GRANT PROGRESS REPORT REVIEW

Grant: 01577: *Fine Mapping of Loci for Transitional Cell Carcinoma in the Scottish Terrier, West Highland White Terrier, and Shetland Sheepdog*

Principal Investigator: Dr. Elaine Ostrander, PhD

Research Institution: National Human Genome Research Institute

Grant Amount: $45,000.00

Start Date: 1/1/2012 **End Date:** 12/31/2013

Progress Report: 6 month

Report Due: 6/30/2012 **Report Received:** 7/23/2012

Recommended for Approval:

(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:

Cancer is a major cause of death in older dogs and treatment is often ineffective. We wish to identify the causes of cancer in order to learn how to more effectively predict, prevent, and treat the disease. Genetic (heritable) factors are important in development of Transitional cell carcinoma (TCC) of the bladder. The Scottish and West Highland White terriers and the Shetland sheepdog are at high risk for TCC, and a subset of dogs of each breed are born with errors in critical genes that predispose them to the disease. We wish to develop ways to identify dogs with genetic risk factors for TCC. Dogs at risk could then either enter cancer prevention trials, undergo screening tests to detect cancer at its earliest state, and in the future, possibly receive â€œgeneticâ€ therapy. In the first years of this grant, we found two regions of the genome where error-prone genes lie. We were able to determine how the gene errors were unique for each of the three breeds. We narrowed the first region to a few hundred bases in an interval that has only two genes. We are requesting continued funding to allow us to find the mutation as well as fine map the remaining critical gene. Methods developed in this effort will translate to other cancers and thus have the potential to help dogs of many breeds.

Grant Objectives:

Aim 1) Identify the mutation(s) in Locus 1 that are responsible for increased susceptibility to TCC in the ST.

Aim 2) Fine map Locus 2 by finding a critical haplotype shared by affected dogs.

Aim 3) Sequence genes, promoters and conserved regions within Locus 2.

Aim 4) Calculate mutation prevalence and risk within breeds based on genotype.

Publications:

Report to Grant Sponsor from Investigator:

Cancer is the number one cause of disease related death in dogs, with estimates for overall risk of developing cancer as high as one in four. Treatments for canine cancers are most often developed based on human disease equivalents. For diseases such as invasive transitional cell carcinoma of the bladder (TCC), standard human treatments such as complete cystectomy are not feasible in dogs and current chemotherapeutics are only marginally effective. Therefore, new treatments must be tailored specifically for canine patients. Understanding the cause of the disease is by far the best starting place for developing new treatments as well as improving diagnostics and enabling prevention. Genetic alterations play a major role in TCC susceptibility, especially in breeds such as the Scottish terrier, West Highland white terrier, and Shetland sheepdog; where incidence is 5 to 20 times higher than in the average dog. The long-term goal of our study is to identify the genetic risk factors for TCC in these highly predisposed breeds. Thus far we have completed whole genome association studies on more than 250 dogs from the three most highly susceptible breeds and have found two regions of the genome that differ between dogs that have and do not have the disease. These regions contain genes that are likely to contribute to TCC development and/or progression. One region has been narrowed to include only one gene sequence but multiple regulatory regions that may contribute to disease susceptibility. The second contains a family of genes that are suspected to contribute to disease progression and severity. We are currently analyzing data from both of these regions to identify the causative mutations and to understand how they are interrupting normal gene function in order to create an invasive tumor. Both regions are undergoing complete sequencing using a combination of traditional and innovative methods. In addition, we are analyzing genomic data from the tumors and combining the two sources to enhance our understanding of the genetic modifications that lead to TCC development. These methods will not only enable us to identify genetic contributors to TCC development but will also provide needed information for additional cancer studies, potentially contributing to health improvements in many diverse breeds.