GRANT PROGRESS REPORT SUMMARY

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 A 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: Mid-Year 2

Report Due: 6/30/2013 **Report Received:** 7/8/2013

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:

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:

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

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

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

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

Publications:

- Both ends of the leash: the human link to good dogs with bad genes (2012) Ostrander, EA. New England Journal of Medicine, 367(7):636-46.

- Subcutaneous 5-azacitidine treatment of naturally occurring canine urothelial carcinoma: A novel epigenetic approach to human urothelial carcinoma drug development. Hahn NM, Bonney PL, Dhawan D, Jones DR, Balch C, Guo Z, Hartman-Frey C, Fang F, Parker HG, Kwon EM, Ostrander EA, Nephew KP, Knapp DW. (2012) Journal of Urology 187:302-309.

Report to Grant Sponsor from Investigator:

Transitional cell carcinoma (TCC) of the bladder is the most common tumor of the urinary bladder in dogs. Invasive TCC of the bladder, the most common form found in dogs, is highly aggressive and results in thousands of canine deaths each year. In general, treatments for canine cancers are developed based on human disease equivalents. For diseases such as TCC, standard human treatments such as complete cystectomy, or removal of the bladder, are not feasible in dogs and current chemotherapeutics are only marginally effective. In order to improve the prognoses for dogs with TCC, 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. Susceptibility to TCC is strongly influenced by genetic alterations, especially in breeds such as the Scottish terrier, West Highland white terrier, and Shetland sheepdog wherein the incidence of disease 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. We have completed whole genome association studies on more than 250 dogs from these three breeds and have found two regions of the genome that play a significant role in disease development. The first region has been narrowed, through successive rounds of sequencing and genotyping, to include only one gene sequence and three regulatory regions that may contribute to disease susceptibility. Multiple mutations have been identified within one of the regulators that are currently being assessed for disease related function. The second region contains a family of

genes that are suspected to contribute to disease progression and severity. We have sequenced >90% of both these regions using traditional and innovative methods. Analysis of variant frequencies has produced a list of ~80 genetic alterations that are potential candidates for increased disease susceptibility. These data are currently being verified in a second set of dogs. In addition, we are designing experiments to understand how the variants might interrupt normal gene function in order to create an invasive tumor. Genome wide transcript and histone binding data that we have produced from tumors and tumor cell lines has been included in the analysis 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.