Development of a Pediatric Tissue Bank at the Children’s Hospital and Research Center at Oakland

**Aim:** To develop a comprehensive resource that will procure, characterize, preserve and distribute high quality pediatric human tissue specimens from a wide variety of organ sites to CHRCO biomedical researchers. In addition to normal, benign and malignant tissues, tissues from patients with specific diseases may also be a component of the tissue bank. Trained personnel will coordinate the retrieval, preservation and delivery of specimens obtained from surgical resections and from autopsies.

**Purpose and Value to CHRCO:** Tissues from the Tissue Bank are expected to be utilized in a wide variety of research projects that may improve upon existing knowledge regarding the pathology, genetics, and treatment of pediatric malignancies and other pediatric diseases. Research enabled by the Tissue Bank is likely to contribute to discoveries of the role of genetic alterations in cancer initiation, progression and metastasis and may lead to improvements in the diagnosis and classification of tumors. Tissue Bank specimens may also be critical to determining the relevance to humans of findings from research using animals and cell lines. The Tissue Bank may provide specimens needed for the development of emerging technologies and the application of these technologies to study problems in cancer biology, and to develop markers for diagnosis, prognosis and prediction of response to therapy.

Examples of the types of research projects supported could include:

1) Development of mouse/human chimeric and xenotransplant models for cancer research
2) Studies of carcinogen activation, DNA adduct formation and detoxification in human tissue, organ specificity and inter-individual susceptibility
3) Studies to examine pharmacologic effects of chemotherapeutic drugs in human systems
4) Studies addressing drug transport and delivery
5) Identification of mutations of protooncogenes in pediatric tumors
6) Development of monoclonal antibodies and cell lines
7) Characterization of epigenetic lesions as non-random and tumor specific type events
8) Studies of gene expression profiles and studies to determine their clinical usefulness
9) Identification of novel diagnostic molecular markers via genome wide expression tools
10) Methylation microarray analysis of cancers

Insights and advances from this research are expected to generate publications in high quality peer reviewed journals, funding from external granting agencies, and pilot data sufficient to facilitate researcher access to nation-wide pediatric tumor banks, such as that maintained by the Children’s Oncology Group.

Importantly, the Tissue Bank will provide a critical resource to facilitate translational research in pediatric malignancies and other diseases. This resource is likely to be highly utilized by numerous groups within the medical and research communities, especially those in which the development of translational research projects and/or training programs in translational research areas has become a major goal. Such groups include the Neuro-oncology Center and the newly established Cancer Working Group, both of which are actively moving towards active and robust collaborations between basic science and clinical medicine within the institution.
Tissue Procurement and Storage:

Consent for Tissue Donation for Medical Research: The Tissue Bank coordinating committee has developed an appropriate Informed Consent form and associated literature describing the process of tissue donation for research. The Consent form has been reviewed and approved by CHO Legal Counsel. Tumor procurement will not be initiated until IRB approval for collecting human tissues using this Consent form has been approved. Patient confidentiality must be preserved. All tissue must be given a research code, and no patient identifiers may be used without IRB approval. No patient contact may be performed without explicit patient consent. All investigators must have received Human Subjects Protection Training, as currently required by NIH. See http://www.ucsf.edu/ora/chr/nih-list.htm for instructions and requirements. Investigators may fulfill this requirement through online training, special workshops, review of specific books and manuals, or review of the NIH videotape. The investigator of a project is responsible for ensuring that all investigators are knowledgeable and informed about these rules.

Specimen Procurement
Tissues will be transferred from the operating room to the surgical pathologist who will determine whether any tissue is available for submission to the tissue bank. The diagnostic process cannot be compromised. No tissue will be submitted to the research tissue bank until the pathologist determines that adequate tissue for all diagnostic studies has been secured. No tissue can be taken if it compromises the patient’s care. If necessary, remnant tissue stored in the Tissue Bank must be made available to Pathology for diagnostic purposes. Tissues determined by the pathologist to be remnant tissues may be processed according to several established protocols. Tissues may be snap-frozen, followed by storage at ultra-low temperatures in liquid nitrogen tanks. Intact cells may be obtained by touch preparations. For research involving substances stable after fixation, fixed or paraffin-embedded processed tissues may be provided. Fresh tissues obtained either from surgery or from autopsy may be required in a range of studies including the establishment of viable tissue cultures and cell lines.

