GRANT PROGRESS REPORT REVIEW

Grant: 00947B: *Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma*

Principal Investigator: Dr. Jaime F Modiano, VMD PhD

Research Institution: University of Minnesota

Grant Amount: $184,443.00

Start Date: 7/1/2008 **End Date:** 12/31/2010

Progress Report: 24 month

Report Due: 6/30/2010 **Report Received:** 7/1/2010

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office.)

Original Project Description:
Background: Certain dog breeds are prone to develop certain types of cancer. Yet, there has been little progress to define the genes that account for this risk.

Objective: For this project, the researchers' goal is to identify genetic abnormalities that are shared by bone tumors and segregate with risk in two dog breeds (Rottweilers and Golden Retrievers) where the disease is prevalent. In collaboration with their colleagues at the University of Michigan and the Broad Institute, they have identified preliminary regions of the genome that may influence risk in Rottweilers. The work described here represents a next step to pinpoint specific genes that are associated with breed-dependent risk, and to predict how heritable factors influence bone cancer in Rottweilers, Golden Retrievers, and other dogs.

Original Grant Objectives:
Objective 1: Test the hypothesis that deletion of WT1 and PTEN occur significantly more frequently in Rottweilers than in Golden Retrievers and will investigate these key aberrations and their clinical significance in other breeds comprising our sample population.

Objective 2: Test the hypothesis that, in addition to DNA copy number changes, there are tumor and breed specific gene expression signatures that will allow stratification of samples into pathogenetically significant groups.

Objective 3: Refine tumor and breed-specific gene expression signatures using custom targeted arrays to identify the minimum number of genes that i) have predictive and prognostic value, and ii) will begin to pinpoint pathways defining breed specific risk.

Publications:

Thomas R, Wang HJ, Tsai P-C, Langford C, Fosmire SP, Jubala CM, Getzy DM, Cutter GR, Modiano JF, Breen M. (2009). Influence of genetic background on tumor karyotypes: evidence for breed-associated cytogenetic aberrations in canine appendicular osteosarcoma. Chromosome Res, 17(3):365-377

Scott M, Gavin K, Sarver A, Vijjeswarapu M, Getzy DM, Newman RA, Cutter GR, Hunter LE, Kisseberth WC, Breen M, Modiano JF. Outcome-associated molecular signatures in osteosarcoma. Manuscript in preparation.

Thayanithy V, Sarver A, Kartha R, Scott M, Park CW, Young A, Breen M, Steer C, Modiano JF, Subramanian S. Perturbation in 14q32 miRNAs-MYC-miR-17-92 gene network contributes to osteosarcoma and is associated with outcome

Report to Grant Sponsor from Investigator:

Osteosarcoma is a common and deadly disease that occurs in most large and giant breed dogs, although some risk factors appear to be independent of size or body mass. There are currently no predictors for response to therapy or outcome. The use of robust array technology and bioinformatics has allowed us to re-enforce the concept that a dogs' genetic background (defined by breed) modulates the characteristics of the tumor, including both karyotype and gene expression profiles. These profiles are a first step in identifying potential risk factors that may underlie breed predisposition, and have generated results that may be useful to develop a predictive signature that can be used in the decision-making process regarding treatment decisions. The data also have been applied to comparative analyses of human osteosarcomas, confirming the supposition that canine osteosarcoma and human osteosarcoma share significant biological properties, and lessons from one disease can be extrapolated to the other.