RESEARCH PROGRESS REPORT SUMMARY

Grant 02317: The Role of Complex Translocations Associated with TP53 Somatic Mutations for Aiding Prognosis of Canine Diffuse Large B cell Lymphoma

Principal Investigator: Matthew Breen, PhD

Research Institution: North Carolina State University

Grant Amount: $177,327.00

Start Date: 1/1/2017 **End Date:** 12/31/2018

Progress Report: End-Year 1

Report Due: 12/31/2017 **Report Received:** 12/31/2017

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Original Project Description:

Lymphoma accounts for up to 24% of all cancers diagnosed in pet dogs. Among these cases diffuse large B-cell lymphoma (DLBCL) is the most common subtype. Despite continued advances in veterinary medicine, the response to treatment for canine lymphoma remains highly variable with no reliable means to predict response. Studies of lymphoma in people have identified characteristic genome changes that have both diagnostic and prognostic significance. In human DLBCL, mutations in the TP53 gene, and genome rearrangements involving the MYC, BCL2 and BCL6 genes have been shown to confer particularly poor prognosis in cases treated with standard of care multi-agent (CHOP-based) chemotherapy. The investigator's previous CHF-funded studies have shown that canine cancers, including lymphoma, exhibit genomic changes that are conserved with those observed in the corresponding human cancers, and have identified MYC and BCL2 rearrangements and a high frequency of TP53 mutation in canine DLBCL. This research will screen a well-defined collection of over 450 pre-treatment, canine DLBCL samples to determine accurate frequencies of these genome changes. The researchers will investigate the correlation of these target aberrations with duration of first remission, and identify key genomic signatures that may aid prognosis of prospective canine lymphoma cases. The data generated should assist owners and veterinarians with decisions regarding treatment with CHOP. Patients with signatures predictive of poor response to conventional CHOP chemotherapy may benefit from more aggressive treatment at the outset to improve outcome.

Publications:

None at this time.

Report to Grant Sponsor from Investigator:

This study involves the evaluation of a cohort of canine lymphoma specimens for the presence of tumor-associated abnormalities associated with four key cancer-associated genes. The presence of these abnormalities, alone and in combination, has been shown to be predictive of the response to standard treatment modalities in human lymphoma patients, and provides powerful opportunities to predict prognosis in newly diagnosed patients. We hypothesize that the same may apply in dogs.

Thus far we have screened the full cohort of canine lymphoma cases for abnormalities involving the first of these genes, and have scored approximately 75% of the cases for abnormalities involving the second of these genes. The reagents required for analysis of the remaining genes have been developed and validated on well-characterized control specimens, and will be used to screen the lymphoma cohort in the second year of this study.

On completion of these analyses the data for each gene in each case will be used to assess the frequency and distribution of abnormalities across the dog lymphoma cohort. This information will be used to identify whether there are recurrent patterns evident when comparing the data for each gene within and between cases that would suggest they are not random events. We will also integrate these data with the clinical outcome data for those cases for which this information is available. This will allow us to determine whether the pattern of abnormalities in these four genes can be used to assist with determining prognosis in prospective canine lymphoma cases. During the course of the study we are continuing to accumulate additional clinical data for a proportion of cases for which treatment outcome information was not available at the time the study was initiated. The availability of this additional information will enable us to maximize the statistical power of our study.