RESEARCH PROGRESS REPORT SUMMARY

Grant 02502: Precision Medicine for Canine Lymphoma

Principal Investigator: Nicola Mason, BVetMed, PhD

Research Institution: University of Pennsylvania

Grant Amount: $86,400

Start Date: 3/1/2018 **End Date:** 2/28/2021

Progress Report: End-Year 2

Report Due: 2/29/2020 **Report Received:** 3/20/2020

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Original Project Description:

The clinical response of dogs with lymphoma to multi-agent chemotherapy is highly variable. Although up to 85% of dogs respond initially, some relapse within weeks, while others enjoy remission times of two years. This heterogeneity in clinical response is in part explained by the recognition that "lymphoma" is not a single disease entity, but consists of different subtypes that can be characterized on a molecular level by mutations in specific genes. As in human medicine, it follows that different lymphoma subtypes, driven by different molecular mechanisms, may respond better to therapies that are specifically selected to inhibit the driver mechanisms within that patient's tumor. Recent work using sophisticated genetic sequencing tools (next-generation sequencing (NGS)) has begun to shed light on the different molecular subtypes of canine B cell lymphoma, and specific therapies aimed at targeting patient-specific driver genes and pathways are being developed. To enable targeted therapies to move into the clinic, a personalized diagnostic tool must be developed that can rapidly and cost-effectively determine the mutational profile of a patient's cancer allowing selection of the most effective drug for that patient. The investigators aim to develop a NGS diagnostic test that can be employed on standard biopsy samples to identify molecular drivers of a patient's lymphoma (personalized diagnostics), enabling the most appropriate targeted therapy to be selected for that patient. In addition, they aim to determine whether specific mutational profiles within canine lymphoma identified by their NGS panel are predictive of clinical outcome.

Publications: None at this time

Presentations:

Wang G." Bringing precision medicine into veterinary oncology." American Association of Cancer Research (AACR), Atlanta, Georgia. Apr 2nd 2019.

This work was included as part of a presentation entitled: Bringing precision medicine into veterinary oncology; given by Dr. Guannan Wang at the following locations.

- Mari Lowe Comparative Oncology Seminar, The Penn Vet Cancer Center, Jan 2019, Philadelphia, PA
- American Association for Cancer Research (AACR) Annual Meeting 2019, Mar 2019, Atlanta, GA
- Corporate workshop at Association of Molecular Pathology (AMP2019) Annual Meeting Nov 2019, Baltimore, MD

Dr. Wang also described some of this research in her YouTube presentation which can be found at: https://www.youtube.com/watch?v=TQNzmozP12Y

Report to Grant Sponsor from Investigator:

This AKC-CHF sponsored award supported the successful development of a comprehensive canine tumor sequencing panel ("canine oncopanel") using cutting-edge, next-generation sequencing technology. The canine oncopanel detects a wide-spectrum of changes (nucleotide variations, insertions, deletions, copy number variants etc) in 284 selected genes. The selected genes were chosen based on cancer studies and publically available datasets from human and dog tumor genomic analyses. The selected genes that are interrogated by the canine oncopanel are known to be involved in tumor-driving pathways in canine B cell lymphoma and other cancers, and in pathways that play critical roles in tumor development and progression of many different tumor types. The canine oncopanel covers a large target region across the canine genome and can also be used to estimate the "mutational load" or tumor mutational burden (TMB) of a tumor. In humans, this has been shown to be predictive of response to immunotherapies. We envision that our canine oncopanel can be used to interrogate each individual patient's tumor, rapidly and cost effectively determining its mutation profile, and revealing potential driver mutations, clinically-relevant biomarkers such as druggable targets, prognostic markers and markers that predict treatment response. This would pave the way for personalized diagnostics and precision treatment for dogs with DLBCL (and other tumors). Furthermore, the panel will help to direct future development of targeted therapies or repurposing of pre-existing therapeutics that could be used in those patients mostly likely to benefit from them (based on their tumor's profile). We believe that this approach will lead to improved outcomes for canine patients with DLBCL and potentially other tumors. On-going work will now determine whether tumor profiling using this approach can be used to predict outcome of dog with DLBCL treated with standard CHOP based chemotherapy.