SECTION C - DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

ARTICLE C.1. STATEMENT OF WORK

Independently and not as an agent of the Government, the Contractor shall be required to furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government, as needed to perform the work set forth below:

BACKGROUND INFORMATION

Discovery of disease related genes requires a population of individuals with the genetic variant, as well as a population of control (unaffected) individuals. Thus, a repository of DNA samples, immortalized cell lines, and accompanying clinical and pedigree data is clearly an invaluable resource for the research community studying diseases related to the mission of the NIDDK. This project, which will be referred to herein as "The Genetics Repository", is conceptually related to repositories in existence at other institutes at the NIH. For example, the National Cancer Institute (NCI), National Institute of Mental Health, and National Institute on Drug Abuse all have similar repositories. To date, no such resource has been available to the investigators interested in studying genetics of the many diseases that are the focus of NIDDK research.

The repository will allow storage, maintenance, and quality control, and equitable, ethical distribution of DNA and other resources important to the study of diseases under the mandate of the NIDDK. This will allow sharing of resources, thus encouraging work by a broad group of investigators and, perhaps, increasing the sample size and the resulting power of a study to identify genetic determinants of a disease. It will ensure that research participants will be making a maximal contribution, and decrease duplicative sampling efforts.

Towards the above ends, the objective of this contract will be to establish the NIDDK Genetics Repository, in order to accomplish the following in a highly efficient, rapid, and cost-effective manner:

- Receive blood samples from NIDDK funded grants
- Process these data and materials to create cell lines, and DNA samples; and
- Widely distribute all materials to qualified investigators in the scientific community.

The cell immortalization and other tasks outlined in this statement of work are highly technical, and require extensive experience and expertise. The success rate for cell immortalization is extremely variable. It depends, in large measure, on how well the established methods are implemented. As the entire value of many genetics studies rests on the ability to analyze the DNA of sib-pairs and other relatives, inability to recover DNA from any particular sample may negate the value of multiple samples. Therefore, it is essential that the success rate for establishing cell lines be as close to 100% as possible. The Contractor's project director must have extensive experience in providing these genetics services, including blood cell immortalization and DNA extraction, successfully to a large group of investigators. The Contractor's staff must be highly trained to carry out exacting technical tasks accurately and reproducibly. As all the work is with samples from human subjects, all staff must be familiar with human subjects protections and be sensitive to the bioethical and safety issues involved in handling human biosamples. Finally, the Contractor must have a demonstrable long-term interest in providing these services, to ensure that there is continuity throughout the period of the contract.

There are no grants, cooperative agreements, or contracts currently funded by NIDDK, or by other government agencies, which can perform all of the required work, create all of the required deliverables, and widely distribute biological materials to the scientific community.

Task 1. Establish biospecimen preparation, shipping, receipt, and tracking systems for numerous individual multi-center clinical studies.

a. The Contractor shall work with representatives of studies designated in writing by the Project Officer, with the NIDDK Biosample and Data Repositories to develop appropriate aliquoting, packaging and labeling systems for blood samples.

b. The Contractor shall develop systems to ensure the receipt of approximately 30 mls of whole blood from study subjects.

i. The Contractor shall prepare blood collection kits as needed for shipment to investigators and sites in participating studies designated in writing by the Project Officer.

ii. The Contractor shall develop biosample packaging, marking and shipping systems that are in accordance with Standard Industry Practice, FDA Requirements, approved Standard Operating Procedures, city, state, and/or Federal regulations, and any special instructions given.
iii. The Contractor shall develop notification systems to anticipate shipments and be responsible for recording and monitoring the location of all specimens that are being shipped to minimize delay or loss. The Contractor shall establish procedures for monitoring and maintaining information on the status of specimens upon receipt, including accidental thaws and other adverse conditions, and actions to be taken when such problems occur.
iv. The Contractor shall designate specific individuals, and alternates, to be responsible for after-hours specimen receipt and manipulation.

c. Detailed descriptions of all the systems described in part (b) shall be provided to the Project Officer within 8 weeks of contract award. Revisions specified by the Project Officer will be completed within 2 weeks, and the final version will then be submitted for approval by the Project Officer.

d. The Contractor shall work with the Project Officer and with investigators from studies designated in writing by the Project Officer to modify and adapt these systems to suit the specific needs of individual projects.

