Dear Fellow Dog Lover,

We work together to help improve the health and lives of dogs, accomplished through peer-reviewed excellence in humane canine health research. Within these pages are the currently active research grants being funded through the AKC Canine Health Foundation (CHF). Since 1995 CHF has addressed the important health needs of our closest companions. Alongside our donors and through the funding of peer-reviewed scientific research, CHF’s mission to improve the health and well-being of dogs is being met through our research and educational programs growth and outreach.

This issue of the CHF Research Grants Portfolio represents active research projects categorized by research program area, and specifically selected to advance the Foundation’s mission for healthier dogs. Each grant proposal is reviewed through CHF’s rigorous peer review process including the CHF Scientific Review Committee (akcchf.org/Scientific-Review-Committee) and with experts from across the scientific community. Each grant is assessed for scientific merit, impact in the field of study, and significance to dogs and their people. CHF embraces the concept of One Health where both dogs and people can benefit from scientific advancements. The peer-review process ensures the contributions of our donors will be directed to studies that have the greatest potential benefit for dogs.

You will find the study abstracts listed on the following pages represent cutting-edge research as well as applied clinical studies chosen to improve the lives of dogs and contribute to our understanding of complex disease processes, including genetics. The program areas funded by CHF represent a broad range of concerns across general canine health as well as within specific breeds and body systems. Through defined research program areas (page 2) CHF addresses unmet health needs for dogs and areas of immediate opportunity for impact, while applying recent advancements in science and technology to canine health research.

From the CHF Board of Directors and Staff, and from the dogs whose lives are positively impacted by this work, we thank you for your interest, passion and generosity.

Sincerely,

Calvin B. Carpenter

Calvin B. Carpenter, DVM, MBA, DACLAM
Executive Director

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The Effects of Early Life Experience on Working Dog Temperament and Cognition

Principal Investigator: Emily Bray, PhD; University of Arizona
Total Grant Amount: $105,949
Grant Period: 5/1/2018 - 10/31/2020

Project Abstract: Working dogs provide irreplaceable services and support to their handlers and communities. However, only around 35% of dogs bred for this purpose are ultimately successful. Therefore, improvements to methods for working dog breeding, rearing, training and selection could lead to major advances including increases in the supply of trained dogs and reductions in the expense required to train them. Some of the earliest, yet most formative, interactions that occur in a mammal's life are those involving its mother, and yet, best canine mothering practices are not well-established or studied. In collaboration with Canine Companions for Independence, the investigators will quantitatively assess levels of maternal behavior in order to: 1) examine associations between maternal behavior and offspring temperament, cognition and neuroendocrine profiles at eight weeks of age; 2) compare maternal style and puppy behavioral, cognitive, and neuroendocrine profiles between different types of early rearing environments (private home versus professional center); and 3) identify temperament and neuroendocrine predictors of individual differences in maternal style. These components will reveal how differences in the early environment affect working dog development, and the extent to which individual differences in maternal style can be predicted from temperamental and neuroendocrine characteristics of the dam. This research will provide foundational data regarding how early-life experiences influence puppy development, and how these processes can be optimized to promote the healthy development of dogs well-suited to the demands of diverse working roles.
Longitudinal Comparison of Cognitive and Emotional Development in Assistance Dog Puppies

Principal Investigator: Brian Hare, PhD; Duke University
Total Grant Amount: $107,880
Grant Period: 4/1/2020 - 3/31/2024

Project Abstract: A revolution in our understanding of dog cognition has occurred in the past decade, with previous work by the Hare research group linking individual differences in cognition to working dog performance in adults. However, there has yet to be a large-scale longitudinal study tracking the course of cognitive development in any breed of puppies, and limited understanding of how different rearing strategies influence the development of canine cognition. This study will characterize the development of the cognitive traits that this team’s previous work has shown predicts a dog’s ability to succeed in assistance dog training.

