RESEARCH PROGRESS REPORT SUMMARY

Grant 02890: Characterizing the LINE-1 Transcriptome in Canine High-grade Peripheral T-cell Lymphoma by RNAseq to Gain Insight into Mechanisms of Drug and Immune Resistance

Principal Investigator: Paul Hess, DVM, PhD

Research Institution: North Carolina State University

Grant Amount: $33,234

Start Date: 3/1/2021 **End Date:** 2/28/2022

Progress Report: Mid-Year 1

Report Due: 8/31/2021 **Report Received:** 8/31/2021

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

High-grade lymphomas are common cancers of white blood cells in dogs. T-cell lymphoma is a particularly aggressive form associated with poor outcomes. Chemotherapy ultimately fails in T-cell lymphoma patients because of a tiny subpopulation of cancer cells – so-called minimal residual disease (MRD) – that resists most drugs, and eventually takes over, leading to short survivals. Researchers will investigate the role of "jumping genes," a set of genes able to copy and paste themselves into new places in DNA, in T-cell lymphoma. Genes jumping to new spots is disruptive to the integrity of the genetic code, and is permitted only under certain circumstances but can occur when cells become cancerous. Investigators found that jumping genes are unusually active in canine T-cell lymphoma. When cancer cells can suppress jumping gene activity, they can better tolerate chemotherapy drugs and evade immune detection. Researchers hypothesize that MRD emerges during chemotherapy because that subset of cells hijacks a system normally used by reproductive cells to inhibit jumping genes. Investigators plan to use next-generation genetic techniques to define the currently unknown world of active jumping genes in T-cell lymphoma and investigate the molecular causes and consequences of their activity. A successful study will begin characterizing an unexplored pathway used by lymphoma cells, which could be an important new treatment target in a canine cancer that desperately needs novel therapies.

Publications: None to date.

Presentations: None to date.

Report to Grant Sponsor from Investigator:

Lymphoma, a group of cancers of white blood cells, is the most common malignancy of dogs. At diagnosis, the typical dog has that fast-growing-type lymphoma that is already widely spread. Chemotherapy is remarkably effective short-term, but the cancer invariably becomes resistant during treatment. Consequentially, very few patients are cured. The T-cell type of lymphoma, which we study, develops resistance to treatment much more quickly than other types. Survivals average just 7 months. In profiling the T-cell type, we've found that newly-diagnosed lymphomas have unusually high activity of "jumping genes", so named because they are able to cut and paste themselves into new places in the genetic code. Because this activity is dangerous – inadvertent pasting into a normal gene could stop its function – healthy cells suppress jumping genes, but they are turned back on in some fast-growing cancer cells. Interestingly, when cancer cells re-gain the ability to suppress jumping genes, they more easily resist chemotherapy and evade immune detection. We've found that T-cell lymphomas hijack a suppression system used by spermatozoa, fast-growing cells that have special mechanisms for controlling jumping genes. We believe that a small percentage of cancerous T cells quickly become resistant to chemotherapy and immunity by this mechanism, and that's why treatments only work for a short time. Learning exactly how they exploit this mechanism could yield smarter, better treatments. Jumping genes are extremely numerous and spread throughout the chromosomes. Most are quiet and irrelevant. Simply cataloging their presence in cancerous T cells won't be helpful.

What's needed is to find the very few that are the actual active troublemakers, and learn whether they are the same or unique players in each canine T-cell lymphoma. This is the objective of our study. To accomplish this task, we have to wade through enormous amounts of genetic information. That process can only be done by new, next-generation sequencing methods. In the first half of the study, we extracted and processed the appropriate genetic material (messenger RNA) from canine T-cell lymphoma biopsies, which is currently being sequenced in two different ways at the NCSU high-throughput sequencing core facility. In the second half of the project, which will begin when sequencing data is returned, we will decode this information to provide a completely new picture of jumping gene activity and active suppression mechanisms in T-cell lymphomas of dogs.