AMERICAN KENNEL CLUB
CANINE HEALTH FOUNDATION
PREVENT TREAT & CURE

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:	$168,857.00
Start Date: 3/1/2018	**End Date:** 2/28/2021
Progress Report:	End-Year 1
Report Due: 2/28/2019	**Report Received:** 3/23/2019

(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.

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Presentations:

Graduate Student Seminar Series at the Sackler School; presentation by Megan Gutwillig as part of her graduate training.

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 6 months we have characterized the expression of the 4 isoforms that make up PI3K family in HSA cell lines, and have evaluated the effectiveness of a variety of small molecule inhibitors against cell lines targeting either individual or all PI3K isoforms. We have also generated cell lines deficient in two of the isoforms and are beginning to analyze the effects on the cells. Lastly, we have extended our collaboration with the Broad Institute to more completely explore the genetic targets in HSA and develop techniques for minimally invasive detection of HSA (i.e., a genetic screening test) using a new technique called the blood biopsy. Over the next 6 month we should be able to finish generating the cell lines and then begin the identification of potentially new targets for therapy.