

CANINE HEALTH FOUNDATION

Grants Needing Funding

February 22, 2010



Please note: A minimum contribution of \$2,500 is required to be considered a “sponsor” (ACORNs, indicated by a –A after the grant number, require a minimum contribution of \$1,000 to be considered a “sponsor”).

00613: *The Prognostic Significance of Chromosome Aneuploidy in Canine Lymphoma*

Primary Investigator: Dr. Matthew Breen, PhD

Institution: North Carolina State University

Total Grant Amount: \$113,929.00

Project Abstract:

Background: Lymphoma is the most common life-threatening cancer in dogs, accounting for up to 24 percent of all canine malignancies. A large proportion of canine lymphomas are responsive to chemotherapy, increasing both the length and quality of an affected dog's life. However, there is considerable difference in the response to therapy working and overall survival time. This shows that there is a need to develop more improved forms of classification. In human lymphoma, the use of cytogenetics has been used to show the presence of frequent chromosome abnormalities that have both diagnostic and predictive importance. In previous studies the researchers have identified frequent chromosome abnormalities in canine lymphoma, including copy number changes (aneuploidy) of dog chromosomes 6, 15, 16, and 18.

Objective: In this project the researchers will use molecular cytogenetics to study a collection of lymphoma specimens, taken from dogs that were all treated with the same chemotherapy procedure as part of a clinical trial. This approach will allow us to determine if these frequent copy number abnormalities are able to predict response. This project hopes to increase the sophistication of diagnosis and life expectancy for canine lymphoma.

00615B: *Heritable and Sporadic Genetic Lesions in Canine Lymphoma*

Primary Investigator: Dr. Matthew Breen, PhD

Institution: North Carolina State University

Total Grant Amount: \$149,369.00

Project Abstract:

Background: Certain dog breeds are prone to develop certain types of cancer. Between the late 1960's and the early 1980's researchers related the risk of lymphoma for different dog breeds. Yet, there has been little progress since then to define factors that account for this risk. As part of ongoing programs supported by the AKC CHF, the researchers recently showed that the breed-specific risk of lymphoma extends beyond the simple disease condition to a tendency for specific forms of lymphoma. More importantly, the researchers showed there are frequent chromosomal abnormalities that separate with specific forms of lymphoma and that are more common in Golden Retrievers than in other breeds. This suggests breed-specific profiles of genetic abnormalities will be found in canine lymphoma.

Objective: To continue this work, the researchers are using contemporary "array-based" technologies to identify genes that map to these regions and how they contribute to the disease. The researchers anticipate that the results from this work will allow them to predict how genetic factors influence the occurrence of abnormalities in these genes, and will set the groundwork to identify specific genes associated with breed-dependent cancer risk.

00741: *Polymicrobial Bacteria-Associated Inflammatory Stifle Arthritis/Degenerative Cranial Cruciate Ligament Rupture in Dogs*

Primary Investigator: Dr. Peter Muir, PhD
Institution: University of Wisconsin - Madison

Total Grant Amount: \$153,742.00

Project Abstract:

Background: Knee inflammation that develops in dogs with cruciate rupture is little studied and likely underestimated.

Objective: The researchers are determining whether a relationship exists between joint bacteria and development of knee inflammation/cruciate rupture. The researchers will pursue the following specific plan: determine that a relationship exists between bacteria within the knee joint and the development of inflammatory knee arthritis/degenerative CCL rupture. They expect to determine that bacteria reach the knee joint via the blood stream and then induce persistent inflammation of the lining of the knee joint, degradation of joint tissues, and eventual CCL rupture. With this research, the researchers aim to produce improved medical treatment that will prevent cruciate rupture from developing.

00748: *SNP Association Mapping for Canine Epilepsy*

Primary Investigator: Dr. Ned Patterson, DVM PhD

Institution: University of Minnesota

Total Grant Amount: \$235,872.00

Project Abstract:

Background: Epilepsy is a serious, often inherited, seizure disorder affecting a large number of breeds. The inconsistency in seizure types between breeds suggests that many different genes are likely to contribute to canine epilepsy.

Objective: This project aims to identify chromosomal regions associated with epilepsy in English Springer Spaniels and Australian Shepherds, as a start to identify the contributing gene or genes, and to develop a marker test. The researchers expect to identify an associated chromosome region or regions in English Springer Spaniels and Australian Shepherds, and to develop a screening genetic marker test. Future studies could then look in other breeds to see if they share the same genetic risk factor(s). If successful, this project would serve as excellent proof of the usefulness of this technology for epilepsy and lead to full - scale testing of other breeds in future studies.

00762: *The Mapping and Characterization of Canine Epilepsy Loci*

Primary Investigator: Dr. Gary S. Johnson, DVM PhD

Institution: University of Missouri, Columbia

Total Grant Amount: \$129,600.00

Project Abstract:

Background: Epilepsy is a neurological condition characterized by seizures which result from abnormal brain activity. There is no cure and the medications used to reduce the frequency of seizures are often ineffective and/or have unsatisfactory side effects. While there is strong evidence that canine epilepsy is inherited in many breeds, the patterns of inheritance are often complex.

Objective: The researchers' goal is to identify mutations responsible for epilepsy so that they can devise DNA tests that detect the mutations. These tests can be used by dog breeders to help them avoid matings that produce puppies destined to develop epilepsy. The researchers have collected DNA samples from over 1100 epileptic dogs and nearly 6000 of their relatives. The researchers will study epilepsy in dog breeds from their collection. Then, they will use DNA samples from these four breeds and appropriate mapping strategies to determine the locations of the epilepsy mutations on the dog chromosomes. Then they will examine the genes at these chromosomal locations to identify epilepsy-causing mutations. DNA tests that detect these mutations will be validated and then offered to the dog-owning public.

