

**Saturday, October 20, 2007**

## **Development of a National Canine Cancer Biospecimen Repository: The Canine Comparative Oncology and Genomics Consortium**

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### **I. CCOGC Background**

In June of 2004, an informal collaboration of veterinary and medical oncologists, pathologists, surgeons, geneticists, and molecular and cellular biologists emerged at a meeting hosted by the Broad Institute, in Boston, MA. These investigators shared a common interest, the comparative study of canine and human genomics and cancer. With the imminent availability of a high quality canine genome assembly, they sought to leverage opportunities that would result from a better defined understanding of the genetics and biology of cancers in companion animals, to provide a forum for discussion and sharing of resources and reagents, and to guide the development of novel technologies that would allow the study and use of appropriate canine cancers in the global study of cancer biology and therapy. Over the ensuing months this collaboration named itself the Canine Comparative Oncology and Genomics Consortium (CCOGC) and began drafting an agenda and list of priorities. In 2007 the CCOGC incorporated as a Not-For-Profit and obtained 501(c)3 status. The goals of the CCOGC are to facilitate strategic partnerships and collaborations across a diversity of disciplines, focused on the problem of cancer in dogs. Early priorities of the CCOGC include advocacy for the field of Comparative Oncology, the development of a mechanism to share reagents and resources in the community, and the development of a biospecimen repository.

### **II. Biospecimen Repository**

CCOGC collaborators determined that an essential resource needed in the field was the development of well-described repository of tissues (tumor and normal) from tumor bearing dogs. To be optimally useful this biospecimen repository would be:

- Focused on specific cancers of interest to the field
- Centrally housed with multiple contributors
- Populated with prospectively collected tissues and fluids
- Annotated with robust parallel clinical data-base
- Managed through a web-enabled entry and retrieval port
- Publicly accessible based on scientific merit or requesting individuals

Based on this the repository has begun with a goal of collecting tissues and fluids from 3,000 dogs with specific cancer types over a three-year period. The specific cancers will represent those that are not only major problems in the dog population, but which also have comparative value in human cancer investigation. Universal and cancer specific standard operative procedures have been defined for the collections. The bank is housed centrally within a contract biospecimen repository in Frederick Maryland with contributors including qualified schools of veterinary medicine in the United States. A caBIG (<https://cabig.nci.nih.gov/>) compliant web-based relational data-base has been implemented to track sample shipment, to describe sample characteristics and clinical annotation of patients, and to allow review of bank assets.

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### **III. Biospecimen Repository Operating Model and Funding**

The operating model developed for the CCOGC Biospecimen Repository was based on a population phase that would require \$2.2 million of start up funds, sufficient for the collection of 3000 patient samples at 10 institutional collection centers in the United States. Upon population, requests for use of tissues would be reviewed and granted to individuals and institutions based on scientific review. In an effort to repopulate the repository, the CCOGC has designed a perpetual support model for the bank. Using a nominal fee cost structure, differentially applied to not-for-profit (NFP) and for profit requests the CCOGC Biospecimen Repository will generate income sufficient to maintain the tissue resource that will be depleted through sample use and sustain the administrative activities of the CCOGC (Figure 1 - omitted). A final component of the operating model would be to use the repository collection infrastructure service contract requests for prospective collection of samples (Figure 2 - omitted). Agreements have been drafted to define ownership of material and intellectual property emerging from requests made to the 3000 patient bank and for prospective collection contracts.

In 2006, the CCOGC entered into a strategic partnership with Morris Animal Foundation (MAF) and the AKC Canine Health Foundation (CHF) to see the funding needed to establish the tissue bank. This partnership resulted in the boards of the CHF and MAF approving funding to the CCOGC of \$250,000 each and a further commitment to assist in seeking the remaining \$1,700,000. With \$500,000 in initial funding, the CCOGC released a request for proposals from US institutions that wished to be considered as CCOGC collection sites. In the summer of 2007, Pfizer Animal Health provided a lead gift in the amount of \$1,100,000 through a working relationship with the MAF. In recognition of the importance of this gift, the formal name was changed to "Pfizer-CCOGC Biospecimen Repository".

