GRANT PROGRESS REPORT REVIEW

Grant: 00615B: *Heritable and Sporadic Genetic Lesions in Canine Lymphoma*

Principal Investigator: Dr. Matthew Breen, PhD

Research Institution: North Carolina State University

Grant Amount: $149,369.00

Start Date: 8/1/2008 **End Date:** 7/31/2011

Progress Report: 24 month

Report Due: 7/31/2010 **Report Received:** 9/10/2010

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. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:

Background: Certain dog breeds are prone to develop certain types of cancer. Between the late 1960's and the early 1980's researchers related the risk of lymphoma for different dog breeds. Yet, there has been little progress since then to define factors that account for this risk. As part of ongoing programs supported by the AKC CHF, the researchers recently showed that the breed-specific risk of lymphoma extends beyond the simple disease condition to a tendency for specific forms of lymphoma. More importantly, the researchers showed there are frequent chromosomal abnormalities that separate with specific forms of lymphoma and that are more common in Golden Retrievers than in other breeds. This suggests breed-specific profiles of genetic abnormalities will be found in canine lymphoma.

Objective: To continue this work, the researchers are using contemporary "array-based" technologies to identify genes that map to these regions and how they contribute to the disease. The researchers anticipate that the results from this work will allow them to predict how genetic factors influence the occurrence of abnormalities in these genes, and will set the groundwork to identify specific genes associated with breed-dependent cancer risk.

Grant Objectives:

Objective 1: Test the hypothesis that deletions of chromosome 14 are associated with high grade (diffuse large) B cell lymphoma, gain of chromosomes 15 and 36 are associated with high grade (lymphoblastic) T cell lymphoma, and these abnormalities occur significantl more frequently in Golden Retrievers than in other dogs.

Objective 2: Define the minimal region of loss for each of these regions using high-resolution arrays.

Publications:

Report to Grant Sponsor from Investigator:
At the end of the second year of this project we have completed genome wide assessment of DNA copy number variation to profile tumor DNA from 252 dogs diagnosed with lymphoma. Tis is far in excess of our initial goal. We have performed a detailed statistical evaluation of the genome wide data derived both from 'fresh' lymphoma tissue and from archival lymphoma tissues in the form of formalin fixed paraffin embedded (FFPE) specimens. Our analysis has indicated that in many cases we can obtain robust data from FFPE specimens and use this alongside data obtained from fresh cases. While fresh tissue is always preferred, this finding means that we are able to access pathology archives to substantially increase sample numbers and so rapidly verify genomic changes that we have discovered. In essence, we are able to take a step back in time as a means to take a leap forward in discovery.

Ongoing analyses of our genome wide data have identified several high frequency aberrations some of which are associated recurrently with either B cell or T cell canine lymphoma and some of which may be associated with further subtypes. In addition many of the cases used in this study were treated with standard of care chemotherapy and so as we follow the outcome of these patients we will be n a position to determine if any of the recurrent chromosome changes we have identified are associated with prognosis. As we proceed we now are using much higher resolution technology which is allowing us to narrow down the regions of interest and this ultimately will lead to more accurate gene discovery.

When considering the breed specific nature of copy number changes of dog chromosomes 14, 15 and 36, the frequency with which we see aberrations of chromosome 14 has continued to remain evident, while those involving chromosomes 15 and 36 have declined. There are a number of subchromosmal changes along the length of these chromosomes, however, that may be breed specific, as well as numerous other regions of the genome. These regions are now being evaluated at ~100 fold increase in resolution and so as these data become available we will be ale to determine if these are significantly associated with breed.