00768: A Collaborative Study by Veterinary Oncologists, Pathologists and Diagnostic Laboratories to Enhance the Detection, Diagnosis and Treatment of Canine Lymphoma

Primary Investigator: Dr. Ted Valli, DVM

Institution: University of Illinois

Total Grant Amount: \$42,128.00

Project Abstract:

Background: Lymphoma is the most common canine cancer treated by chemotherapy and a most common neoplasm that afflicts dogs of all breeds and ages. Many of the malignancies that occur in dogs are like those that occur in humans, especially for the tumors of the lymphoid system. The World Health Organization has devised a new system of recognizing and categorizing the many subtypes of lymphoid tumors with very different characteristics that must be considered in providing effective treatments. Currently lymphomas in dogs are treated as if they are all of the same type, but we now find that like those in humans the canine lymphomas are of many types that also benefit from specific identification and treatment.

Objective: The goal of this study is to demonstrate that veterinary diagnosticians can effectively apply the human criteria to the canine tumors and thus permit much more effective treatment by veterinary oncologists. This application will alter costs of treatment according to tumor type and increase survival in animal companions that share our lives and environments.

00908: Serotonin Type 2A Receptor Antagonist Therapy for Preventing the Progression of Myxomatous Mitral Valve Disease

Primary Investigator: Dr. Mark A. Oyama, DVM

Institution: University of Pennsylvania - School of Veterinary Medicine

Total Grant Amount: \$81,918.00

Project Abstract:

Background: Canine myxomatous mitral valve disease is very common in older dogs and is similar to the human disorder. Serotonin (5HT) related mechanisms has been found in the certain forms of human heart valve disease, and a beginning study by the investigators has shown heightened 5HT signaling in diseased canine mitral valve interstitial cells (MVIC).

Objective: The researchers are investigating the hypothesis that 5HT signaling contributes to the progression of canine myxomatous mitral valve disease. The researchers seek to 1) further characterize the 5HT signaling pathway in normal and diseased human and canine mitral valve specimens, 2) determine the effects of 5HT-2A receptor antagonism in diseased canine MVIC, 3) perform a dose escalation (Phase I) study of a candidate 5HTR-2A receptor antagonist, ketanserin, in client-owned dogs with myxomatous mitral valve disease, and 4) perform a

controlled comparison (Phase II) study in dogs using ketanserin. Ultrasound studies and measurement of neurohormonal markers will assess effects of therapy on progression of mitral valve disease. This study represents a novel translational study that targets a potential underlying pathogenesis of canine mitral valve disease.

00935A&B: *Positional Cloning of Two Genes for Malignant Histiocytosis (MH) in the Bernese Mountain Dog*

Primary Investigator: Dr. Elaine Ostrander, PhD; Dr. Catherine Andre, PhD
Institution: National Human Genome Research Institute; CNRS - University of Rennes

Total Grant Amount: \$166,400.00

Project Abstract:

Background: Malignant histiocytosis (MH) belongs to a group of histiocytic disorders, which represent a broad array of clinical symptoms. The disease is found in excess in Bernese Mountain Dogs (BMD), Flat Coated Retrievers (FCR), and a small number of other breeds. MH is an aggressive tumor from which affected dogs die quickly. Working together, the Ostrander and Andre labs have each clearly identified two regions of the genome (on chromosomes 8 and 20) with genes causing MH in the BMD.

Objective: The researchers are working to find the exact genes and genetic variants responsible for the disease. It involves finding a common piece of each chromosome that affected dogs likely inherited from a single affected ancestor. Whether the disease is caused by the same mutations in breeds other than the BMD is unknown. Preliminary data suggest they are distinct. As studies are most advanced in the BMD, once genes are identified the researchers will move to the FCR and other breeds to determine if the same, or different mutations are responsible for the disease. Their long-term goal is to produce the information needed for genetic test development.

00945: *Mucosal Gene Expression Profiles in Canine Inflammatory Bowel Disease*

Primary Investigator: Dr. Albert E. Jergens, DVM, PhD
Institution: Iowa State University

Total Grant Amount: \$60,000.00

Project Abstract:

Background: Canine inflammatory bowel disease (IBD) is a chronic intestinal disorder likely resulting from the interaction between genes and environmental factors. While it is generally accepted that luminal bacteria play a critical role in provoking gut inflammation, genetic factors

may also contribute to the bacterial-driven inflammatory response. Several susceptibility genes, such as NOD2/CARD15, have recently been identified in humans with IBD and provide a basis for the development of aberrant immune responses to bacteria in certain individuals. It is reasonable to hypothesize that susceptibility genes also affect clinical disease in dogs with IBD by negatively affecting the interaction with intestinal bacteria and/or their products. Genetic factors are thought to contribute to the pathogenesis of canine IBD as in humans. A role for luminal bacteria is suggested by observations that antibiotics reduce clinical signs, and by reports of increased bacterial numbers in intestinal biopsy specimens obtained from dogs with IBD. Given the recognized breed predispositions, genetic susceptibility to IBD is also likely, although studies are lacking.

Objective: The researchers are utilizing unique molecular biology tools to: (1) identify key genetic factors contributing to disease expression, (2) characterize gene expression profiles which may predict responsiveness to specific therapies, and (3) provide the framework upon which to facilitate identification of IBD susceptibility genes that predispose specific canine breeds to clinical disease.

00947A&B: *Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma*

Primary Investigator: Dr. Matthew Breen, PhD; Dr. Jaime Modiano, VMD PhD
Institution: North Carolina State University; University of Minnesota

Total Grant Amount: \$332,335

Project Abstract:

Background: Certain dog breeds are prone to develop certain types of cancer. Yet, there has been little progress to define the genes that account for this risk.

