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: 36 month

Report Due: 7/31/2011 **Report Received:** 8/8/2011

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:

- Thomas, R., E. L. Seiser, A. A. Motsinger-Reif, L. Borst, V. E. Valli, K. Kelley, S. E. Suter, D. Argyle, K. Burgess, J. Bell, K. Lindblad-Toh, J. F. Modiano and M. Breen (2011). "Refining tumor-associated aneuploidy through 'genomic recoding' of recurrent DNA copy number aberrations in 150 canine non-Hodgkin's lymphomas." Leukemia and Lymphoma 52(7):1321-1335

Report to Grant Sponsor from Investigator:

The overall goal of this study was to use molecular cytogenetics to evaluate recurrent DNA copy number changes in canine lymphoma. Initially we aimed to evaluate 100 cases, but by merging data with a parallel study we were able to generate data from over 250 cases. This resulted in a substantial volume of data that allowed us to determine which regions of the canine genome are subject to copy number changes in lymphoma subtypes. A subset of 150 cases of lymphoma, available as fresh lymph node biopsies, was used initially to provide optimum quality cytogenetic data. These data revealed that in canine B cell lymphoma, the number of DNA copy number aberrations is far fewer than has been reported in human B cell lymphoma, while the extent of aberration in canine and human T cell lymphoma was comparable. The clinical and pathological presentation of lymphoma in both dog and human are highly comparable. In consideration of these data, we concluded that while human lymphoma presents with a large number of DNA copy number aberrations, our canine data suggest that many of these aberrations are likely consequential changes, the key changes being those few that are shared between human and dog.

While fresh tissue specimens are ideal for cytogenetic analysis, we also have developed a means to obtain data from archival specimens, represented by tumor samples that have been fixed in formalin and stored in paraffin blocks. These are the specimens that are evaluated by a pathologist during diagnosis. A major advantage to the use of archival samples is that we can select cases associated with detailed clinical and pathological information from the outset. In this study we analyzed cytogenetic data from 102 archival cases of canine lymphoma and demonstrated that the distribution of DNA copy numbers was comparable to that we had identified in 150 cases of fresh tissue. These data suggest that we are able to make use of large pathology archives as a source of case material for cytogenetic analysis. In this particular project the net results were that we were able to assess DNA copy number changes in all 252 cases and add substantially to the overall cohort.

With this large data set we identified several high frequency DNA copy number aberrations, some of which are associated recurrently with either B cell or T cell phenotype 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 in 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, allowing us to narrow down the regions of interest and ultimately lead us to more accurate gene discovery.