Working with the Canine Companions for Independence (CCI), cognitive traits will be characterized using a longitudinal design during the critical period of brain development from 8-20 weeks of age. Next, to test for the influence of different but common service dog rearing strategies on these skills, the investigators will test individual CCI puppies reared in human homes or together with same age peers on a college campus. In studying the cognitive abilities of service dogs, a better understanding of what psychological mechanism(s) successful service dogs rely on or are constrained by when helping humans will be detailed. This information can be used to better predict which puppies will be successful service dogs – improving the success of training while increasing the potential number of service dogs available. These findings will also provide the first set of baseline data on normal cognitive development in dogs as it relates to success in training programs and socialization strategies.
Whole Blood Transcriptome Profiling of Dogs with Immune-Mediated Hemolytic Anemia (IMHA)

**Principal Investigator:** Steven Friedenberg, DVM, PhD; University of Minnesota

**Total Grant Amount:** $53,471

**Grant Period:** 4/1/2018 - 9/30/2020

**Project Abstract:** Immune-mediated hemolytic anemia, or IMHA, is a common autoimmune disease in dogs in which the body's immune system attacks its own red blood cells. Red blood cells are critical for transporting oxygen. Many dogs affected by IMHA require extensive hospitalization and blood transfusions, and often have fatal disease-related complications. While dogs of every breed can get IMHA, many spaniel breeds are overrepresented. Despite its high morbidity and mortality, IMHA and its triggers are still not well understood, which hinders the potential to develop treatments and stop this disease in its early stages. In this study, the investigators will use RNA sequencing to evaluate the genes that are active in the blood of dogs who have been newly diagnosed with IMHA. Comparing this data with that of healthy dogs without IMHA will allow the investigators to determine which genes are turned on in the early stages of IMHA. Additionally, this data may have future use in determining if any specific genetic changes are associated with activating these early onset genes. The investigators hope to identify genes which might be novel therapeutic targets for intervention in IMHA and identifying specific variants in these genes may improve understanding of which dogs are at risk for developing IMHA.
Immunoprofiling to Combat Canine Immune Thrombocytopenia

**Principal Investigator:** Marjory Brooks, DVM; Cornell University  
**Total Grant Amount:** $16,106  
**Grant Period:** 8/1/2018 - 1/31/2021

**Project Abstract:** Autoimmune disease develops in dogs when their immune system destroys normal healthy cells in the body. Immune thrombocytopenia (ITP) is a serious bleeding disorder that results from immune destruction of platelets, small blood cells that play a critical role in preventing bruising and bleeding after injury. Old English Sheepdogs and Cocker Spaniels appear to have a susceptibility to ITP, however, ITP afflicts all dogs regardless of breed. Dogs with ITP develop bruises and, in the most severe cases, may bleed from the intestinal and urinary tract or have fatal blood loss. Fortunately, most dogs survive ITP, but may relapse months to years after a first episode. The treatment of ITP involves protracted courses of potent immunosuppressive drugs that impact quality of life for both dog and owner. This study will use a genetic approach to understand what causes ITP. The investigators will identify laboratory markers that predict bleeding severity to aid veterinarians in treatment selection. The goals of this research are to improve ITP diagnosis and predictions of relapse, leading to targeted therapies that minimize treatment side effects.

*Funding for the research is provided through the collaborative efforts and generosity of the Old English Sheepdog Club of America and English Cocker Spaniel Club of America Health and Rescue Organization. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Reducing Misdiagnosis of Immune-Mediated Hemolytic Anemia

**Principal Investigator:** Unity Jeffery, VetMB, PhD; Texas A&M AgriLife Research

**Total Grant Amount:** $5,995

**Grant Period:** 2/1/2019 - 7/31/2020

**Project Abstract:** Immune-mediated hemolytic anemia (IMHA) is a common life-threatening disease requiring intensive and expensive therapy. Veterinarians often diagnose IMHA using a saline agglutination test. This test aims to distinguish red cell aggregates induced by antibodies from non-immune-mediated red cell interactions. However, this test can produce up to 20% false positives, thus requiring an improved test. One reason for the high false positive rate may be the test’s use of a 1:1 ratio of saline to blood, which may not be sufficient to break apart non-immune-mediated red cell interactions. This study will determine if increasing the ratio of saline to blood will reduce false positive results. The results could improve the diagnostic test and prevent misdiagnosis of IMHA and unnecessary immunosuppressive therapy.
Resolving the Major Dyslipidemia Phenotypes and Genetic Risk Factors for Familial Hyperlipidemia in Miniature Schnauzers