Objective: For this project, the researchers' goal is to identify genetic abnormalities that are shared by bone tumors and segregate with risk in two dog breeds (Rottweilers and Golden Retrievers) where the disease is prevalent. In collaboration with their colleagues at the University of Michigan and the Broad Institute, they have identified preliminary regions of the genome that may influence risk in Rottweilers. The work described here represents a next step to pinpoint specific genes that are associated with breed-dependent risk, and to predict how heritable factors influence bone cancer in Rottweilers, Golden Retrievers, and other dogs.

00970: *Tissue Regeneration Using Canine Mesenchymal Stem Cells: Effects of Donor Characteristics and ex vivo Expansion on Cell Pluripotency*

Primary Investigator: Dr. Susan Volk, VMD PhD
Institution: University of Pennsylvania - School of Veterinary Medicine

Total Grant Amount: \$165,348.00

Project Abstract:

Background: Special cells can be isolated from bone marrow (mesenchymal stem cells or MSCs) and used to produce different types of cells that form bone, muscle, cartilage or nervous tissue. These cells can be put back into the body in order to replace cells damaged by inherited diseases, trauma, or age associated conditions in order to restore function to a wide variety of tissues and organs. Clinical trial using MSCs in humans are currently underway and provide a basis for exciting new therapies for many of the most common ailments of dogs: heart failure, neurologic conditions, osteoarthritis, kidney and liver diseases and diabetes. A major hurdle in the development of rational stem cell therapy clinical trials in dogs is a general lack of understanding of basic properties of canine MSCs.

Objective: This study will define optimal donor characteristics, culture conditions, and safety for using these MSC to treat dogs. Understanding basic properties of these specialized cells from dogs will bring promising stem cell therapies closer to reality in veterinary medicine.

00982: *Evaluation of Efficacy of Fasaret in Dogs with Osteosarcoma*

Primary Investigator: Dr. Don Bellgrau, Ph.D.

Institution: ApopLogic Pharmaceuticals, LLC

Total Grant Amount: \$199,692.00

Project Abstract:

Background: Osteosarcoma (bone cancer) is a severe disease that occurs commonly in large and giant breed dogs, with as many as 10,000 cases diagnosed each year. More than 85 percent of cases occur in the limbs; treatment, which usually requires amputation of the affected limb plus follow-up chemotherapy, extends the life of dogs by an average of about 1 year. Invariably, death is due to distant spread of the tumor (metastasis), most often to the lungs or to other bones. Metastatic tumors are notoriously resistant to treatment and extended remissions or "cures" are rare, with less than 20 percent of dogs surviving more than 2 years from their diagnosis. The researchers have developed a new gene-based therapy that activates the immune system to prevent or delay recurrence and metastatic spread. The treatment is based on the brief delivery of a gene that induces tumor killing directly or indirectly (by recruiting inflammatory cells to the site), but more importantly, under the conditions this gene is expressed in the treatment setting, it also activates the immune system to recognize and kill the tumor cells. In the laboratory, this response effectively protects animals (mice) from tumor challenges that would otherwise be lethal. Presently, there is no information regarding the safety and efficacy of this therapy in companion animals. The researchers have shown that bone cancer cells are a valid "target" for therapy and have done extensive pre-clinical work to define appropriate starting doses.

Objective: This study will allow us to evaluate if Fasaret can be administered safely as an addition to standard of care for dogs with bone cancer, and if it improves the quality of life and

overall survival of these patients. Specifically, the design will enable us to determine if there are side effects that would limit the application of Fasaret, and the planned 2-year follow-up will allow us to define any increased survival attributable to Fasaret as compared to the expected ~20 percent of dogs that would be alive at this time with standard of care alone.

01093A&B: *Positional Cloning of the Gene(s) for Gastric Cancer in the Chow Chow*

Primary Investigator: Dr. Elaine Ostrander, PhD; Dr. Elizabeth McNeil, DVM PhD
Institution: National Human Genome Research Institute; Michigan State University

Total Grant Amount: \$70,063.55

Project Abstract:

Background: Chow Chows are 10-20 times more likely to develop stomach cancer (gastric carcinoma) compared to dogs of other breeds. This cancer is very difficult to diagnose and is almost always fatal. Studies suggest that this cancer is caused, at least in part, by a faulty gene or genes. Although human studies suggest several candidate genes, none explain the disease in dogs. The researchers have now established a DNA bank for Chow Chows and related breeds.

Objective: The researchers are using new genomic tools, which allow them to question the genome of many dogs simultaneously at 127,000 points in the genome. Looking for differences in DNA variation between affected and unaffected dogs should allow them to identify the region of the genome carrying the causative gene. Additional studies will pinpoint the precise DNA variant causing the disease. These studies are critical for developing effective ways to prevent and treat this devastating cancer in Chows well as other "at risk" breeds.

01099: *Degenerate PCR for Detection of Viral, Bacterial, and Rickettsial Genera in Pugs and Maltese Dogs with Necrotizing and Granulomatous Meningoencephalitis*

Primary Investigator: Dr. Scott Schatzberg, DVM PhD
Institution: University of Georgia

Total Grant Amount: \$67,612.50

Project Abstract:

Background: Meningoencephalitis (ME), inflammation of the brain and its outer layer (the meninges), occurs commonly and typically is fatal in Pugs and Maltese dogs. They are likely many causes for Pug and Maltese ME. Genetic predispositions, environmental triggers (vaccination, infections), and inappropriate immune responses are all likely to play roles in the disease pathogenesis. The environmental triggers for Pug and Maltese ME are unknown. In

human neurology, recent scientific advancements have identified numerous infectious "triggers" for ME. These advances have improved survival rates in people with ME dramatically compared to the situation in Pugs and Maltese dogs.

