GRANT PROGRESS REPORT REVIEW

Grant: 01147: *Identifying Mutations in Genes Associated with Canine Hemangiosarcoma*

Principal Investigator: Dr. Chieko Azuma, DVM PhD

Research Institution: Tufts University

Grant Amount: $75,000.00

Start Date: 1/1/2009 **End Date:** 6/30/2010

Progress Report: 18 month

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

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: Hemangiosarcoma (HSA), a malignant tumor of blood vessels, is a significant health concern in dogs, with a reported incidence of up to 2% of all tumors. HSA can affect all dogs, but a particularly high disease incidence has been reported in certain breeds, such as golden retriever (15%), German shepherd (10%), and Labrador retriever. The higher incidence in these particular breeds suggests that genetic risk factors exist. The researchers have identified seven regions in the canine genome associated with HSA in golden retrievers using a newly developed powerful analytical method in order to search for small differences in the patterns of DNA. Subsequently, DNA patterns have been compared with five other breeds and all risk factors appear to be shared with at least one other breed.

Objective: The researchers aim to identify the actual mutations and to then survey multiple breeds to see if they share the same mutations. They also aim to perform tumor appearance studies to confirm if the amount of product from genes near to the mutations is altered. Once the mutations have been identified and their presence in different breeds assessed, it will be possible to rapidly develop genetic tests for carriers of HSA. Ultimately, understanding of the disease biology will lead to prevention and better treatment of HSA.

Original Grant Objectives:

Objective 1: Collect genomic DNA samples from healthy and hemangiosarcoma-affected dogs of many breeds.

Objective 2: Identify specific mutations in the seven candidate regions associated with hemangiosarcoma.

Objective 3: Describe the frequency of these mutations in other breeds.

Objective 4: Perform RT-PCR on candidate genes to assess expression differences.

Publications:
6/30/10 - None at this time

Report to Grant Sponsor from Investigator:
Hemangiosarcoma (HSA), a malignant tumor of blood vessels, is a significant health concern in dogs, with a reported incidence of up to 2% of all tumors. HSA can affect all dogs, but a particularly high disease incidence has been reported in certain breeds, such as Golden Retriever (15%), German Shepherd Dog (10%), and Labrador Retriever, suggesting that genetic risk factors exist. We have identified six regions in the canine genome that differ in golden retrievers with and without HSA and verified the findings with more advanced technology in this project. We are currently identifying the actual mutations. So far no mutations in candidate genes have been found, supporting the major role of regulatory mutations.

Once the mutation has been found, it will be possible to rapidly develop genetic tests for risk assessment for susceptibility of HSA. Interpretation of these DNA tests will require the consideration of markers for all genes simultaneously as well as assessing risks for different types of cancer. The presence of multiple interacting genes, some at high frequency in the population, will make it difficult to reduce the disease frequency quickly, but should still allow for informed breeding. In addition, by examining the frequency of these mutations in other breeds we can determine which other breeds need to be screened for these mutations and to what degree they contribute to the risk of HSA in specific breeds. Still, perhaps the most significant outcome of knowing the actual mutations is that it might suggest which dogs should be under surveillance or preventive care.

The identification of actual mutations should also lead to further study of functional effects of the causative mutations thereby increasing the understanding of the disease mechanism. A better molecular understanding will suggest novel treatment options and possible new drug targets. Due to aggressive nature, HSA is uniquely qualified for studying local invasion, angiogenesis and metastasis, and developing therapeutic intervention in dogs and humans.