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: Mid-Year 1

Report Due: 2/28/2020 **Report Received:** 3/6/2020

(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: None at this time.

Presentations:

Megan Gutwillig was a Master's student in my laboratory who completed her thesis work this past 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 hemagniosarcoma and human angiosarcoma.

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 10-12 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 2 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 are currently using these lines to identify how best to combine targeted therapies (PI3K pathway plus another pathway) for future translation into dogs with HSA. We are also working on a non-invasive blood based diagnostic and disease monitoring test (also known as the blood biopsy) with the goal of applying this to future patients.