Objective: The goal is to identify infectious agents associated with Pug and Maltese ME and to ultimately apply targeted antimicrobial therapies to improve survival. The researchers plan to use the polymerase chain reaction (PCR), a molecular biology tool, to study cerebrospinal fluid and brain tissues for the presence of viral, bacterial, and rickettsial organisms. The identification of infectious agents associated with Pug and Maltese ME will profoundly impact diagnostics and treatment for these fatal conditions.

01113: Canine Non-Hodgkin Lymphoma: Characterization and Prognostic Value of Cancer Stem Cells

Primary Investigator: Dr. Timothy D. O'Brien, DVM PhD

Institution: University of Minnesota

Total Grant Amount: \$150,071.40

Project Abstract:

Background: Stem cells are cells which, in general, have the ability to increase to multiple different cell types while at the same time maintaining their own population of different stem cells. Embryonic stem cells are the quintessential stem cell and have the ability to form any tissue of the embryo, fetus, and adult. However, in the adult animal, most tissues or organs also have a stem cell population (adult stem cells) with a more limited collection, which can increase to any of the mature cell types of that organ or tissue (eg. skin, brain, liver, or blood and lymphocyte stem cells). Recently, cells have also been identified in several human and animal cancers that have the essential features of cancer stem cells and which are thought to be responsible for the growth and spread of the tumor. The researchers have identified cells within dog lymphomas that have features highly suggestive of a cancer stem cell. They have also found evidence that increased numbers of these cells tend to correlate with worsening prognosis.

Objective: In this study the researchers goals are: 1) to evaluate the numbers of these suspected cancer stem cells in various subtypes of lymphoma to firmly establish whether increasing numbers of these cells do correlate with worsening prognosis across all forms of canine lymphoma, and 2) to obtain key information regarding which genes are characteristically shown in the cancer stems cells in contrast to those found in the remainder of the tumor cells. Thus, this study will potentially give us a new tool to diagnose canine lymphoma and assess prognosis, and secondly, give a detailed look into the biology of the cancer stem cells, revealing much about their origin and functions and possibly indicating new methods to eliminate these common and lethal cancers.

01130: *Measurement of Minimal Residual Disease Using Real Time PCR in Canine Lymphoma*

Primary Investigator: Dr. Susan E. Lana, DVM
Institution: Colorado State University

Total Grant Amount: \$83,259.00

Project Abstract:

Background: Most canine patients treated for lymphoma (>80%) will achieve complete remission. Cures however, are rare and pets relapse and die of their disease. The cause of this relapse is the presence of lasting malignant cells that eventually grow and become clinically detectable.

Objective: The researchers' goal is to use more sensitive molecular techniques to measurement of minimal residual disease (MRD). Then, it could be incorporated into clinical case management to strengthen treatment strategies; improve patient outcome, and to gain additional insight into the basic biology of lymphoma.

01139: *Immune Targeting of Canine Hemangiosarcoma Using a Canine Derived Single Chain Antibody Approach*

Primary Investigator: Dr. Nicola Mason, PhD
Institution: University of Pennsylvania - School of Veterinary Medicine

Total Grant Amount: \$123,125.40

Project Abstract:

Background: Canine hemangiosarcoma is a common and highly aggressive tumor of blood vessels that is often fatal. At diagnosis most dogs have evidence of metastatic disease and despite chemotherapy, survival times rarely exceed 6 months. New approaches to the treatment of this disease are needed. The use of monoclonal antibodies and antibody fragments to directly target different tumors has shown promise in clinical trials in man.

Objective: This project aims to use a new canine synthetic antibody system to target the tumor and deliver cytotoxic agents directly to both primary and metastatic lesions. Using advanced molecular techniques, the researchers intend to review antibody responses that dogs with hemangiosarcoma may make against their own tumors and use these as a template to generate canine antibody fragments that specifically recognize tumor particles. Tumor-specific antibody fragments will be linked to an exotoxin and evaluated for their ability to kill canine hemangiosarcoma cells in vitro. This allows for the direct delivery of cytotoxic agents to the tumor, which decreases side effects and increases therapeutic value. This work aims to develop the first canine-derived, tumor-specific targeting approach for the treatment of HSA and to

provide proof-of-principal for this approach that can then be used to therapeutically target many other tumor types in this species in vivo.

01142: *Cutting Balloon Valvuloplasty for Dogs with Subaortic Stenosis*

Primary Investigator: Dr. Amara H. Estrada, DVM

Institution: University of Florida

Total Grant Amount: \$38,433.60

Project Abstract:

Background: Treatment for subaortic stenosis (SAS) in canine clinical patients is frustrating and there exists a great need from both the veterinary community and the dog owner/breeder population for better treatment options. Balloon dilation of the stenosis is a type of interventional procedure used in veterinary medicine for dogs with stenosis of the pulmonary valve. Balloon dilation in dogs with SAS however, has not proven effective or beneficial. A new balloon dilation catheter has been developed for use in the management of resistant coronary artery and peripheral pulmonary artery lesions in humans. The balloon has been modified to also have very small blades, approximately 2mm, which are used to score or cut the stenotic, or narrowed, tissue when the balloon is maximally inflated. This technique has proven successful in children and young adults with lesions previously resistant to balloon dilation.

Objective: The study is using these new techniques and procedures in dogs with severe SAS, in hopes of providing a new treatment option for this currently untreated disease in dogs.

01152: *Liposomal Bisphosphonate Therapy for Malignant Histiocytosis*

Primary Investigator: Dr. Steven W. Dow, DVM PhD

Institution: Colorado State University

Total Grant Amount: \$47,277.90

Project Abstract:

Background: Malignant histiocytosis (MH) is a common and aggressive and often fatal tumor of Bernese Mountain dogs. The tumor also affects flat-coated retrievers, Golden Retrievers, and Rottweilers. There are currently no effective medical treatments for the disease, which often spreads widely. Preliminary studies in the laboratory suggest that a compound known as liposomal clodronate (LC) can kill dog MH cell lines in vitro and elicit significant tumor shrinkage in at least one dog with MH.

Objective: The researchers are conducting additional studies to understand better how LC kills MH cells, whether LC can be combined with other types of chemotherapy to increase tumor

control, and to assess the potential safety and efficacy of this novel treatment approach in a pilot study of dogs with MH. If shown to be effective, LC would offer a non-toxic and relatively inexpensive new approach to the treatment of MH In dogs.

01227-A: *Specificity and Sensitivity of the Pancreatic Lipase Immunoreactivity (SPEC cPL) Test for the Diagnosis of Canine Pancreatitis*

Primary Investigator: Dr. Stanley L. Marks, BVSc, PhD

Institution: University of California, Davis - School of Veterinary Medicine

Total Grant Amount: \$11,531.00

Project Abstract:

Background: Pancreatitis is a common, debilitating disease in dogs. The non-invasive diagnosis of canine pancreatitis remains a challenge despite the start of abdominal ultrasound and pancreas-specific blood tests. The pancreatic lipase immunoreactivity (PLI) test was developed to address these concerns. A modification of this test, the SPEC cPL, is currently marketed as a non-invasive diagnostic test for canine pancreatitis. Interpretation of abnormal SPEC cPL test results in the absence of other supportive signs or diagnostic tests has been problematic.

Objective: The purpose of this study is to assess exocrine pancreatic lesions in the dog and compare the severity of lesions or lack thereof with changes in SPEC cPL and other commonly performed blood tests.

01232-A: *Investigation of NF-kB as a Therapeutic Target in Canine Lymphoma*

Primary Investigator: Dr. Nicola Mason, PhD

Institution: University of Pennsylvania - School of Veterinary Medicine

Total Grant Amount: \$12,878.57

Project Abstract:

Background: Lymphoma is the most common hematopoietic cancer in dogs and is currently treated using a combination of chemotherapeutic agents which inhibit cell division and induce cell death. Over the past 30 years, many chemotherapeutic protocols have been used and most induce remission in 65-96% of patients. However, regardless of induction protocol, 85-90% of patients relapse with lethal, drug-resistant lymphoma within 6 to 9 months of diagnosis.

Objective: The researchers hypothesize that constant activation of a major intracellular signaling pathway (the NF-kB pathway) in the cancerous lymphoma cells contributes to their enhanced increase, survival, and resistance to chemotherapeutic drugs. The researchers aim to investigate NF-kB signaling pathways as potential targets for inhibition. This preliminary work aims to build

the groundwork for the use of selective NF- κ B inhibitors as extra agents to increase the sensitivity of cancer cells to chemotherapy. It is anticipated that this work will provide the preliminary data necessary to initiate a pilot clinical trial to evaluate NF- κ B inhibition as an adjunct to chemotherapy to enhance clinical response at the time of diagnosis and/or during rescue therapy.

01248: *Whole Genome Association Analyses for Cryptorchidism in Dogs*

Primary Investigator: Dr. Max Rothschild, PhD

Institution: Iowa State University

Total Grant Amount: \$74,104.00

Project Abstract:

Background: Cryptorchidism, or retained testicles, is one of the common congenital problems in dogs. The testes of cryptorchids are more prone to testicular cancer and infertility. Therefore, cryptorchids and animals carrying genes for cryptorchidism should be eliminated from the breeding population. Some evidence exists to suggest that it appears to be a multigenic trait but single genes with large effects may exist. In earlier studies, the researchers utilized a candidate gene approach using 50 polymorphisms (called SNPs) in 22 candidate genes and found that collagen 2A1 (COL2A1) was significantly associated with cryptorchidism in Siberian Huskies. Now, they need to use the whole genome association analysis which typically provides more comprehensive analyses of chromosomal regions associated with a particular trait. This will then allow them to confirm previous findings or suggest other contributing regions or genes.

Objective: The researchers will utilize a new tool called the canine SNP chip which allows them to genotype for over 200,000 genetic differences between affected and unaffected animals. All results will be published and available freely to all dog breeders and they also aim to develop a test to remove the defect from the population.

01262: *Sequencing and Functional Analysis of the Canine Y Chromosome*

Primary Investigator: Dr. William J. Murphy, PhD

Institution: Texas A&M University

Total Grant Amount: \$106,309.00

Project Abstract:

Background: Studies of the human and mouse Y chromosomes have shown they contain many testis-specific genes that, when defective, cause infertility and sperm abnormalities. The causes of male infertility in dogs are not well known. Though a high quality draft genome sequence

exists for the canine autosomes and X chromosome, virtually nothing is known about the canine Y chromosome and the genes it harbors.

Objective: The researchers will use an existing map of the canine Y chromosome to generate a comprehensive sequence of the chromosome, and explain the sequence for coding and non-coding potential using cDNAs selected from a large number of canine tissues. The identification of a comprehensive set of canine Y chromosome genes, their regulatory regions and noncoding RNAs will provide targets for development of molecular diagnostic tests that examine the influence of these genetic elements on canine male infertility as well as many other sexually dimorphic traits.

01265: Understanding Mechanisms Involved in Canine Autoimmune and Inflammatory Disorders

Primary Investigator: Dr. Ronald Sluyter, Ph.D.

Institution: University of Wollongong

Total Grant Amount: \$48,730.00

Project Abstract:

Background: Autoimmune and inflammatory disorders have a major impact on the quality of life and lifespan of dogs. Studies in humans show an important role for an immune cell molecule (termed P2X7) in autoimmune and inflammatory disorders including inflammatory pain. P2X7 in these disorders has an ability to cause the release of key molecules (termed interleukins) that drive immunity and inflammation. Thus, P2X7 is attracting international interest as a therapeutic target in humans and currently undergoing clinical trials in patients with autoimmune or inflammatory disorders. The researchers have recently identified P2X7 on immune cells from dogs.

Objective: The researchers will study P2X7 on canine immune cells, and its role in canine immunity and inflammation. They will also study the P2X7 gene in various dog breeds to determine if P2X7 differs between breeds and whether these differences contribute to disease susceptibility. New information about canine P2X7 will enable the use of currently available compounds and the development of other compounds to target P2X7, and treat autoimmune and inflammatory disorders, as well as inflammatory pain in dogs.

01271A&B: Mapping of Additional Genes Associated with Canine Degenerative Myelopathy

Primary Investigator: Dr. Kerstin Lindblad-Toh, PhD; Dr. Joan Coates, DVM

Institution: Broad Institute; University of Missouri, Columbia

Total Grant Amount: \$160,000.00

Project Abstract:

Background: Degenerative myelopathy (DM) is a fatal disease of the spinal cord causing progressive paralysis in mature dogs. In grant 821 these researchers performed genome-wide association mapping and identified an SOD gene mutation which is present in many breeds. A DNA test can now identify dogs at risk of developing DM, although many dogs that have the mutation never develop clinical symptoms. The availability of the DM test has raised questions that must be answered before the test can be used by dog breeders.

Objective: The researchers aim to find out if there genetic modifiers that could explain why some dogs with the mutation develop DM at 8 years of age while other 15 year-old dogs with the same mutation remain symptom free and if there are other mutations in the SOD1 gene or elsewhere that can cause DM or DM-like-diseases. The identification of modifier genes could prove particularly useful in breeds like the Boxer and Pembroke Welsh Corgi where the primary mutation is common, because it might provide an option for selecting away from DM without disrupting breeding programs. Identification of additional genes will also give a better understanding of the disease and allow development of potential treatment strategies.

01272: *Isolation and Characterization of Canine Induced Pluripotential Stem Cells (iPS)*

Primary Investigator: Dr. Jorge Piedrahita, PhD

Institution: North Carolina State University

Total Grant Amount: \$82,610.00

Project Abstract:

Background: Stem cells have tremendous promise to alleviate clinical conditions in dogs such as spinal cord damage, hematopoietic malignancies, and cardiac and hepatic disease. While a range of adult stem cells have been isolated and studied, most of these have a limited capacity to differentiate outside a living organism and inside a living organism. Recently, approaches have been developed to convert differentiated cells into cells resembling embryonic stem (ES) cells by the use of "reprogramming" factors. These cells referred to as induced pluripotential stem cells (iPS) have the ability, like ES cell, to differentiate into multiple tissue types. As virtually any cell can be converted to an iPS cell this means that it is now possible to isolate patient-derived stem cells.

Objective: The researchers will utilize this technology for the development of canine iPS. Briefly, adipocyte-derived mesenchymal cells and keratinocytes will be transformed with the required reprogramming factors and plated under a condition that allows development of iPS cells. Colonies will be selected, expanded, and studied for their ability to differentiate outside a living organism into multiple tissue types. The development of patient-specific pluripotential

stem cells is a critical step toward the successful scientific application of this promising technology.

01311: *Genome-wide association mapping study of hypertrophic osteodystrophy in Irish Setters*

Primary Investigator: Dr. Keith E. Murphy, PhD

Institution: Clemson University

Total Grant Amount: \$74,237.00

Project Abstract:

Background: Hypertrophic osteodystrophy (HOD) is a debilitating, metabolic bone disease that, in mild cases, can lead to deformation of mature bone, and in severe cases, can require euthanasia of affected dogs. At present, the cause of HOD is unknown. Most cases of HOD are observed shortly after vaccinations, the most often proposed causes are distemper virus infection, post-vaccination infection, bacterial infection, or other viral infections. The predominance of HOD in several breeds of dog suggests a heritable component of the disease. Due to the complex nature of the immune system and its many components, analysis of candidate genes would have to be exhaustive.

Objective: The researchers aim to identify genes involved in HOD with the whole genome association mapping using the canine single nucleotide polymorphism (SNP) chip. This resource will identify regions exhibiting linkage with HOD. Such regions will then be assessed for gene(s) involved in the disease.

01312: *Association mapping study of Legg-Calve-Perthes Disease in the West Highland White Terrier, Yorkshire Terrier, and Miniature Pinscher*

Primary Investigator: Dr. Keith E. Murphy, PhD

Institution: Clemson University

Total Grant Amount: \$78,688.00

Project Abstract:

Background: Legg-Calve-Perthes Disease (LCPD) is a debilitating developmental disease that affects small breeds of dog, particularly terrier breeds. The only outward indications of this condition are pain, lameness, and muscle atrophy of the hip joint. These signs are not exclusive to LCPD, and are often attributed to minor trauma during the early stages of disease. LCPD is primarily diagnosed by radiographic changes of the femoral head within the hip joint. Due to the developmental nature and the unknown etiology of the disease, LCPD is difficult to predict and prevent. No disease mapping strategies have been employed to date.

Objective: This study is using the Affymetrix canine single nucleotide polymorphism (SNP) chip to identify regions that are linked to LCPD in the West Highland White Terrier, Yorkshire Terrier, and Miniature Pinscher breeds.

01313: Identification of a Genetic Marker for Familial Aortic Stenosis in the Rottweiler

Primary Investigator: Dr. Kathryn Meurs, DVM PhD
Institution: Washington State University

Total Grant Amount: \$27,651.00

Project Abstract:

Background: Subvalvular Aortic Stenosis is a congenital heart defect characterized by a fibrous ridge located below the aortic valve. Affected dogs are at risk of developing heart valve infections, congestive heart failure or sudden death. This trait has been reported with increasing frequency in the Rottweiler and the researchers have previously determined it to be inherited in this breed. They have collected DNA samples from affected and unaffected Rottweilers.

Objective: The researchers aim to use the most modern genetic techniques to identify the genetic location of this trait in the Rottweiler and eventually identify the actual genetic mutation associated with this trait.

01317: Mutation Detection and Functional Analysis of Multiple Loci for Osteosarcoma

Primary Investigator: Dr. Kerstin Lindblad-Toh, PhD
Institution: Broad Institute

Total Grant Amount: \$80,692.20

Project Abstract:

Background: Osteosarcoma (OSA) is a considerable canine health concern, affecting 8,000-10,000 dogs in the United States annually. In the completed CHF study "Mapping Genes Associated with OSA in Large Breed Dogs", the researchers identified six genomic regions associated with osteosarcoma (OSA) in Rottweilers and Greyhounds. In study 758, they conducted fine-mapping of these candidate regions using additional Rottweiler and Greyhound samples as well as samples from eight other breeds (Golden Retrievers, Labrador retrievers, Leonbergers, Great Pyrenees, Mastiffs, Great Danes, Irish Wolfhounds and boxers). All six loci are supported and have been narrowed to a discreet size. Some loci are present in some breeds,

some in others. The majority of candidate genes in associated regions have been re-sequenced, but no associated protein changes identified.

Objective: The researchers will re-sequence the whole regions of association in cases and controls to identify candidate mutations. Once mutations have been found they aim to survey multiple breeds to see if they share the same mutations. This will make it possible to develop and apply genetic tests for OSA. The researchers will also study the functional consequences of the mutations, which will lead to a better understanding of the disease, enabling development of more targeted treatment options.

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

Primary Investigator: Dr. Deborah Knapp, DVM; Dr. Elaine Ostrander, PhD
Institution: Purdue University; National Human Genome Research Institute

Total Grant Amount: \$86,899.75

Project Abstract:

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.

01341-A: *Sample Collection, Pedigree Analysis and Candidate Gene Screen for Protein-Losing Enteropathy in Yorkshire Terriers*

Primary Investigator: Dr. Nate Sutter, PhD
Institution: Cornell University

Total Grant Amount: \$12,722.00

Project Abstract:

Background: Protein-losing enteropathy (PLE) is a life threatening condition diagnosed in many breeds including Soft Coated Wheaten Terrier, Basenji, Lundehund, Chinese Sharpei and Yorkshire Terrier. The syndrome is particularly prevalent in Yorkshire Terriers. These dogs commonly suffer from chronic diarrhea and lose protein into the intestine. A variety of abnormalities in the intestinal lining are thought to be involved. While dietary changes sometimes help, treatment is supportive rather than curative. As many as half or more of all cases of PLE in Yorkshire Terriers become fatal.

Objective: The researchers want to identify the genetic risk factor(s) that predispose Yorkshire Terriers to this syndrome. These genetic factors may also be present in other breeds, a hypothesis that can be tested once the factors are identified in Yorkshire Terriers. The researchers are collecting blood samples for DNA, pedigrees, and clinical data from affected and unaffected Yorkshire Terriers. They will analyze the pedigrees for patterns of co-ancestry. They will also sequence a gene, syndecan 1, that is a key player in PLE in people, as they hypothesize it plays a role in canine PLE.

01344-A: *Comparison of percentage of T regulatory cells in dogs with spontaneously occurring lymphoma following oral versus intravenous cyclophosphamide*

Primary Investigator: Dr. Kimberly A. Selting, D.V.M.

Institution: University of Missouri, Columbia

Total Grant Amount: \$12,852.00

Project Abstract:

Background: Lymphoma, a cancer of the lymph nodes, is among the most common cancers seen in dogs. Although highly responsive to chemotherapy, almost all dogs ultimately relapse and die of this disease. Subsets of immune cells called T regulatory cells (Tregs) determine what cells belong in your body. Tregs can prevent other immune cells from attacking cancer in the body, and are therefore thought to be harmful to the body's ability to fight off cancer. They have not been evaluated in dogs with lymphoma. Additionally, some drugs that treat lymphoma, such as cyclophosphamide, can decrease Tregs.

Objective: The researchers aim to characterize the population of Tregs in dogs with lymphoma before they are treated, and then after they receive cyclophosphamide. This will also allow them to compare injected to oral cyclophosphamide. No study has ever appropriately compared these two ways to give cyclophosphamide to decide which is better. By considering the effects on Tregs, the side effects and the efficacy, the researchers will be able to recommend the best way to use this drug, and will understand more about Tregs in lymphoma so that they can do more studies to learn how to use this to their advantage when they treat dogs.

01345-A: *Circulating Isoforms of B-type Natriuretic Peptide and the Pathogenesis of Canine Heart Failure*

Primary Investigator: Dr. Phillip F. Solter, DVM, PhD
Institution: University of Illinois

Total Grant Amount: \$12,740.00

Project Abstract:

Background: Congestive heart failure is a common cause of morbidity and mortality in many dog breeds. The physiological changes responsible for the debilitating symptoms caused by sodium and fluid buildup are poorly understood. This has hampered the development of appropriate treatments and management of this disease. One important factor responsible for the progression of the symptoms of canine congestive heart failure may be that such dogs develop an apparent lack of response to a major rescue hormone that is normally produced by cardiac cells to prevent the symptoms of heart failure. The hormone, B-type natriuretic peptide (BNP), is produced in large amounts, but appears ineffective in alleviating the symptoms of heart failure. Studies in non-canine species suggest that the cause of this may be production of inactive forms of BNP.