Task 2. Maintain the confidentiality of subjects by removing all traditional personal identifiers from samples

a. Traditional personal identifiers that may be utilized to establish the identity of individual subjects (e.g., surname, address, social security number, etc.) shall not be provided nor accepted by the Contractor. Instead, the Contractor shall work with the NIDDK Data Repository and with researchers submitting samples to develop an identifier code for each subject that will link the sample to the clinical and descriptive data associated with the sample. Thus, all data and biological materials received by the Contractor shall be untraceable to their original sources.

b. Neither the investigators receiving samples from the Contractor, nor the Contractor him/herself will use information collected under this contract to establish the identity of a given subject or query the databases and retrieve information for an individual subject whose identity is known from some other source.

c. The Contractor shall assure that all investigators have adequate approval from an Institutional Review Board (IRB), for the collection and use of samples submitted to the analysis facility. The Contractor shall apply to the Office for Human Research Protections (OHRP) at the Department of Health and Human Services for a project assurance number, if such a number has not been assigned to the Contractor. Obtaining a project assurance number represents a binding commitment to minimum standards for the protection of human subjects, which safeguards the rights and welfare of all human research subjects. The Contractor shall submit the relevant documentation showing that a project assurance number has been issued and that submitting investigators have IRB approval to the Project Officer for review and approval before samples are accepted.

d. The Contractor shall obtain blank copies of all the informed consent forms used in the collection of the samples received by the Contractor.

Task 3. Establish one or more subcontracts for timely and cost-effective shipping of biosamples between multiple sites and the repository.

The Contractor shall establish subcontracts with commercial carriers for overnight shipping of biosamples between multiple sites, domestic and international, and the repository in accordance with Standard Industry Practice, FDA Requirements, approved Standard Operating Procedures, city, state, and/or Federal regulations, and any special instructions given. All shipments of blood collecting materials to these projects and blood samples from these projects shall be paid for by the Contractor and charged to the contract.

Task 4. Create and store viable cell lines via Epstein-Barr virus transformation of lymphocytes from blood samples, with a success rate of 97% or greater and expanding the lymphoblastoid cell lines.

a. The Contractor shall process blood drawn from each subject and shall establish high-quality lymphoblastoid cell lines via Epstein-Barr virus transformation of lymphocytes from blood samples, with a success rate of 97% or greater for samples from domestic collection sites. The transformation success rate for samples shipped from international sites shall be 90% or greater.

b. All cell lines shall be free of contamination by bacteria, fungi, mycoplasma, other cells, etc.

c. An aliquot of blood shall be frozen for future verification of sample identity. In addition, live cells from each sample shall be cryopreserved for backup in the event of a transformation failure.

d. In the event of cell transformation failure, where a cell line cannot be established for a subject from a blood sample received (including the use of cryopreserved blood), the Contractor shall

i. Notify the Project Officer within 2 calendar weeks of the determination of failure and the suspected reason for failure.
ii. Notify the submitter within 2 calendar weeks of the determination of failure and the suspected reason for failure.
iii. Request that the submitter obtain additional blood from the subject, with the goal of correcting the reason for failure on re-submission, for up to total of three attempts for a given sample. After three attempts, the sample will be considered unsuitable for transformation and nor further attempts will be made.

e. The lymphoblastoid cell lines shall be expanded for DNA extraction and aliquoted for long-term storage. An aliquot of each stored cell line shall be checked to ensure viability.

f. The Contractor shall process, aliquot and store the cell lines during the time of the contract, and during the transition period after the termination of the contract.