Data Management
A dedicated inventory and data management software system (Freezerworks Unlimited by Datworks Development, Inc. Mountlake Terrace, WA) has been selected that meets all regulatory requirements, including 21 CFR Part 11, and provides a robust audit trail. This system allows us to meet the following objectives for all samples:
1. All samples and sub-samples will have a unique identifier
2. The system will adhere to a standard coding mechanism
3. The system will maintain an up-to-date inventory by unique identifier to include: original and current quantity, where specimens have been sent, when (if) they have been returned, and when they have been exhausted. The system will also be able to invalidate samples.
4. The data base containing information on sample locations (inventory) will reside at the bank and will not be accessible by systems outside the bank.
5. The system will be able to flag (reserve) specimens for a particular study.
6. The system will be able to track the type of informed consent for research that is allowed.
7. The system will track specimens and allow for withdrawal of consent.
8. The system will provide quality control/checks on imported data.
9. The system protects samples and data from unauthorized access with security levels that either permit or restrict access at department and individual level.
Operational Personnel: The experience of personnel from all divisions of CHRCO will be utilized in a Coordinating Committee that formulates policies for the operation of the Tissue Bank. These members currently include Dr. Jonathan Rowland, Dr. Peter Sun, Dr. James Feusner, Dr. Julie Saba, Dr. Joanna Lee. The coordinating committee will meet monthly during the initiation phase to develop operating policies. The committee will meet periodically thereafter to assess the operation of the Tissue Bank and to change or modify operating policies. Partial FTE support will be required to provide personnel to support the operation of the tissue bank. A pathology assistant (0.25 FTE) will be utilized to help process tissues, document tissue obtained and details of processing, proper storage and retrieval of these tissues, and maintenance of the tissue bank freezers, storage areas, and supplies. A data manager/coordinator (0.25 FTE) will maintain databases of patients who have consented to tissue collection, approved requests for tissue from the bank, tissue bank inventory, disbursement of tissues to investigators and documentation of appropriate use of provided tissues. The data manager will also assist investigators with developing budget requests for grant applications using tissue bank resources. (For banking, tissue release and database management, a partial FTE to cover the time and effort for a pathology technician under Dr. Rowland’s supervision will be required. For review of specimen characteristics, a partial FTE for Dr. Rowland will be required).

Supplies and Equipment: The initial phases of the tissue bank will require a liquid nitrogen freezer and a –80 degree C freezer, insulated thermos for transportation of liquid nitrogen, insulated gloves and tongs. Consumable supplies will include liquid nitrogen, dry ice, isopentane, OCT, storage containers, transport media and fixatives, slides and labels. Software for database management and barcode printers and readers will also be needed for management of the bank. During the initial startup period, space is available in a liquid nitrogen freezer already purchased by the Department of Pathology and Laboratory Medicine. This is expected to be adequate for the first year of operation but an additional freezer will be required by year two of operation. –80 degree C freezer space is already quite limited and a new freezer will be required during year one.

Specimen Distribution: Investigators who wish to gain access to materials available in the Tissue Bank must submit a Request for Tissues Form. The Tissue Bank requires researchers to agree to obtain Institutional Review Board (IRB) approval before receiving specimens for their research. Documentation of both IRB and IBC approvals for the use of human tissues in research are required before requests are reviewed. All new projects require a new application for tissue and a new IRB approval for the study. Patient identity or other identifying information cannot be provided to investigators. This ensures complete confidentiality regarding medical information of patients. Requests for tissue will be reviewed by a Tissue Bank Scientific Review Board. Tissues will be distributed with the first priority assigned to CHRCO investigators undertaking peer reviewed funded research projects, second priority to CHRCO investigators with pilot projects, and third priority to non-CHRCO investigators in academic centers or non-profit research institutions and who are currently collaborating with a CHRCO investigator. Requests from investigators in other academic centers or non-profit research institutions will be considered on a case by case basis. This Board will make every effort to ensure that there is an equitable distribution of tissue to CHRCO investigators. Investigators are obligated to acknowledge the Tissue Bank in any publications that result from their use of specimens received. Recommended wording to the methods or acknowledgement section is as follows: Tissue samples were provided by the Pediatric Tissue Bank of the Children’s Hospital and Research Center at Oakland.
Policies and Procedures for the Scientific Review Board:

1. The Scientific Review Board will consist of members from the CHORI Scientific Advisory Committee and/or Clinical Scientists from CHRCO, Chair of the Department of Pathology, Director of CHRCO Oncology Program, a statistician/epidemiologist, and an IRB representative. Members will serve for two years and may be reappointed. Current board members include Jonathan Rowland, Julie Saba, James Feusner, Bertram Lubin, Mark Hudes, and John Waterson.

