GRANT PROGRESS REPORT REVIEW

Grant: 01336A&B: *Finding the Mutations that Increase Susceptibility to Transitional Cell Carcinoma in the Scottish Terrier, West Highland Terrier, and Shetland Sheepdog*

Principal Investigator: Dr. Deborah Knapp, DVM; Dr. Elaine Ostrander, PhD

Research Institution: Purdue University; National Human Genome Research Institute

Grant Amount: $86,899.75

Start Date: 1/1/2010 **End Date:** 12/31/2011

Progress Report: 18 month

Report Due: 6/30/2011 **Report Received:** 7/1/2011

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:
Background: Cancer is a major cause of death in older dogs. The treatment of advanced cancer is often ineffective. There is interest in discovering the causes of cancer in order to learn how to prevent cancer, or at least to detect cancer earlier when treatment may be more effective. Genetic (heritable) factors are important in cancer development.

Objective: The researchers wish to determine ways to identify dogs with genetic risk factors for cancer. These dogs could then: enter cancer prevention trials, undergo screening tests in order to detect the cancer earlier when it might be more treatable, and in the future to possibly receive "genetic" therapy. This team of researchers has recently identified "loci" (regions of the DNA) that are strongly associated with increased risk for urinary bladder cancer (transitional cell carcinoma, TCC) in Scottish Terriers, West Highland White Terriers and Shetland Sheepdogs. Now, they will identify which gene(s) are involved within these loci and the causative mutation(s) in the gene(s). This is the crucial next step in being able to identify dogs at risk for TCC. Methods being developed will also facilitate work in other cancers, and thus the potential to help dogs in many breeds.

Grant Objectives:

Objective 1: Fine map two genetic loci associated with TCC.

Objective 2: Identify the mutations and the affected genes that are associated with increased cancer susceptibility.

Objective 3: Examine the presence of the mutations and changes in the expression of the affected genes within tumors tissues.

Objective 4: Calculate mutation prevalence and risk based on genotype.

Publications:

- Shearin, Al and Ostrander, Ea (2010) Leading the way: canine models of genomics and disease. Disease Models & Mechanisms. 3, 27-34. 10.1242/dmm.004358 http://dmm.biologists.org/content/3/1-2/27.abstract

- Shearin, Al and Ostrander, Ea (2010) Canine Morphology: Hunting for Genes and Tracking Mutations. PLoS Biol. 8, e1000310. http://dx.doi.org/10.1371%2Fjournal.pbio.1000310

- Parker, Hg, Shearin, Al and Ostrander, Ea (2010) Man's Best Friend Becomes Biology's Best in Show: Genome Analyses in the Domestic Dog*. Annual Review of Genetics. 44, 309-36. http://www.annualreviews.org/doi/abs/10.1146/annurev-genet-102808-115200

Report to Grant Sponsor from Investigator:

Cancer is a major cause of death in older dogs and treatment of the disease 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. Several breeds such as the Scottish terrier, West Highland White terrier, and the Shetland Sheepdog, are at high risk for the disease, and a subset of dogs from each breed are born with errors in critical genes that then predispose them to the disease. Our goal is to determine ways to identify dogs with genetic risk factors for TCC. Dogs at risk could then either enter cancer prevention trials, undergo screening tests for early detection, and in the future, possibly get treated with 'genetic' therapy. Thus far we have found two regions of the canine genome where error-prone genes lie and are able to discern how the genetic errors are similar and different between dogs with TCC and healthy dogs. We narrowed the responsible gene for one region to a few hundred bases in an interval that has only two genes that are excellent candidate genes for cancer development. In the next 6 months, we expect to evaluate effects of candidate mutations on these genes using innovative genomic tools. We are currently working to reduce the second region to a similar size in order to define the risk haplotype and to identify causative genes. Furthermore, methods developed in this effort will translate to other cancer studies underway, and thus offer the potential to help dogs of many breeds.