g. The Contractor shall submit, within 8 calendar weeks of award, a detailed protocol of sample processing, lymphocyte transformation, cell line storage, quality control, re-growth, safety, and facilities for this work. The work plan shall document the precise transformation methods that will be employed including the rationale for method selection, reliability, feasibility, and documented evidence that the method has been successful. In addition, the work plan shall describe the actions to be taken to maximize the transformation success rate and to ensure that it is maintained at a minimum of 97% for domestic samples during the performance of the contract. Finally, the work plan shall describe the procedures that will be used to ensure freedom from contamination by bacteria, fungi, mycoplasma, other cells, etc. Revisions specified by the Project Officer will be completed within 2 weeks, and the final version will then be submitted for approval by the Project Officer.

Task 5. Cryopreserve blood cells for eventual transformation and/or DNA extraction

a. Some studies may choose not to establish cell lines immediately for each subject. Instead, for those studies, identified in writing by the Project Officer, the Contractor shall prepare and cryopreserve blood cells from the submitted blood samples. The cryopreservation should be carried out in such a manner as to maximize the potential to immortalize the frozen cells in the future.

b. At the beginning of the designated study, and annually thereafter, the Contractor shall assay 25 cryopreserved samples to determine the transformation success rates. The success rate for transformation of cryopreserved samples shall be greater than 85%. The Project Officer may approve a lower cell line establishment rate if data provided by the Contractor and by an independent laboratory document that underlying medical conditions of subjects or sample shipment conditions preclude the possibility of achieving 85% success in immortalization.

Task 6. Extract and store DNA from cell lines or from isolated blood cells.

a. The Contractor shall extract DNA from lymphoblastoid lines in sufficient quantities for genetic analysis (i.e., at least 1 mg DNA from lymphoblastoid cell lines in 30 microgram aliquots).

b. The Contractor shall aliquot and store the extracted DNA samples during the time of the contract.

c. The contractor shall extract DNA directly from blood samples or ffrozen blood cells, in varying amounts depending on the volume of the starting material. The DNA shall be aliquoted and shall be of high quality, with a 260/280 OD ratio of 1.6-2.0, and high molecular weight, and suitable for molecular genetic analysis.

Task 7. Distribute cell lines and biosamples to investigators submitting blood samples and to other qualified investigators granted access by the PO, including packaging, handling, and coordinating sample shipments to domestic and international sites.

a. In specific studies, as directed in writing by the Project Officer, the Contractor shall return a viable cell line and 30 microgram DNA sample prepared from the whole blood sample, without charge, to sample submitters at regular intervals (e.g. semi-annually) when a sufficient number accumulates or when requested.

b. The Contractor shall have, or shall establish, an Internal Review Board that will approve the overall operation of the repository, including storage and distribution of human biosamples. Having received that approval, the Contractor shall then provide DNA and/or cell lines only to the specific researchers who have been granted access by NIDDK.

c. The Contractor shall charge an access fee and shipping charges per sample. When available, additional details about access will be provided by NIDDK. The Contractor shall establish an appropriate system for the accounting and reporting of fees in accordance with the fee schedule established jointly with NIDDK. The Project Officer retains the right to waive the access charge for a recipient. In these cases, the Contractor shall pay any and all shipping charges. The Contractor shall establish a process, with approval of the Contracting Officer, to ensure that all such fees are promptly collected and accounted for accurately, and offset against contract costs in a proper and timely manner. The Contractor shall not distribute materials before payment in full is received, unless the Project Officer has waived the fees. Payment shall be in the most expeditious format (e.g., check, purchase order) possible. Income received from fees charged for access to cell lines and DNA shall be utilized to offset contract costs. Such income shall be reflected on the Contractor's invoice for the month it is received. (The DNA and cell line charges for NIDDK approved investigators at Rutgers or Robert Wood Johnson School of Medicine is hereby waived).

d. The Contractor shall not use the biosamples for any purpose other than that specified in this contract, without written approval of the PO.

e. Packaging, marking and shipping shall be accomplished in accordance with Standard Industry Practice, FDA Requirements, approved Standard Operating Procedures, city, state, and/or Federal regulations, and any special instructions given. The Contractor shall guarantee that all required materials be delivered in immediate usable and acceptable condition. The Contractor shall be responsible for recording and monitoring the location of all specimens that are being shipped through use of an electronic tracking system of all requests and specimens.