**Principal Investigator:** Eva Furrow, VMD, PhD; University of Minnesota  
**Total Grant Amount:** $98,404  
**Grant Period:** 4/1/2020 - 3/31/2022

**Project Abstract:** Familial hyperlipidemia reportedly afflicts more than 75% of Miniature Schnauzers by 10 years of age. This condition is defined as too much circulating lipid (fat) in the bloodstream. Familial hyperlipidemia predisposes dogs to other serious diseases which impact their health and wellbeing. Management of familial hyperlipidemia is hampered by gaps in the understanding of its metabolic and genetic origin. Investigators aim to uncover the metabolic and genetic causes of hyperlipidemia in Miniature Schnauzers. Preliminary data revealed evidence for more than one type of familial hyperlipidemia within the breed. In this study, metabolomics/lipidomics will be used to identify and quantify over 2000 substances in the blood related to metabolism of lipids and other nutrients, classifying them into types of familial hyperlipidemia. Whole genome sequencing will be used to generate a list of hyperlipidemia mutations that may contribute to one or more types of familial hyperlipidemia. Identifying the different types of familial hyperlipidemia and their respective genetic risk factors in Miniature Schnauzers will lead to improved understanding and treatment of the condition, with individualized therapies and genetic tests used to identify at risk dogs that will benefit from early intervention and monitoring.
Use of Gene Therapy to Treat Dilated Cardiomyopathy

Principal Investigator: Margaret Sleeper, BS, VMD; University of Florida
Total Grant Amount: $146,774
Grant Period: 9/1/2016 - 2/28/2021

Project Abstract: Dilated cardiomyopathy (DCM) is the second most common cause of heart disease in dogs, and medical management of the secondary signs is the only therapeutic option. The outcome for affected dogs depends on the stage of disease and the breed. Once diagnosed, dogs typically exhibit rapid and uniform progression to congestive heart failure (CHF), with most living less than 6 months. Previous research has shown that heart function is critically dependent upon calcium channel function. These gate-like channels found within the wall of cardiac muscle cells open and close, allowing calcium ions to flow into the cell. Calcium influx then regulates muscle contraction. Heart disease is strongly associated with malfunctioning calcium channels within cardiac cells. Gene transfer strategies to reduce calcium cycling abnormalities improve heart function in animal models as well as in human clinical trials. In this study, Dr. Sleeper will conduct a placebo-controlled, double blinded study to evaluate gene delivery approaches for treatment of Doberman Pinschers affected with DCM and CHF. If results show that the gene delivery slows progression of heart failure in Dobermans with DCM, the results will have significant ramifications for all dogs with heart disease, as calcium handling proteins are abnormally expressed in dogs with heart disease of varying causes.
Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Bullmastiffs

**Principal Investigator:** Joshua Stern, DVM, PhD; University of California, Davis  
**Total Grant Amount:** $55,173  
**Grant Period:** 4/1/2017 - 8/31/2020

**Project Abstract:** Subvalvular Aortic Stenosis (SAS) is a 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. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Bullmastiffs and other breeds. Studying this disease in Bullmastiffs has the potential to identify a genetic mutation and develop a test for this condition. Ultimately the identification of a mutation in Bullmastiffs would aid breeders in making decisions to reduce the prevalence of this condition. The objective of this study is to use the most modern genetic techniques to identify the genetic cause of SAS in Bullmastiffs. The investigators have collected DNA samples from affected and unaffected Bullmastiffs and will study inheritance to identify genetic variants associated with SAS.

