Scientific investigations of living donor liver transplantation using clinical information and tissue and blood samples from adult liver transplant recipients

Collaboration in scientific investigations of living donor liver transplantation using clinical information and tissue and blood samples from adult liver transplant recipients in the areas of cellular and genetic aspects of liver regeneration; liver function and metabolic mass; markers of liver injury and repair; treatment of hepatitis C; hepatocellular carcinoma (liver cancer); immunosuppression and immune tolerance; drug metabolism; gene expression; psychometric measures of quality of life; electronic media for patient education; and other scientific issues relevant to living donor liver transplantation.

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) to investigate scientific issues in the recently formed Clinical Research Network termed Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL). The core theme of A2ALL is comparison of outcomes of candidates for liver transplant who receive or do not receive Living Donor Transplantation (LDT). See http://www.nih-a2all.org/default.asp for more information and list of participating centers. The potential Collaborator's capability statement should provide proof of expertise in the design and implementation of studies of the relevant area of investigation and should include the scientific rationale for the study proposed, proposed methods, and access to potential therapeutic or diagnostic molecules. Examples of potential studies include:

1) Characterization of changes in liver function, mass, and metabolic capacity during regeneration following liver transplantation. The impact of changing liver function on the immune response as well as its effect on metabolism of immunosuppressants could be investigated using novel biochemical and imaging techniques.
2) Identification of host genetic factors associated with liver regeneration and the syndrome of graft failure due to inadequate liver mass. This will require the identification of genes involved in successful liver regeneration in humans, as well as pathophysiologic events in the failure of grafts.
3) Assessment of the interrelationship of LDT with immunosuppression. Cylosporine, tacrolimus, and other immunosuppressive drugs have been associated with proliferative effects which impact liver regeneration. In addition, changes in liver function affect the pharmacokinetics of most immunosuppression.
4) Exploration of serum markers for liver injury and repair 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.
5) Evaluation of the impact of liver regeneration on the kinetics of viral replication in subjects with hepatitis C, and the impact of interferons and other therapeutic molecules on these phenomena.
6) Prevention of liver injury from recurrence of hepatitis C in LDT recipients by pre- and post-transplant treatment of hepatitis C.
7) Improved staging and treatment of hepatocellular carcinoma
8) Develop gene expression arrays that are diagnostic of liver regeneration and repair 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.
9) Study novel approaches to tolerance induction in a defined cohort of patients being prepared for elective transplantation from living donors.
10) Study the process of informed understanding of living liver donors using electronic media education technology to provide patient information and correlate understanding with outcomes.
11) Development of effective psychometric instruments to evaluate the quality of life effects of living donation in this cohort of patients who will be followed long term.

SUPPLEMENTARY INFORMATION:

- Study Goal: The overall goal of this study is to perform clinical, epidemiological and therapeutic research in patients with LDT using a standardized and coordinated approach to the evaluation and therapy of patients undergoing liver transplantation and to provide sufficient numbers of patients for the research. This will be done by development of a structured, prospective database on patients who are evaluated for LDT and either undergo LDT or instead, for various reasons, receive cadaveric livers or do not undergo transplantation at all. Blood and tissue samples will be collected from all donors and recipients at pre-determined time points.
- Applicants to support this study must include a description of investigators and staff that would facilitate collaboration in multicenter clinical studies of liver transplant patients. Applicants should provide a detailed description of the methods and drugs which might be used. A description of the laboratory tests that are needed including assays to determine levels of target molecules or the genes encoding them 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. If an intervention is proposed, 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's capability statements received in response to this announcement to help in its deliberations. It is the intention of 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:

1. The statement should provide specific details of the methods to be utilized and clearly describe important issues surrounding the proposed tests and technology.
2. The statement should include a detailed plan demonstrating the ability to provide sufficient quantities of the required materials or 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 LDT, 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.

DATES: Only written capability statements received by NIDDK by close of business **July 21, 2003,** will be considered. Applicants meeting the criteria as set forth in this announcement may be invited at the Applicants' own expense to discuss their plans, capabilities, and research findings pertinent to the study at a meeting of the Study's Steering Committee in Washington D.C.

FOR ADDITIONAL INFORMATION AND QUESTIONS: Capability statements should be submitted to Rochelle 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. Scientific inquiries should be directed to James Everhart, M.D., M.P.H. Chief, Epidemiology and Clinical Trials Branch, 2 Democracy Plaza, Room 655 6707 Democracy Boulevard, MSC 5450 BETHESDA MD 20892-5450 (20817 for overnight mail); Phone: (301) 594-8878, fax: (301) 480-8300, email: JE17G@NIH.GOV.