The Contractor is responsible for monitoring and shipping of specimens to minimize delay or loss. The Contractor shall have a procedure for the notification of recipients of anticipated delivery time, and the Contractor shall follow-up with the recipient to ensure that specimens are received at the anticipated delivery time. If a specimen shipment is not received within four hours of expected delivery time, the Contractor shall inform the intended recipient by telephone or electronic mail. The Contractor shall then initiate immediate tracking to locate the delinquent specimen shipment. Upon finding the delinquent specimen shipment, the Contractor shall notify the intended recipient with the location and new expected delivery time.

f. When samples are requested by investigators granted access by the Project Officer, the Contractor shall ship samples within 2 weeks of request for DNA and 3 weeks for cell lines, unless shipment within this window would jeopardize the viability of the sample due to holidays, natural disasters, or other factors.

Task 8. Withdraw and destroy samples from the repository as directed in writing by the Project Officer

During the course of a study, or after a study is concluded, a subject may choose to withdraw from the research project. When notified by an investigator who submitted the sample that the subject (identified by the identifier code) has withdrawn from the study, the Contractor shall request confirmation from the Project Officer. Upon receiving written confirmation, the Contractor shall withdraw and destroy all biosamples, cell lines, DNA, and other materials associated with that subject's identifier code, and record the materials as "withdrawn" in the database.

Task 9. Establish and maintain Quality Assurance (QA) and Quality Control (QC) programs.

a. The Contractor shall develop and implement QA/QC programs covering activities critical for the successful operation of the repositories.The QA/QC programs shall include, but not be limited to:

i. Each protocol used for the processing and storage of biosamples
ii. Mechanical functioning of freezers and other storage equipment, including alarm and back-up systems
iii. Cell immortalization, viability of frozen cells, quality of extracted DNA, preservation of biosamples.

iv. Storage of an aliquot of each sample of whole blood to verify sample identity
v. Monitoring the flow of biosamples into and out of the repository.
vi. Packaging and shipping of materials to domestic and international sites.
vii. Accuracy of data entry and database maintenance in the inventory database, including regular comparisons of shipping and receipt records with the study's data coordinating center

b. The Contractor shall conduct a physical inventory of not less than one-tenth of one (0.1) percent of the repository samples annually. The Project Officer will assist the Contractor in selection of a representative sample to be inventoried. The inventory shall include both samples handled in the previous 12 months and freezer positions that may or may not include samples. As part of the inventory, the Contractor shall assess the viability of randomly selected frozen cell lines and the quality of randomly selected DNA samples.

The Contractor shall submit, within 8 calendar weeks of award, a detailed protocol for QA/QC. Revisions specified by the Project Officer will be completed within 2 weeks, and the final version will then be submitted for approval by the Project Officer.

Task 10. Provide security and back-up systems and a plan for disaster recovery.

a. The Repository shall have an adequate number of empty, functional storage units, constantly running, to serve as back-up units in the event of freezer failures. The back-up units shall be appropriate to the sample inventories at respective temperatures, including mechanical and liquid nitrogen freezers.

b. The Repository shall store aliquots of each cell line and extracted DNA sample in a back-up facility located at a second site, so that there is independent back-up storage of each and every sample in case of catastrophic loss.

c. The Contractor shall ensure that the repository is equipped with fire, smoke, and mechanical failure alarms, and appropriate fire control equipment. The Contractor shall ensure that key repository personnel can be contacted at any time in case of fire, mechanical failure of one or more freezers, or other emergency.

