AKC Canine Health Foundation, Inc.
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RESEARCH PROGRESS REPORT SUMMARY

Grant 02510-T:
Identification of Novel Synthetic Lethal Partners to Optimize PI3K Targeted TherA1PIes 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: 2/28/2021
Progress Report: Mid-Year 2
Report Due: 8/31/2019 - Report Received: 9/1/2019
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Original Project Description:

Splenic masses comprise ~50% of all canine splenic disease. Despite advances in imaging and pathologic definition, the etiology and medical relevance of splenic lesions in dogs are often ambiguous. While some splenic tumors are benign, approximately two-thirds are highly malignant and carry a poor prognosis. Hemangiosarcoma (HSA) accounts for the majority of canine malignant splenic tumors and occurs in many large dog breeds, including mixed breeds. A less common site of HSA localization is the heart (cardiac HSA). Risk factors for both cardiac and splenic HSA remain unclear, confounding development of preventative strategies. The investigators recently reported a high prevalence of species of the bacterial genus *Bartonella* in dogs with HSA from North Carolina, suggesting a potential role in the initiation and/or progression of this cancer. *Bartonella* species exist worldwide and are transmitted by blood-sucking arthropods (e.g. ticks, fleas) and their presence in splenic tissue could potentially be explained by the fact that the spleen is primarily responsible for removal of blood-borne parasites from the systemic circulation. The investigators will perform a comprehensive examination of the potential association between *Bartonella* infection and HSA by comparing the prevalence of *Bartonella* DNA in tumor and blood samples from both splenic and cardiac HSA cases, and also within and between distant geographical locations in the US. Ultimately, demonstration of a robust association between *Bartonella* infection and the development of HSA may lead to new opportunities for improved diagnosis, treatment and prevention of this devastating cancer.

Publications:

- Gutwillig, Megan. January 2019. The role of PI3K-β and PI3K-δ in canine hemangiosarcoma and human angiosarcoma (oral presentation). Genetics Seminar Series at Tufts University.

- Gutwillig, Megan. April 2019. The role of PI3K-β and PI3K-δ in canine hemangiosarcoma and human angiosarcoma (poster presentation). Charleton Research Symposium at the Sackler School.
- Gutwillig, Megan. June 2019. The role of PI3K-β and PI3K-δ in canine hemangiosarcoma and human angiosarcoma (poster presentation). Genetics Program Retreat.

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 year 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 found that in some of the lines loss of the PI3K β isoform causes the cells to reduced migration suggesting that this isoform may play a role in tumor spread. Megan Gutwillig, a combined DVM/MS student, finished her MS work and has returned to complete the last 3 years of her veterinary training. A new student will begin working on the project in the lab this fall.