*Funding for the research is provided through the collaborative efforts and generosity of the American Bullmastiff Association. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Identification of Mitral Valve Disease DNA Variants in the Miniature Schnauzer

Principal Investigator: Kathryn Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: $56,635

Grant Period: 8/1/2017 – 7/31/2021

Project Abstract: Mitral valve degeneration is the most common heart disease in the dog, and is particularly common in small breed dogs. Miniature Schnauzers are one of the most commonly affected breeds. Although some dogs live comfortably with the disease, many affected dogs die of congestive heart failure and sometimes sudden death due to rupture of a weakened heart. Mitral valve degeneration is thought to be an inherited disease in the dog although the causative mutation(s) have not been identified. Failure to understand the underlying cause of canine mitral valve degeneration has slowed the development of effective treatment and prevention plans. The investigators will identify genetic variants that lead to the development of mitral valve degeneration in Miniature Schnauzers, and use this information to develop treatment and prevention plans for dogs with high-risk DNA variants.
Genetic Markers for Familial Subvalvular Aortic Stenosis in Newfoundlands

Principal Investigator: Joshua Stern, DVM, PhD; University of California, Davis
Total Grant Amount: $58,949
Grant Period: 9/1/2017 - 8/31/2020

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a 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. Severely affected dogs have an average lifespan of 19 months. A previous study identified a single gene mutation associated with a cohort of Newfoundland dogs with SAS, however this mutation does not explain all SAS in the breed and requires further evaluation. Studying this disease in Newfoundlands has the potential to identify causative genetic mutations and develop a reliable genetic test for this condition to further aid breeders to reduce the prevalence of this condition. The investigators will study pattern of inheritance and use the most modern genetic techniques to identify the genetic cause of SAS in Newfoundlands, further expanding our understanding of this disease in dogs.

Funding for the research is provided through the collaborative efforts and generosity of the Newfoundland Club of America Charitable Trust. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Characterization of Ventricular Arrhythmias in Rhodesian Ridgebacks

Principal Investigator: Kathryn Meurs, DVM, PhD; North Carolina State University
Total Grant Amount: $26,919
Grant Period: 9/1/2017 - 8/31/2020

Project Abstract: The investigators recently identified a genetic mutation associated with heart arrhythmias in Rhodesian Ridgebacks. Dogs with the mutation appear to be at the most risk of developing an arrhythmia and suffering sudden death between 12-24 months of age, however, this timeline is variable, and some dogs appear to outgrow the arrhythmia. Due to the lack of knowledge of the specific at-risk age, owners of dogs with the mutation must repeat the Holter monitor (a test to monitor heart rhythm) every few months to identify when their dog is at greatest risk and may need treatment. The objective of this study is to repeatedly perform regular Holter monitor testing on dogs with the mutation (including dogs with one copy and with two copies) every 4 months from 6-24 months of age with a final evaluation at 36 months to narrow in on the age when the arrhythmias appear to be the most severe. Gaining this increased clinical understanding of the disorder will decrease the risk of sudden death by helping owners and veterinarians in monitoring and providing treatment intervention for their dogs, and will further inform breeders and owners by characterizing the clinical and genetic manifestations of the disorder.

Funding for the research is provided through the collaborative efforts and generosity of the Rhodesian Ridgeback Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Identification of Genetic Variants Associated with Pulmonary Valve Stenosis in Bulldogs through Whole-Genome Sequencing

Principal Investigator: Joshua Stern, DVM, PhD; University of California, Davis
Total Grant Amount: $56,880
Grant Period: 4/1/2018 - 9/30/2020