d. The Contractor shall ensure that the repositories have emergency back-up generators with the capabilities of handling the complete power supply, notably all freezers and facility HVAC, in the case of electrical power failure, except as noted below. The Contractor shall ensure that at a minimum, 72 hours of fuel is available for the generator(s). The Contractor shall conduct biweekly tests of the generators to ensure proper operation.

e. The Contractor shall establish systems to ensure data security and to prevent loss of inventory data in case of physical damage or equipment failure.

f. The Contractor shall submit, within 8 calendar weeks of award, a detailed protocol for recovery of stored materials and data following a natural or man-made disaster. Revisions specified by the Project Officer will be completed within 2 weeks, and the final version will then be submitted for approval by the Project Officer.

Task 11. Maintain high quality, secure information systems to allow detailed tracking of sample receipt, processing, storage and distribution, rapid retrieval of samples, storage of QA/QC information associated with the sample, and listing of investigators using the repository.

a. The Contractor shall maintain accurate databases that are regularly updated and verified. The databases shall allow real-time tracking of samples as they are received, processed, stored and distributed. In addition, the databases should include location information to allow rapid, efficient retrieval of samples.

b. The Contractor shall maintain a database of information about qualified investigators using the repository who submit and/or receive data and biological materials. The database shall minimally include for each investigator the following information:
    a. Name of the principal investigator
    b. Title of the research project
    c. NIH grant, contract, or cooperative agreement # of project
    d. Administrative official mailing address, telephone number, fax number, e-mail address, and recipient

institution.

e. Samples submitted
    i. Date of submission
    ii. Sample Id
f. Samples withdrawn
    i. Dates of withdrawal
    ii. Charges and date fees paid
    iii. Ids of samples withdrawn

This database shall be continuously updated with information including, but not limited to, subsequent shipments of cell lines and/or DNA as authorized by the Project Officer.

c. This database shall also include creation and maintenance of an e-mail list of all qualified investigators, to enable rapid and efficient electronic communication among the investigators, the Contractor, and the Project Officer.

d. The databases shall be organized to permit rapid and efficient downloading and uploading of information, and shall be designed to facilitate transfer of information with researchers submitting samples, and with the NIDDK Data and Biosample Repositories,. The Contractor shall assure that ASCII files and other formats (e.g., SAS system files) can be rapidly and efficiently generated from all databases. The Contractor shall maintain a daily backup of all electronic databases to protect against the accidental data loss. In addition, the Contractor shall ensure that the information systems include standard security measures, and that new security measures are implemented as they become available.

e. The Contractor shall submit, within 8 calendar weeks of award, a detailed description of the proposed information systems, including a description of security and back-up provisions. Revisions specified by the Project Officer will be completed within 2 weeks, and the final version will then be submitted for approval by the Project Officer.

Task 12. Work in a cooperative fashion with the Project Officer, the External Advisory Committee, and the Steering Committee.

a. The Contractor shall cooperate with the Project Officer, the External Advisory Committee, and with Contractors and their representatives from the NIDDK Data and Biosample Repositories, through participation in the Steering Committee and through other activities. This includes, but is not limited to, cooperation in developing a sample labeling system, methods for cross-referencing, and database integration. In addition, the Contractor shall facilitate site visits by the Project Officer, the Steering Committee, and other groups, as directed in writing by the Project Officer.

b. The Contractor shall also assist the NIDDK Data Repository in developing a public website that includes data regarding the Genetics Repository's inventory, policy, forms, procedure, and other information. The Contractor shall maintain a list of publications of researchers who received samples from the Genetics Repository, in which the publications has resulted from the use of those samples, and provide these to the NIDDK Data Repository for inclusion on the website. The Contractor shall also search relevant scientific literature databases, including those maintained by the National Library of Medicine, to identify publications that used samples supplied by the NIDDK Genetics Repository. Electronic literature searches shall be carried out at least every 3 months