RESEARCH PROGRESS REPORT SUMMARY

Grant 01759: Disrupting the Differentiation of Cancer Stem Cells to Prevent the Spread of Hemangiosarcoma

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: End-Year 2
Report Due: 12/31/2014   Report Received: 1/7/2015

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:

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 (since 01/2013):


Papers


Report to Grant Sponsor from Investigator:

We have made substantial progress. Our results confirm and extend the notions that interactions between the tumor and its local environment regulate hemangiosarcoma progression. Yet, variability in cells within tumors can reduce the predictability of hemangiosarcoma behavior, and possibly contribute to therapy resistance. For example, hemangiosarcomas respond to the degradation of their supporting matrix by recruiting inflammatory cells and blood vessels. But the magnitude of this effect is variable among different hemangiosarcomas, which requires us to consider that these tumors might adapt efficiently to very different microenvironments. The hemangiosarcoma microenvironment also tends to be rich in a molecule called CXCL12, which is used as a means of communication between the tumor cells and the normal supporting cells. Only some of the tumor cells have the receptors that transmit the signals from CXCL12. These cells help to support the tumor, and also can be efficient mediators of metastasis. But in their absence, other mechanisms might perform these functions. This suggests that blocking this pathway and others like it could have a positive therapeutic effect, but managing this disease will require combining strategies that lower the capacity of cells to simply switch their behavior to use alternate pathways to survive and thrive.