Notice of Opportunity for Collaboration

ACUTE LIVER FAILURE STUDY GROUP MULTICENTER CLINICAL TRIALS OF NOVEL THERAPEUTICS AND DIAGNOSTICS

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health of the Public Health Service (PHS) of the Department of Health and Human Services (DHHS) seeks collaborations with Industry to provide novel therapeutic agents, diagnostic markers and devices for use in NIH-sponsored multi-center clinical trials in patients with acute liver failure.

Introduction:

Acute liver failure (ALF) is a rare condition which impacts more than 2,000 individuals annually in the United States. ALF often affects young people and carries a high morbidity and mortality rate (80%). There is no accepted treatment for this critical illness; in nearly 30% of cases liver transplantation may be performed. Causes of ALF include acetaminophen toxicity, prescription drug idiosyncracy, viral hepatitis and several genetic diseases. Further studies are needed to improve the current understanding of ALF's overall pathogenesis and to develop new therapies for the overall condition of liver failure. Treatments for specific causes of ALF might also lead to improved outcomes for patients with ALF.

The NIDDK funded Acute Liver Failure Study Group (ALFSG) includes 22 clinical centers and a data coordinating center. Among the achievements of the ALFSG is an ongoing registry of more than 1,200 cases of ALF, a large clinical database that includes serum, plasma, urine, DNA and tissue samples. The ALFSG has recently completed a clinical trial using N-acetylcysteine or placebo for the treatment of ALF not caused by acetaminophen; the results are currently being analyzed. New clinical trials would complement the current work of the group and could be used to explore new, targeted therapies and diagnostics for these critically ill patients. For further information concerning the ALF Study Group, visit www.acuteliverfailure.org.

Study Goals:

The ALFSG is interested in conducting clinical trials to significantly improve the outcomes of ALF patients including:

- Use of devices to reduce body temperature to determine whether mild hypothermia can improve the outcome of patients with acetaminophen-induced liver failure, the most common cause of ALF in the United States. Experimental and clinical data support the premise that mild hypothermia may improve outcomes in ALF by preventing cerebral edema and its complications; however controlled trials will be necessary to demonstrate efficacy and to ensure that there are no unrecognized safety issues with these devices.
- Use of recombinant factor VIIa to determine its effects on the severe alterations in clotting observed in patients with ALF.
- Use of nucleoside analogues for patients with severe hepatitis B.
- Other potential trials directed toward new treatments for ALF. For example, inhibitors of apoptosis might have merit in this population where rapid cell death and

failure to regenerate new hepatocytes are defining features. Those seeking initial data or pilot studies as proof of principle will be considered for collaborations.

- The availability of important bio-samples (serum, plasma, urine and DNA as well as detailed de-identified data) offers an opportunity for innovative research into the genetics, pathogenesis or outcomes of this unique and important patient population.

SUPPLEMENTARY INFORMATION: 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. 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.

Capability Statements: The Collaborator Capability Statements received in response to this announcement will be reviewed by a Selection Committee. The 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 ten (10) pages of narrative (not including appendices) and should address all of the following selection criteria:

1. The proposed preparation or device must have been tested in Phase I trials in humans.
2. The statement should provide specific details of the methods to be utilized in the investigation of therapeutic agents including drugs, biologics, and devices in patients with acute liver failure and clearly describe important issues surrounding the evaluation of disease management in these patients.
3. The statement should include a detailed plan demonstrating the ability to provide sufficient quantities of the laboratory test agents or devices in a timely manner for the duration of the study.
4. 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.
5. A description of other core facilities and interactions with core facilities that are needed.
6. A description of the methods that would be used to assure privacy and maintain confidentiality of data.
7. 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 acute liver failure, personnel,

services, facilities, equipment, or other resources that would contribute to the conduct of the commercial development.
8. If appropriate, specific funding commitment to support the advancement of scientific research.
9. Must agree to have their preparation used in the above-mentioned ALFSG-developed protocols which will be conducted by ALFSG and will have data collection and analysis performed by the ALFSG Data Coordinating Center.
10. Must provide IND/IDE sponsor of the ALFSG studies with cross-reference access to a US FDA filing that contains the chemistry, manufacturing and controls information for the drug substance and drug product or device Mater File.
11. Dosing and Pharmacokinetic data from human studies must be provided for novel agents**.**
11**.** Adverse event profile from human studies must be provided.
12. Must agree to share (with ALFSG) all safety data from other studies involving their preparation or device as well as relevant efficacy data from other studies (updated Investigator Brochure, etc).
13. The statement must address willingness to promptly publish research results.

SUBMISSION DATES: Only written capability statements received by the NIDDK on or before September 30, 2007 will be considered.

CONTACT INFORMATION:

Capability Statements should be submitted to:
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A formatted version of the Notice of Opportunity will be posted at:
http://techdev.niddk.nih.gov/ALF-pub.pdf