RESEARCH PROGRESS REPORT SUMMARY

Grant 02217: A Novel Mechanism to Regulate the Growth of Canine Hemangiosarcoma

Principal Investigator: Erin Dickerson, PhD

Research Institution: University of Minnesota

Grant Amount: $86,206.00

Start Date: 1/1/2016 **End Date:** 6/30/2018

Progress Report: FINAL

Report Due: 6/30/2018 **Report Received:** 7/16/2018

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

Hemangiosarcoma is an extremely aggressive cancer that is rapidly fatal in dogs. While the lifetime risk is alarmingly high for some breeds such as Golden Retrievers and German Shepherd Dogs, the disease does not discriminate, and it can strike any dog at any time. Despite considerable efforts by veterinarians and scientists to find effective treatments, the outcome for dogs with hemangiosarcoma has changed very little over the past few decades. Recent evidence provides essential clues into how these tumors grow and progress, generating new ideas for treatment approaches. Such new evidence suggests that hemangiosarcoma cells rely on the metabolism of lipids or fatty acids to supply energy for tissue invasion or continued tumor growth. To obtain these lipids, hemangiosarcomas may take over the metabolic machinery of neighboring cells, forcing them to produce nutrients for the tumor cells to help them proliferate and grow. This study will verify that tumor cells rely on lipid metabolism for growth, and determine if tumor cells alter the metabolism of fat cells to obtain cellular nutrients and accelerate tumor cell lipid metabolism. Identifying and exploiting a novel mechanism that may disrupt this process by inhibiting the interactions between tumor cells and cells in the tumor environment will speed clinical investigations, and ultimately lead to improved outcomes for dogs with this devastating disease.

Publications:

We have not yet published any of our findings. We anticipate that the following data will be part of a paper that is currently in preparation, and we plan to submit this paper in 2018:

1) Immunohistochemistry of □-AR and tyrosine hydroxylase expression in primary hemangiosarcomas.

2) Expression of □-ARs and the catecholamine enzymes in hemangiosarcoma cell lines.
3) Expression norepinephrine and dopamine in hemangiosarcoma cell lines.
4) Treatment of hemangiosarcoma and angiosarcoma cell lines with doxorubicin leads to an increase in TH expression, as well as an increase in the synthesis of dopamine and norepinephrine.

We also anticipate the publication of a second paper in 2019 describing the majority of the findings described in this report.

Presentations:

I attended a Keystone Conference on tumor metabolism in cancer cells in Whistler Canada in March 2017. A PhD student in my lab (Derek Korpela, DVM) also attended this meeting, and he presented some of the work described here. Dr. Korpela and I also attended the annual Veterinary Cancer Society meeting, held in Portland, OR, October 2017. Both abstracts were chosen for oral presentation. I presented some of this work as a State of the Art presentation at the conference; Dr. Korpela presented some of his work showing the metabolic impact of propranolol and its enantiomers on hemangiosarcoma cell metabolism. Funding support by the AKC Canine Health Foundation was acknowledged for all presentations.

Report to Grant Sponsor from Investigator:

Hemangiosarcoma is an incurable cancer that is almost uniformly fatal. The tumors often grow quickly and spread rapidly, with half of all dogs dying within six months of diagnosis, even with treatment. Because the prognosis has not changed over several decades, a better understanding of the disease is needed to develop new treatment approaches. We have found that hemangiosarcoma cells appear to rely on the metabolism of lipids to supply some of the energy and essential building blocks needed for tumor growth. We also found that propranolol, a common drug used to treat heart disease in both dogs and people, limits the uptake of lipids into cells and blocks the cell's ability to process these compounds. Cancer cells have been shown to impose a self-serving metabolic program on normal cells by forcing normal cells to supply nutrients, such as sugars and lipids, to the tumor. Recent studies have shown that cells like adipocytes (fat cells) can be remodeled by tumor cells to help create a niche favoring tumor growth. Because propranolol can block the use of lipids by tumor cells, propranolol may be able to reverse the cancer-imposed metabolic reprogramming on adipocytes or other normal cells, limiting tumor growth. For this study, we sought to: 1) characterize the lipid metabolic program(s) in hemangiosarcoma cells and determine if the use of lipids by these cells could be blocked by propranolol; 2) determine if hemangiosarcoma cells alter the metabolic program(s) of adipocytes; and 3) whether these changes in adipocytes enhanced the tumor cell growth programs and the invasive nature of hemangiosarcomas. We found that propranolol inhibited key metabolic processes in hemangiosarcoma cells, including the uptake and processing of lipids. We also found that hemangiosarcoma cells reprogrammed normal adipocytes in a way that may force the adipocytes to produce nutrients for hemangiosarcoma cells to help them proliferate and grow. Parallel studies

supported this idea by showing that adipocytes accelerated metabolic growth programs in hemangiosarcoma cells and enhanced programs favoring more aggressive disease. Future studies will be directed toward further assessing the metabolic programs of hemangiosarcomas and determining whether drugs like propranolol can be used to prevent the manipulation of adipocytes by tumor cells and reduce tumor growth and invasion.