2. New members of the Review Board will be elected by a majority of the committee members and will be formally approved by the Chief Executive Officer of CHRCO.

3. Meetings will be held on an ad hoc basis until requests are frequent enough to warrant meetings on a quarterly basis.

4. Requests for materials from the Tissue Bank will require submission of a formal proposal including the following information:
   a. Title of Proposal
   b. Principal Investigator’s name, address, phone number, email
   c. Abstract, Hypothesis, Specific Aims, Background and Preliminary Results
   d. Indication of whether the study is linked to a clinical trial, how it may promote future clinical studies, or whether the study is exploratory in nature
   e. Statistical analysis and justification of sample number
   f. Funding for project
   g. NIH biosketch of relevant Investigators including Other Support
   h. Full IRB protocol and documentation of approval by Investigator’s IRB
   i. Required samples including diagnosis, number of samples needed, form of storage, acceptable specimen parameters (time to freeze-down, % tumor, % necrosis, amount tissue, normal adjacent tissue), patient information required (i.e. age, ethnicity, diagnosis, disease stage, prior chemotherapy or radiation)
   j. Agreement to provide Investigator Feedback and to acknowledge Tissue Bank in publications resulting from studies employing materials from the Tissue Bank.

5. Requests for tissues from the Tissue Bank will be evaluated on the basis of the following criteria:
   a. Scientific merit of the proposal
      1. Proven investigator experience with the method proposed.
      2. Standardized, validated research biomarker assay methodology
      3. Research plan appropriate to answer the study question
      4. Statistical evaluation which shows that the study question can be addressed with the samples available.
      5. Investigator has defined a study interval and will provide information about the project outcome at the end of that period.
   b. Feasibility of the proposed studies
   c. Demonstrated necessity for human tissues
   d. Studies linked to clinical trials will be given highest priority
   e. Availability and rarity of tissue type requested
   f. Amount and number of tissues requested
   g. Form of tissue requested (frozen versus fixed tissues)
   h. Requesting Investigator affiliation (CHRCO investigator, CHRCO collaborator, non-CHRCO affiliated investigator)
   i. Investigator has defined funding and agrees to compensate tissue bank for specimen preparation and shipping.
   j. Documentation of IRB approved protocol for proposed research
k. Investigator agreement covering confidentiality, use, disposition, and security of specimens and associated data.
l. Investigator’s written agreement in a Material Transfer Agreement covering publication and sharing of research results, and ownership of future intellectual property.

6. Under no circumstances will tissues be distributed to investigators who do not provide documentation of current IRB approval for the proposed research.

**Implementation and Monitoring:** A tissue bank working group has been formed. The tissue bank has been designed to comply with guidelines developed by the National Cancer Institute (First-Generation Guidelines for NCI-Supported Biorepositories, National Cancer Institute, National Institutes of Health, 12/05/05)

**Time Line** - Our goals for the first six months will be to:

1) Develop a three year plan for development and implementation of the tissue bank.
2) Develop procedures to ensure compliance with all state and federal regulatory requirements pertaining to a Research Tissue Bank.
3) Develop appropriate consent forms and processes.
4) Identify space and equipment for start-up phase.
5) Establish a Quality Assurance Program (which addresses data management, quality control, document control, and tracking of anonymized samples).
6) Identify and train personnel.
7) Establish policy regarding appropriate triage between diagnostic pathology (which takes priority), COG, and Tissue Bank.
8) Determine logistics for tissue banking during and after routine business hours.
9) Establish a Tissue Bank Scientific Review Board.
10) Obtain IRB approval for the Tissue Bank project.

During the second six months and beyond, the Tissue Bank will begin acquiring specimens. It is expected that tissue acquisition will begin slowly and increase over time until it becomes routine practice for all involved. Availability of resources from the Tissue Bank will be advertised to all CHRCO investigators through a variety of means, including the Medical Director’s Letter, the Cancer Center meetings and website, the CHORI Scientific Advisory Committee meetings, electronic mailings, and other venues. Distribution phase will begin as soon as investigators begin to request Tissue Bank resources.