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:** 2/28/2022
Progress Report:	End-Year 3
Report Due: 2/28/2021	**Report Received:** 3/14/2021

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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:

Canine Oncopanel: a capture-based, NGS platform for evaluating the mutational landscape and detecting driver mutations in canine cancers. Guannan Wang, Ming Wu, Amy C. Durham, Nicola J. Mason, David B. Roth

Submitted to Veterinary and Comparative Oncology Jan 2021

Presentations:
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

None at this time. An update on our results will be given at the AKC-CHF National Parent Club Canine Health Conference to be held in St. Louis, Missouri in September 2021.

Report to Grant Sponsor from Investigator:

We have successfully developed a canine cancer gene panel that we have called the Canine Oncopanel, using cutting-edge, next-generation sequencing technology (NGS). The Canine Oncopanel allows sequencing of 283 cancer-related genes and detection of mutations within these genes that may drive the tumor cells to proliferate and survive. The canine oncopanel sequences a total target region that equates to ~3% of the canine genome. Analyzing the genomic composition of this broad target region allows evaluation of common genomic alterations that can lead to the development of cancer. The Canine Oncopanel is suitable to map mutation profiles and identify driver mechanisms in both common and rare canine cancers to provide a better understanding of the tumor genome and its biology. Furthermore, as in human cancer genetics, targeted sequencing panels like the canine oncopanel are being used to provide an estimate of total mutational burden of the tumor, which has relevance in predicting response to certain immunotherapies. In addition, through identification of clinically-actionable biomarkers, the Canine Oncopanel serves as a genomic diagnostic tool that may guide selection of appropriate targeted therapies and possibly predict treatment response and patient outcome. To date, we have analyzed 60 canine DLBCL (cDLBCL) cases using the validated Canine Oncopanel. Putative driver genes were found in 51 cases, which included driver genes previously identified by whole exome sequencing and RNA sequencing in cDLBCL or human DLBCL (hDLBCL), as well as novel drivers found in other cancers. Clinical follow-up data were collected retrospectively and analyzed in the context of mutational profiles. Mutations in genes including TRAF3 and TP53 appeared to occur more frequently in cases with shorter overall survival times, suggesting that these mutations might delineate a more aggressive subgroup of cDLBCL and serve as prognostic markers. However, this hypothesis will need to be tested in a prospective clinical trial.