GRANT PROGRESS REPORT SUMMARY

Grant: 01759: *Targeting Multipotency to Arrest Hemangiosarcoma Progression and Improve Outcomes*

Principal Investigator: Dr. Jaime F Modiano, VMD PhD

Research Institution: University of Minnesota

Grant Amount: $233,914.00

Start Date: 1/1/2013 **End Date:** 12/31/2015

Progress Report: Mid-Year 1

Report Due: 6/30/2013 **Report Received:** 6/24/2013

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:

Hemangiosarcoma is a rapidly fatal disease. The lifetime risk is alarmingly high for some breeds like Golden Retrievers (~20% will die of this disease) and Portuguese Water Dogs (~15% will die of this disease). Furthermore, the risk of hemangiosarcoma is not limited to a single breed. In fact so many dogs are at risk to develop hemangiosarcoma that 40 Breed Clubs designated it as a research priority for 2012. Despite considerable efforts to find effective treatments, the outcome for dogs with hemangiosarcoma has changed very little over the past 30 years. We believe this is because our understanding of this disease is still rudimentary, but that is changing. Recent evidence suggests hemangiosarcoma conforms to the "cancer stem cell" model, where a defined subset of cells is responsible for initiating and maintaining the tumor. These cells are resistant to conventional therapies and they also are very adaptable, being able to survive in a variety of niches. In the case of hemangiosarcoma, the cancer stem cells also retain or acquire the potential to differentiate along several different lineages. For this project, we will use this property against the tumor by modulating factors that support the self-renewal of the stem cell compartment and by inducing their terminal differentiation along alternate pathways that have reduced malignant potential. We propose that disrupting the interactions between hemangiosarcoma cancer stem cells and their microenvironment will enhance the sensitivity of these cells to conventional and targeted therapies and improve the outcomes of dogs with this disease.

Grant Objectives:

For this project, we will examine the potential to use the multipotency of hemangiosarcoma cells to our advantage by forcing them to differentiate into lineages with reduced malignant potential.

Publications:

Abstracts:

- Graef AJ, Kim JH, Sarver AL, Frantz AM, O'Brien TD, Sharkey LC, Dickerson EB, Modiano JF (2013). Gene expression profiling reveals a role of CXCR4/7 in canine hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

- Kim JH, Sarver AL, Frantz AM, Scott MC, Graef AJ, Tonomura N, Elvers I, Thomas R, Lewellen M, Dickerson EB, Breen M, Lindblad-Toh K, Modiano JF (2013). Germ-line risk factors are associated with upregulation of genes mediating cell cycle arrest and stem cell activity in canine hemangiosarcoma. Proceedings of the 2013 International Conference on Advances in Canine and Feline Genomics and Inherited Diseases

Report to Grant Sponsor from Investigator:

We are on track to achieve the milestones laid out for this project. We have made considerable progress on the first aim and have completed initial experiments for the second aim. Our data suggest that IL-8 and CXCL12 mediate maintenance of the cancer stem cell phenotype, as well as interactions between hemangiosarcoma cells and the microenvironment. Our preliminary data suggest that applications for clinical use may be possible and feasible, but they will likely require precise timing and effective targeting.