### **Biospecimen Repository Physical Structure and Procedures**

The Pfizer-CCOGC Biospecimen Repository has received support from the intramural National Cancer Institute to establish and maintain a physical bank in Frederick Maryland and to have this bank linked to a web-enabled interface for access to tissues. The physical bank is managed by Fisher Bioservices and is part of the NCI Frederick Central Repository Services. The facility is over 33,000 sq ft, has 24-hour temperature monitoring, four 250KW generators, and back-up generators (Figure 3) The bank consists of -80C freezers, chemical storage for formalin fixed and paraffin embedded tissues, bar coding hard and soft ware and web enabled sample management system. The bioinformatics platform for the repository includes a relational database that will connect clinical information on samples entered to the study with a front and back end retrieval system. Biological data derived from samples in the Biospecimen Repository are uploaded into the bioinformatics database and become part of the progressive value of the Repository. It is expected that the value of this biological data will exceed the physical value of tissues over time.

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**Figure 3. Pfizer-CCOGC Biospecimen Repository housed at NCI Frederick Central Repository.**

The biospecimen repository houses tumor tissue, normal tissues, serum, plasma, peripheral blood mononuclear cell preparations, genomic DNA, RNA and urine samples. Each of the 3000 cases will have tumor and normal tissue collected and processed in both ethanol and two frozen formats (both flash frozen and OCT embedded). Whole blood is collected and divided between DNA and RNA PAX-gene™ collection tubes. Approximately 5 to 6 ml of serum and plasma will be processed in addition to 3 ml of urine. The repository follows many parts of the organization and structure of the proposed National Biospecimen Network Blueprint<sup>1</sup>. Standard operating procedures of tissue/sample collection have been established and are subject to annual review.

Standard operating practices (SOP) for collection of a diverse set of disease and normal tissues from each canine patient have been developed as part of the Biospecimen Repository SOP. When developing the SOP, the CCOGC Bank Committee referenced the National Biospecimen Network Blueprint<sup>1</sup>, the American College of Surgeons Oncology Group SOP<sup>2</sup> and the IUPUI/ Clarian SOP<sup>3</sup>. The SOP describes the procedures for tissue and sample collection to be used at defined CCOGC Collection Sites. The procedures described in the SOP cover universal aspects of sample acquisition, preparation, and shipping to the CCOGC Biospecimen Repository. The Universal SOP focuses on the collection of whole blood, serum, plasma and urine. Each histology of interest has a separate SOP that is an appendix to the Universal SOP. The appendices outline the collection of normal and tumor tissue relevant to each histology. All prospective collections will be added as an appendix to the SOP.

Sample quality and assurance will be reviewed and recorded contemporaneous with sample collections.

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**Pfizer CCOGC Biospecimen Repository Tissues**

It was decided that the specific cancers to be selected should represent those that were not only major problems in the dog population, but which also have significant comparative value in human cancer investigation. Accordingly cancer specific goals included the collection of 600 samples each from dogs with lymphoma, osteosarcoma and melanoma. Samples collected from each patient will include tumor, normal tissue, blood, and urine. An additional 1,200 samples would represent four other histologies (300 each), selected in consultation with the broader community and sponsoring agencies. These additional cancer histologies will be selected during 2007.

**Comparative Pathology Review**

For each cancer histology identified for collection a web-based and digital pathology review will be organized. The goal of this pathology review will be to validate the diagnosis of submitted tissues and to provide a forum for comparative assessment of canine and human cancers. The pathology reviews are being organized by Mark Simpson, DVM, PhD, ACVP. These reviews will involve highly regarded veterinary and human pathologists and will yield position papers on the pathological description and comparative description of cancers by histology.

