



RESEARCH PROGRESS REPORT SUMMARY

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

Principal Investigator: Dr. Jaime F Modiano, VMD, PhD

Research Institution: University of Minnesota

Grant Amount: \$360,933.00

Start Date: 1/1/2014

End Date: 12/31/2016

Progress Report: Mid-Year 3

Report Due: 6/30/2016

Report Received: 6/28/2016

Recommended for Approval:

(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

Related Manuscripts:

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

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The work described in this manuscript was supported in part by CHF grants 615, 2254, 422, 1131, 593, 1147, 1168, and 1169

Rodriguez AM, Graef AJ, LeVine D, Cohen IR, Modiano JF, Kim JH. (2015). Association of sphingosine-1-phosphate (S1P)/S1P receptor-1 pathway with cell proliferation and survival in canine hemangiosarcoma. *J Vet Intern Med*, 29(4), 1088-97. PMID: 26118793

The work described in this manuscript was supported in part by CHF grants 01759 and 2081-A

Kim JH, Graef AJ, Dickerson EB, Modiano JF. (2015). Pathobiology of hemangiosarcoma in dogs: research advances and future perspectives. *Veterinary Sciences*, 2, 388-405

The work described in this manuscript was supported in part by CHF grant 01759

Project Specific Manuscripts:

Published

Im KS, Graef AJ, Breen M, Lindblad-Toh K, Modiano JF, Kim JH. (2015). Interactions between CXCR4 and CXCL12 promote cell migration and invasion in canine hemangiosarcoma. *Vet Comp Oncol*, 2015 Sep 3. doi: 10.1111/vco.12165. [Epub ahead of print]. PMID: 26337509

The work described in this manuscript was supported in part by CHF grants 1889-G and 01759

Elvers I, Turner-Maier J, Swofford R, Koltookian M, Johnson J, Stewart C, Zhang CZ, Schumacher SE, Beroukhim R, Rosenberg M, Thomas R, Mauceli E, Getz G, di Palma F, Modiano JF, Breen M, Lindblad-Toh K, Alföldi J. (2015). Exome sequencing of lymphomas from three dog breeds reveals somatic mutation patterns reflecting genetic background. *Genome Res*, 2015 25(11), 1634-45. PMCID: PMC4617960

The work described in this manuscript was supported in part by CHF grant 1889-G



Report to Grant Sponsor from Investigator:

This project has completed the first thirty months. 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 and their microenvironment interactions.