corticosteroids compared to placebo.

Applicants for a collaborative arrangement 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 biliary atresia and neonatal cholestasis. 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 to monitor therapy, including assays to determine specific drug levels and/or biological effects 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. **Capability statements related to the investigation of corticosteroids, a liquid formulation of ursodeoxycholic acid, fat-soluble vitamins and MCT-containing formula in patients with biliary atresia and/or neonatal cholestasis should address the following selection criteria:**

1. The statement should provide specific details of the methods to be utilized 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 therapeutic agents and nutritional products 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 therapeutic treatment and evaluation of biliary atresia or neonatal cholestasis, 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 if a CRADA is entered (see CRADA: http://ott.od.nih.gov/newpages/crada.pdf).

DATES: Only written capability statements received by the NIDDK on or before **July 9, 2003,** 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 Study Steering Committee their plans, capabilities, and research findings pertinent to the study at a meeting of the Study's Steering Committee on 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