**Access to Tissues**

Once the repository has been populated with the initial 3000 samples, access will be granted to the bank. Rules for governing the access to the CCOGC Biospecimen Repository have been established. The CCOGC will solicit proposals annually. The Biospecimen Repository Committee (BRC) will perform review of these proposals and will consider several factors including the attainability of the proposed objectives, scientific merit, adequacy of experimental design, and the ability to support further definitive studies. Principle investigators of approved projects will provide updates to the BRC every six months to ensure that satisfactory progress is being made.

**Progress**

Collection Site Selection. The Pfizer CCOGC Biospecimen Repository has initiated collection of tissues at three institutions (Colorado State University, Ohio State University and the University of Wisconsin-Madison). Institutional sites were selected by competitive review of applications responding to a CCOGC RFP. Sites were selected based on case-load, experience with sample collection, personnel and physical infrastructure, and institutional commitment to the banking effort. A second RFP has been recently distributed to all US Colleges of Veterinary Medicine that seeks to identify up to seven additional collection sites that will work towards the initial 3000 patient collection goals for the repository.

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Sample accrual. As of August 1st, active collection sites have collected tissues from 37 cases. This rate of patient accrual has exceeded our goal of collecting 25 patients in the first six months of collection. (Figure 4 – omitted.)

### **Resources and References**

1. National Biospecimen Network Blueprint. Stern, Susan et al. 2003
2. American College of Surgeons Oncology Group. Standard Operating Procedure. SOP ID: SpecBank. 2003
3. IUPUI/Clarian SOP for Collection, Storage And/or Use of Biological Specimens

### **Biographical Profile**

Dr. Matthew Breen completed his PhD in cytogenetics in 1990 and then spent two years as a Post Doc in Molecular Genetics at the UK Medical Research Council's Human Genetics Unit in Edinburgh, Scotland, where he was responsible for developing novel ways to map genes to chromosomes as part of the Human Genome Project. Dr. Breen then spent four years working for the research arm of the Australian Thoroughbred industry, returning to the UK in 1996 where his laboratory developed molecular cytogenetics reagents, resources and techniques for application to canine genome mapping, comparative cytogenetics and cancer studies. In 2002 Dr. Breen relocated his laboratory to North Carolina State University's College of Veterinary Medicine, where he is Professor of Genomics and also a member of the Center for Comparative Medicine and Translational Research (CCMTR). He also serves as Director of the CCMTR's Clinical Genomics Resources Laboratory.

Dr. Breen's major research interests continue to focus on the genomics, genome mapping and the comparative aspects of canine cancer. Dr. Breen played a key role in the mapping of the canine genome and now used his skills and resources to focus on the molecular cytogenetic evaluation of canine tumors as a means to discover the genes involved in the initiation and progression of cancers. Dr. Breen's lab is the recipient of numerous grants from a variety of agencies including the AKC-Canine Health Foundation, Morris Animal Foundation, National Canine Cancer foundation and the National institutes of Health.

In addition to his activities at NCSU, Dr. Breen was a founder member and now serves on the Board of Directors of the Canine Comparative Oncology and Genomics Consortium Inc. The CCOGC is a national organization that serves to gather tumor tissues that may be used for the advancement of canine (and human) cancer research. He also serves on the Scientific Advisory Board of the Morris Animal Foundation and the National Canine Cancer Foundation.

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*2254B: Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma*

*249: Genomics of Canine Brain Neoplasia*

*2667: Cellular Genomics - Molecular Cytogenetic Investigation of Canine Soft Tissue Sarcomas*

*403: Application of the 7.5X Canine Genome Assembly to Generate a 1 Mb Cytogenetic BAC-Map of the Canine Genome*

*613: The Prognostic Significance of Chromosome Aneuploidy in Canine Lymphoma*

*615B: Heritable and Sporadic Genetic Lesions in Canine Lymphoma*

*760: Cellular Genomics - Molecular Cytogenetic Investigation of Canine Soft Tissue Sarcomas*

*947A: Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma*