RESEARCH PROGRESS REPORT SUMMARY

Grant 01889-G: Innovations in Prevention, Diagnosis, and Treatment of Cancer - Goldens Lead the Way

Principal Investigators: Dr. Jaime F Modiano, VMD PhD, Matthew Breen PhD, CBiol, FSB
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Research Institution: University of Minnesota, North Carolina State University
Broad Institute of MIT and Harvard

Grant Amount: $360,933.00

Start Date: 1/1/2014 **End Date:** 12/31/2016

Progress Report: Mid-Year 2

Report Due: 6/30/2016 **Report Received:** 7/6/2015

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:

Lymphoma and hemangiosarcoma are major health problems in golden retrievers, causing both suffering and premature death. As part of our ongoing project, Discovery and Characterization of Heritable and Somatic Cancer Mutations in Golden Retrievers, we have identified several regions of the genome that contain genetic heritable risk factors for lymphoma and hemangiosarcoma in Golden Retrievers. We also identified additional somatic mutations in tumors that occur recurrently in both cancers, some of which are linked to duration of remission when treated with standard of care. Our results indicate that a few heritable genetic risk factors account for as much as 50% of the risk for these cancers. These findings offer the potential to develop tests and strategies for DNA tests that can predict risk for individual dogs, as well as to manage risk across the population as a whole. Indeed, both the inherited risk factors and tumor mutations point to pathways that have been implicated in the pathogenesis of LSA and HSA, and thus should inform the development of targeted therapies. In this proposal we aim to find the precise mutations for the heritable genetic risk factors and to validate markers (mutations) used to determine risk at the heritable loci in a larger independent population of Golden Retrievers from the USA and from Europe in order to develop robust risk

prediction tools and an accompanying DNA test. We will identify and characterize tumor mutations and study their relationship to the heritable risk factors, tumor pathogenetic mechanisms, and disease outcome.

Grant Objectives:

To determine whether newly identified risk loci harbor key genes or regulatory elements that contribute to and/or lower the threshold for initiation of lymphoma (LSA) and hemangiosarcoma (HSA), and furthermore, if they cooperate with acquired mutations that are necessary for clinical progression of these two diseases.

Publications:

Thomas R, Borst L, Rotroff D, Motsinger-Reif A, Lindblad-Toh K, Modiano JF, Breen M. (2014). Genomic profiling reveals extensive heterogeneity in somatic DNA copy number aberrations of canine hemangiosarcoma. Chromosome Res, 22(3), 305-19. PMID: 24599718

Gorden BH, Kim JH, Sarver AL, Frantz A, Breen M, Lindblad-Toh K, O'Brien TD, Sharkey LC, Modiano JF, Dickerson EB. (2014). Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization. Am J Pathol, 184(4), 985-95. PMID: 24525151

Tonomura N, Elvers I, Thomas R, Megquier K, Turner-Maier J, Howald C, Sarver AL, Swofford R, Frantz AM, Ito D, Mauceli E, Arendt M, Noh HJ, Koltookian M, Biagi T, Fryc S, Williams C, Avery AC, Kim JH, Barber L, Burgess K, Lander E, Karlsson E, Azuma C, Modiano JF, Breen M, Lindblad-Toh K. (2015). Genome-wide association study identifies shared risk loci common to two malignancies in golden retrievers. PLoS Genet, 11(2):e1004922. doi: 10.1371/journal.pgen.1004922. eCollection 2015 Feb. PMID: 25642983

Report to Grant Sponsor from Investigator:

This project has completed the first eighteen months. For analysis of the DNA sequence mutations we identified previously, whole genome sequencing of DNA from many golden retriever blood samples from dogs affected by lymphoma and hemangiosarcoma has been performed. Thousands of DNA sequence variants have been detected and are being carefully analyzed. Collection of blood samples from golden retrievers across the US and Europe is complete and over the coming months we will assess the frequency of the risk haplotypes within these two populations.

For evaluation of DNA sequence changes in lymphoma and hemangiosarcoma tumor samples, we have compiled cases providing sufficient material for multiple analytical

approaches and the first manuscript is in the pipeline for publication. More than 100 genes were found to have multiple mutations in lymphoma tumors. These genes and mutations are now being further studied to find the mechanisms involved in tumor progression, and to investigate shared and distinct genomic features within and between breeds and tumor subtypes.

We have made new and exciting discoveries that will help us to understand mechanisms of tumor progression and response to therapy, and we have created the infrastructure to integrate clinical performance and outcome data with the molecular properties of the tumors.