Objective: The goal of this project is to determine whether circulating forms of inactive BNP occur in dogs with heart failure and therefore play a potential role in the occurrence of heart failure symptoms. The results of this study will be used to direct further studies into the diagnosis and management of this debilitating and common canine disease.

01346-A: *Genetic Basis of Sebaceous Adenitis in Dogs*

Primary Investigator: Dr. Sandra N. Koch, DVM
Institution: University of Minnesota

Total Grant Amount: \$12,960.00

Project Abstract:

Background: Sebaceous adenitis (SA) is an inflammatory skin disease of unknown cause. It has been reported in several breeds of dogs, most commonly Standard Poodles, Akitas and many others, including Havanese dogs. Dogs with SA often present a dull and brittle haircoat and variable degrees of hair loss. If secondary bacterial skin infection is present, itching and discomfort may occur. Very importantly, SA cannot be cured, requiring long term treatment. There seems to be a genetic predisposition in SA; however, the exact mode of inheritance remains unknown. The clustering of SA in Havanese dogs indicates that there is very likely a significant genetic component and possibly a related gene of major effect.

Objective: The purpose of this study is to enroll several affected and non-affected Havanese dogs in order to develop a DNA bank of samples and hopefully determine the mode of inheritance of SA in this breed. The ultimate goal of this study is to provide preliminary data for identification of the genes causing susceptibility to SA in Havanese dogs and potentially for production of a DNA-based marker test to assist breeders in reducing the incidence of SA.

01354-A: *Heritability of Calcium Oxalate Urolithiasis in Miniature Schnauzers*

Primary Investigator: Dr. Ned Patterson, DVM PhD

Institution: University of Minnesota

Total Grant Amount: \$12,960.00

Project Abstract:

Background: Urinary stones composed of calcium oxalate are common in Miniature Schnauzers. In fact, Miniature Schnauzers have more than 10 times the risk of developing calcium oxalate stones compared to other dog breeds. The predisposition of Miniature Schnauzers to this disease strongly supports an underlying genetic basis.

Objective: This project involves the collection of pedigrees and DNA samples from Miniature Schnauzers with and without calcium oxalate stones. The goal is to identify how the disease is inherited and lay the groundwork for future genetic studies to identify a susceptibility gene or genes. An understanding of the genetic basis of calcium oxalate stones is fundamental to the development therapeutic and preventative strategies in Miniature Schnauzers and other breeds.

01384-A: *Improved Imaging to Monitor Therapy Response of Urinary Bladder Cancer Using 3D Volume Ultrasonography*

Primary Investigator: Dr. James F. Naughton, DVM

Institution: Purdue University

Total Grant Amount: \$12,960.00

Project Abstract:

Urinary bladder cancer (transitional cell carcinoma, TCC) strikes 20,000 to 30,000 pet dogs each year in the United States, and TCC prevalence is increasing. Breeds with the highest risk for developing this type of cancer include the Scottish Terrier, West Highland White Terrier, Shetland Sheepdog, Beagle and the Wire Hair Fox Terrier. Although substantial progress is being made in TCC treatment, most dogs eventually die from the cancer. The purpose of the proposed work is to determine a new method to measure TCC masses in the bladder, and therefore to be able to accurately determine the response to TCC therapy. There are three main

reasons that this is so important. 1. In each individual dog, the change in tumor size is used to determine if the treatment the dog is currently receiving is being effective in that dog. If the cancer is regressing or remaining stable, the same treatment is continued. If the cancer is increasing in size, it is important to recognize this and switch to a different treatment. 2. There are several new therapies that may potentially work against TCC, and it is crucial to be able to measure the tumor size and thus the efficacy of these new therapies in dogs in clinical trials. 3. The currently available methods to measure TCC all have disadvantages or serious limitations. Computed tomography (CT, CAT scan) is the most accurate way to measure tumor volume, but this test is prohibitively expensive for most pet owners. CT also requires general anesthesia, and visualization of bladder masses requires urinary catheterization, both of which involve some risks. Two dimensional ultrasound (2D US) is currently most often used to measure TCC at our institution and other institutions. Tumor volume is estimated by evaluating US images that are made from two different angles, as the US probe is moved over the bladder multiple times. This technique may be inaccurate if the bladder is not distended to the same degree each time the ultrasound exam is done on the dog, or if the US probe angle varies. To increase the accuracy, at our institution, the same person performs the US on each dog at each of the dog's visits. This is not a practical approach for many hospitals. Here we propose the evaluation of an exciting novel approach to measure TCC masses: three dimensional ultrasound (3D US). New, cutting edge technology allows 3D images to be produced from a single scan with a 3D US probe. In fact, once the US probe is placed in an optimal position over the bladder, the operator does not move the probe. Instead, an automated process captures the 3D volume with no operator movement. Thus the results are much less dependent on the same person doing each scan. In addition, the images are produced with the dog awake, and bladder catheterization is not expected to be required. In the study, 3D US will be tested in 10 dogs with comparison made to the gold standard, CT. The success of this study will allow an accurate, repeatable and cost-effective method for monitoring therapeutic success and allow for more timely and accurate adjustments in therapeutic regimens. Although the cost of 3D US equipment has been initially high, like most new technologies, the costs are rapidly dropping to an affordable investment in veterinary hospitals. In addition to imaging TCC, gaining experience with this technique is expected to allow its use to be expanded into assessing other types of cancer.