GRANT PROGRESS REPORT REVIEW

Grant: 00632: *MicroRNAs and Canine Lymphoma*

Principal Investigator: Dr. William C Kisseberth, DVM PhD

Research Institution: Ohio State University

Grant Amount: $98,766.00

Start Date: 10/1/2005 **End Date:** 9/30/2010

Progress Report: FINAL

Report Due: 9/30/2010 **Report Received:** 5/16/2011

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:
Lymphoma is one of the most common cancers in the dog. The current classifications of lymphoma do not explain or predict its changing clinical behavior. Much of the progress in diagnosis, prognosis, and treatment of lymphoma and other cancers in people has been the result of advances in "genomics." Recently the canine genome has been sequenced, providing the opportunity to apply new genomic approaches to better understand and treat cancer in the dog. MicroRNAs (miRNA) are small non-protein coding molecules that have been linked in humans as having an important role in cancer and a variety of other diseases. In this study, the researchers will identify miRNAs using bioinformatic methods. The researchers will then use miRNA microarrays to study normal canine tissues and canine lymphoma biopsies. These results (miRNA expression profiles) will be linked with previous diagnosis and clinical restrictions. The goals of this study are to identify canine miRNAs and their normal patterns of expression and to determine if specific subtypes of lymphoma are characterized by unique miRNA expression profiles, if specific miRNAs have predictive importance, and to identify potential goals for future investigation and therapies. This study will also generate new tools for future miRNA investigation in the dog.

Grant Objectives:
Hypothesis: A custom canine miRNA microarray can be used to determine miRNA expression profiles in canine lymphoma. Canine lymphomas can be classified based upon their miRNA

expression profiles. Individual and coordinately regulated miRNAs may have diagnostic, prognostic, and/or therapeutic significance.

Objective 1: Identify canine miRNAs and characterize their expression in canine tissues.

Objective 2: Determine the miRNA expression profiles of canine lymphomas using a modified custom oligonucleotide mircoRNA microarray.

Publications:

Report to Grant Sponsor from Investigator:
MicroRNAs (miRNAs) are small non-coding RNAs that have been implicated in humans as having a fundamental role in cancer initiation and progression. Canine diffuse large B cell lymphoma (DLBCL) represents one of the most frequently encountered canine neoplasms. We hypothesized that canine DLBCL possess a unique miRNA expression signature and that miRNA dysregulation contributes to chemoresistance and prognosis. In this study we confirmed that miRNAs in the dog are very similar to those in humans, i.e. are highly evolutionarily conserved, and that different miRNA analysis technologies that are applied to human cancers can be similarly applied to canine cancers. Furthermore, miRNA expression in healthy normal tissues is similar in dogs and humans. When we used "next generation" sequencing of canine DLBCL tumor samples to determine their miRNA expression profiles we identified a miRNA that was significantly overexpressed in chemotherapy naïve tumors compared to chemotherapy relapse tumors from the same patients. Significantly, this was a miRNA with known importance in human cancers. Additionally, we identified a unique miRNA expression signature (multiple coordinately expressed miRNAs) that was associated with overall survival in dogs with DLBCL and treated with a standard chemotherapy regimen. These findings provide insights into mechanisms of lymphomagenesis and potential targets for future therapies.