Updates on Current AKC Canine Health Foundation Research Sponsored by the Vizsla Club of America Welfare Foundation (VCA WF) Grant Progress Report Summaries

Grant 01615: *Identification of Idiopathic Epilepsy Genes in Australian Shepherds*

Principal Investigator: Dr. Ned E. Patterson, DVM PhD University of Minnesota
End Date: 12/31/2013 **Report Received:** 12/31/2012

Report to Grant Sponsor from Investigator:
Genetic marker data from 88 Australian Shepherds (44 cases and 44 controls) total has now been analyzed with standard genetic association statistical analysis. This includes 25 new cases and 23 new controls during this grant period. So far there are two different chromosomes that potentially contain an associated epilepsy gene or genes. In the past 6 months we have performed many additional new statistical analyses on the data. We have identified a confirmed a new third potential area in the last 6 months, and the area previously identified on chromosome 1 was not confirmed in the new analysis. These confirmed areas are on dog chromosomes 16,19 and 26.
We are continuing with additional in depth analysis, and working on finding the most likely genes in each area of each these 3 chromosomes that may be related to contributing to epilepsy, and we plan to find additional markers near the genes. Currently we are in the middle of sequencing two candidate genes from these three identified areas. We are now also planning to obtain up to 24 new cases and 24 new controls, from our collaborators in the USA and/or Europe, for additional genetic marker analysis if sufficient funds remain in the budget. In addition we plan to utilize next generation DNA sequencing to sequence portions of these 3 chromosomal areas in the next 6-9 months, if needed, in our search for genetic mutations contributing to epilepsy in Australian Shepherds.

Grant 01131: *Genetic Background and the Angiogenic Phenotype in Cancer*

Principal Investigator: Dr. Jaime F Modiano, VMD PhD University of Minnesota
End Date: 6/30/2013 **Report Received:** 12/31/2012

Report to Grant Sponsor from Investigator:
Certain dog breeds are prone to develop certain types of cancer; yet, there has been little progress to define genes or other factors that account for this risk. Our recent work on hemangiosarcoma was the first to demonstrate that a dog's genetic background, defined by "breed," can influence the profile of genes that are expressed by tumors. Among other important implications, this implies that certain breeds are diagnosed with specific cancers more frequently than others because of the behavior of tumors after they arise, and not simply because they arise more frequently. Specifically, this may apply to the observed predisposition for hemangiosarcoma seen in Golden Retrievers, German Shepherd Dogs, and Portuguese Water Dogs. Here, we continued to test this premise by evaluating genome-wide gene expression profiles in samples from dogs of various breeds. Our results suggest that, while there are subtle differences that are influenced or modulated differently in tumors from dogs of different breeds, these differences may disappear when tumors are considered in their context as "tissues" that include microenvironment constituents. Rather, there appear to be distinct subtypes of hemangiosarcoma (perhaps with different biological behavior and prognosis?), which might arise from different cells of origin, or more likely, which develop in response to adaptation of the hemangiosarcoma cells to environments that show different patterns of inflammation, angiogenesis, coagulation, and hypoxia, each of which alters not only the predominant or favored differentiation of the tumor cells themselves, but also the way they instruct microenvironment cells to create a favorable niche. This underscores the importance of looking at these tumors in their context as "new tissues" or "new growths" rather than at the cells in isolation as we work to develop more effective strategies for detection, diagnosis, and therapy. To follow on this premise, we evaluated new therapy approaches that target both tumor and microenvironment compartments. Specifically, one such approach also shows efficacy to kill tumor-initiating cells. Data funded by this project grant and others allowed us to validate the therapy and move it to the clinic. Angiosarcoma Awareness, Inc. provided the initial funds to support a dose finding and efficacy trial where we will treat ~20 dogs with hemangiosarcoma using a bispecific ligand targeted toxin. We completed production of the molecule under "Good

Manufacturing Practices" (i.e., suitable for use in human patients) and have enrolled two dogs in the trial as of the date of this report (opened for enrollment at the end of November, 2012). Finally, we identified other potential drugs to treat this disease - or perhaps more likely, the pathways they disrupt as potential targets for development of new therapies.

Grant 01426: *c-Kit Mutation and Localization Status as Response Predictors in Canine Mast Cell Tumors Treated with Toceranib or Vinblastine: A Response-Adaptive Randomized Trial*

Principal Investigator: Dr. Douglas H Thamm, VMD Colorado State University
End Date: 6/30/2013 **Report Received:** 12/18/2012

Report to Grant Sponsor from Investigator:
While surgery remains the mainstay of treatment for canine mast cell tumors (MCT), surgery alone is not curative in some cases, and not possible in other cases. Medical therapy remains an important component of MCT therapy. New drugs that affect signaling through the KIT growth factor receptor are showing considerable promise for the treatment of canine MCT, and MCT with mutations in the KIT protein that make it constantly active may be more sensitive to KIT inhibitors. The drug combination vinblastine and prednisone has roughly the same effectiveness as KIT inhibition against canine MCT; however, the two treatments have not been compared head-to-head, and it is not clear whether vinblastine or KIT inhibitors are more appropriate for the treatment of MCT without KIT mutations. We have recently developed a rapid test, which can be performed on fine-needle aspirates, to determine whether MCT possess KIT mutations or not. We are investigating the predictive value of KIT mutation status using this rapid genotyping assay, as well as KIT staining on biopsy sections, in dogs with measurable MCT randomized to receive either vinblastine or the KIT inhibitor toceranib (Palladia). Randomization utilizes a novel adaptive statistical strategy that makes use of the KIT assay results.