RESEARCH PROGRESS REPORT SUMMARY

Grant 02510-T: Identification of Novel Synthetic Lethal Partners to Optimize PI3K Targeted Therapies in Canine Hemangiosarcoma

Principal Investigator: Cheryl London, DVM, PhD

Research Institution: Tufts University School of Medicine

Grant Amount: $168,857

Start Date: 3/1/2018 **End Date:** 2/28/2022

Progress Report: FINAL

Report Due: 2/28/2022 **Report Received:** 4/6/2022

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

Original Project Description:

Hemangiosarcoma (HSA) is a cancer of the cells lining the blood vessels that is very aggressive and has nearly always spread by the time it is diagnosed. HSA accounts for 5-7% of all cancers in dogs resulting in approximately 25,000-50,000 new cases per year. The treatment of choice is surgical removal followed by chemotherapy administration. Unfortunately, despite aggressive therapy, the majority of dogs diagnosed succumb to their disease within 6-8 months. Virtually no improvements in outcome for affected dogs have occurred in the past 30 years despite multiple clinical trials and research efforts. More recently a new therapy has been developed targeting two receptors on HSA cells. However, the majority of dogs still died by 10-12 months after treatment. The molecular pathway known as the PI3K/AKT/mTOR pathway has previously been implicated in the pathogenesis of many forms of cancer including HSA. Indeed, inhibitors of PI3K/AKT/mTOR pathway have some activity against HSA cell lines in the laboratory. The investigators have generated data showing that a subset of canine HSA tumors possess genetic mutations in PI3K that are known to activate the pathway in cancer cells. In this study, they will fully characterize the expression and function of PI3K in canine HSA tumor cell lines and tumor samples. This information will then be leveraged to identify new ways to block the PI3K/AKT/mTOR pathway using a combination of small molecule inhibitors that are most effective at killing tumor cells. These data will then be used to design future clinical trials in dogs with HSA.

Publications:

Papers in preparation:
1. Whole genome sequencing of canine hemangiosarcoma
2. Concordance of liquid biopsy findings with tumor genomic landscape in dogs with hemangiosarcoma.

Presentations:

Megan Gutwillig, the Master's student in my laboratory who worked on this project, completed her thesis work in June 2019. She presented her findings in the Genetics Seminar Series at Tufts University in January 2019 (oral presentation), at the Charleton Research Symposium at the Sackler School in April 2019 (poster presentation), and at the Genetics Program Retreat in June 2019 (poster presentation). The title of these presentations was: The role of PI3K-β and PI3K-δ in canine hemangiosarcoma and human angiosarcoma. Copies of these abstracts/posters have already been provided to the AKC CHF.

Kate Megquier, a postdoctoral research fellow who is being jointly mentored by myself and Elinor Karlson, presented the results of her genomic analysis of ctDNA in the hemangiosarcoma cohort to the PRECINCT collaboration network in Jan 2021, demonstrating ready detection of tumor DNA in the blood biopsy as well as the ability to identify key genomic changes. She also presented an expanded data set at the Oncology Models Forum meeting March 31, 2021 which reached a larger audience. Kate spoke at the Veterinary Cancer Society meeting (October 2021) and detailed an expanded data set of samples that were used for ctDNA detection

Report to Grant Sponsor from Investigator:

Hemangiosarcoma (HSA) is a cancer of the cells lining the blood vessels that is very aggressive and has nearly always spread by the time it is diagnosed. HSA accounts for 5-7% of all cancers in dogs resulting in approximately 25-50,000 new cases per year. The treatment of choice is surgical removal followed by chemotherapy administration. Unfortunately, despite aggressive therapy, the majority of dogs diagnosed succumb to their disease within 6-8 months. Virtually no improvements in outcome for affected dogs have occurred in the past 30 years despite multiple clinical trials/efforts. More recently a new therapy has been developed targeting two receptors on HSA cells. However, the majority of dogs still died, by 10 months. The molecular pathway known as the PI3K/AKT/mTOR pathway has previously been implicated as a key driver of several cancers including HSA. Indeed, inhibitors of PI3K/AKT/mTOR pathway have some activity against HSA cell lines in the laboratory. The purpose of this study is to fully characterize the expression and function of PI3K in canine HSA tumor cell lines and tumor samples to identify new ways to block this pathway using a combination of small molecule inhibitors that are most effective at killing tumors cells. Over the past 3 years we have characterized the expression of the 4 isoforms that make up PI3K family in HSA cell lines, have characterized sensitivities of the lines to individual isoform inhibitors, and have generated cell lines deficient in two of the isoforms. We have finished whole genome sequencing on a large number of tumor samples and have optimized a new non-invasive blood based diagnostic and disease monitoring test (also known as the blood biopsy) with the goal of applying this to future patients. This test should allow us to not only monitor patients with this disease for early relapse, but also screen at risk patients using a specific genetic panel we are in the process of developing. Lastly, we have initiated a clinical trial in dogs with HSA to test a combination of small molecule inhibitors that target specific pathways in the cancer cells based on data generated from the work completed in this research study.