AMERICAN KENNEL CLUB
CANINE HEALTH FOUNDATION
PREVENT TREAT & CURE®

GRANT PROGRESS REPORT SUMMARY

Grant: 01131: *Genetic Background and the Angiogenic Phenotype in Cancer*
Principal Investigator: Dr. Jaime F Modiano, VMD PhD
Research Institution: University of Minnesota
Grant Amount: $254,871.00
Start Date: 1/1/2010 **End Date:** 6/30/2013
Progress Report: Mid-Year 4
Report Due: 6/30/2013 **Report Received:** 6/9/2013

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; yet, there has been little progress to define genes or other factors that account for this risk. The researchers' recent work on hemangiosarcoma is the first to clearly demonstrate that a dog's genetic background, defined by "breed," can influence the type of genes that show up as tumors. This means that certain breeds are diagnosed with specific cancers more frequently than others because of the behavior of tumors after they show up, and not simply because they show up more frequently. Specifically, this may apply to the observed tendency for hemangiosarcoma seen in Golden Retrievers, German Shepherd Dogs, and Portuguese Water Dogs. In addition, one-size-fits-all therapies may be not enough to effectively treat this disease.

Objective: This project will continue the researchers' observations on gene appearance profiles in hemangiosarcoma from Golden Retrievers to German Shepherd Dogs and Portuguese Water Dogs, and it also will define how new targeted therapies may effectively control the disease in these and other dog breeds.

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Grant Objectives:

Objective 1: Use microarray technology and contemporary bioinformatics to establish unique gene expression signatures in HSA samples from each breed.

Objective 2: Test how small molecule inhibitors that act directly and indirectly on angiogenic pathways affect HSA cells derived from dogs of each of these breeds.

Objective 3: Examine how attenuating vascular endothelial growth factor receptors affects pro-inflammatory environments generated by HSA cells.

Publications:

- Scott M, Duckett M, Modiano J, Yang C, Martinez H, Iverson B, Nunez R. (2010). Ambient temperature stabilization of feline and canine tumor cell RNA for use in gene expression assays. GenVault Technical Application Note for GenTegra™. http://www.genvault.com/downloads/case-studies-and-applicationnotes/ambienttemperature-stabilization-app-note.pdf

- Schappa JT, Frantz AM, Dickerson, EB, Vallera DA, Modiano JF. Hemangiosarcoma and its cancer stem cell sub-population are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors. Int J Cancer, 2013 Mar 30. doi: 10.1002/ijc.28187. [Epub ahead of print]. PMID: 23553371

- Koopmeiners JS, Modiano JF. (2012). Extending the TITE CRM to multiple outcomes with application to a phase 1 clinical trial in canine hemangiosarcoma. Clinical Trials, accepted

Report to Grant Sponsor from Investigator:

Certain dog breeds are prone to develop certain types of cancer; yet, there has been little progress to define genes or other factors that account for this risk. Our recent work on hemangiosarcoma was the first to demonstrate that a dog's genetic background, defined by "breed," can influence the profile of genes that are expressed by tumors. Among other important implications, this implies that certain breeds are diagnosed with specific cancers more frequently than others because of the behavior of tumors after they arise, and not simply because they arise more frequently. Specifically, this may apply to the observed predisposition for hemangiosarcoma seen in Golden Retrievers, German Shepherd Dogs, and Portuguese Water Dogs. Here, we continued to test this premise by evaluating genome-wide gene expression profiles in samples from dogs of various breeds. Our results suggest that, while there are subtle differences that are influenced or modulated differently in tumors from dogs of different breeds, these differences may disappear when tumors are considered in their context as "tissues" that include microenvironment constituents. Rather, there appear to be distinct subtypes of hemangiosarcoma (perhaps with different biological behavior and prognosis?), which might arise from different cells of origin, or more likely, which develop in response to

adaptation of the hemangiosarcoma cells to environments that show different patterns of inflammation, angiogenesis, coagulation, and hypoxia, each of which alters not only the predominant or favored differentiation of the tumor cells themselves, but also the way they instruct microenvironment cells to create a favorable niche. This underscores the importance of looking at these tumors in their context as "new tissues" or "new growths" rather than at the cells in isolation as we work to develop more effective strategies for detection, diagnosis, and therapy. To follow on this premise, we evaluated new therapy approaches that target both tumor and microenvironment compartments. Specifically, one such approach also shows efficacy to kill tumor-initiating cells. Data funded by this project grant and others allowed us to validate the therapy and move it to the clinic. Angiosarcoma Awareness, Inc. provided the initial funds to support a dose finding and efficacy trial where we will treat ~20 dogs with hemangiosarcoma using a bispecific ligand targeted toxin. We completed production of the molecule under "Good Manufacturing Practices" (i.e., suitable for use in human patients) and enrollment is ongoing. Finally, we identified other potential drugs to treat this disease - or perhaps more likely, the pathways they disrupt as potential targets for development of new therapies.