Project Abstract: Pulmonary valve stenosis (PS) is a devastating inherited heart disease in dogs and children. It is the most common congenital heart disease in dogs, with Bulldogs being overrepresented. PS is caused by abnormal anatomy of the pulmonary valve that limits ejection of blood into the lungs. Untreated dogs are at risk of sudden death, congestive heart failure, and may die before five years of age. The type of PS (A or B) and presence of abnormal coronary arteries heavily influences prognosis. While treatment aims to open the narrowed valve region, it is expensive, palliative, and not always effective at resolving the clinical condition. Studying the disease in Bulldogs has the potential to identify a genetic mutation for genetic testing. A prior study performed by the investigators has identified chromosomal regions likely to contain mutations for PS Types A/B and coronary anomalies in the breed. Whole genome sequencing will be used to investigate the regions to identify variants of interest that segregate with the disease. If identified, the results can be used to aid breeding practices to reduce the prevalence of this disease. Additionally, identification of the molecular basis of PS and coronary anomalies may help elucidate novel therapeutic or diagnostic strategies for this condition.
Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Rottweilers

Principal Investigator: Joshua Stern, DVM, PhD; University of California, Davis

Total Grant Amount: $44,320

Grant Period: 2/1/2018 - 7/31/2020

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a 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. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Rottweilers. The goal of this research is to identify causative genetic mutations and develop a reliable genetic test for this condition in Rottweilers, to aid breeders in making informed decisions to reduce the prevalence of this condition. Once a chromosomal region of interest is identified via a genome wide association study (GWAS), whole genome sequencing (WGS) will be employed to identify variants associated with SAS. The top variants identified via WGS will be submitted for Sequenom analysis to prioritize variant pursuit.

Funding for the research is provided through the collaborative efforts and generosity of the Rottweiler Health Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Identification of Genetic Markers for Familial Subvalvular Aortic Stenosis in Golden Retrievers

Principal Investigator: Joshua Stern, DVM, PhD; University of California, Davis
Total Grant Amount: $51,880
Grant Period: 2/1/2018 - 7/31/2020

Project Abstract: Subvalvular Aortic Stenosis (SAS) is a 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. Severely affected dogs have an average lifespan of 19 months. SAS is an inherited heart problem reported in Golden Retrievers. Studying this disease in Golden Retrievers has the potential to identify causative genetic mutations and develop a reliable genetic test for this condition. Ultimately, the identification of a mutation would aid breeders in making informed decisions to reduce the prevalence of this condition. The investigators will study the pattern of inheritance and conduct a genome wide association study (GWAS). Once a chromosomal region of interest is identified, whole genome sequencing (WGS) will be employed to identify variants associated with SAS. The top variants will then be studied using Sequenom analysis to prioritize variant pursuit.

Funding for the research is provided through the collaborative efforts and generosity of the Golden Retriever Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Identification of Genetic Risk Allele(s) Associated with the Development of Tricuspid Valve Dysplasia in the Labrador Retriever

Principal Investigator: Kathryn Meurs, DVM, PhD; North Carolina State University
Total Grant Amount: $57,158
Grant Period: 6/1/2018 - 5/31/2021

Project Abstract: Tricuspid valve dysplasia is an inherited heart defect that is characterized by an abnormally formed tricuspid valve on the right side of the heart. It is reported to be most commonly observed in the Labrador Retriever although it has been observed in a few other breeds including the Boxer and Golden Retriever, among others. Although some affected dogs only have a very mild valve malformation and can live quite comfortably with the defect, others are born with a very abnormal valve that results in heart valve leakage and the eventual development of congestive heart failure. Tricuspid valve dysplasia has been shown to be an inheritable trait in the Labrador Retriever. The investigators will study and compare the genome sequences for affected and unaffected dogs. If successful, this study will identify a genetic marker for tricuspid valve dysplasia in the Labrador Retriever and which can be used to develop a strategy to gradually reduce the prevalence of the genetic variant and tricuspid valve dysplasia in the Labrador Retriever.

This research is generously supported by the Labrador Retriever Club of the Potomac Top Twenty Gala Foundation and the Labrador Retriever Club, Inc.
The Role of Bartonella spp. Exposure and Cardiac Genetic Variation on the Clinical Expression of Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer Dog

Principal Investigator: Edward Breitschwerdt, DVM; North Carolina State University

Total Grant Amount: $63,105
Grant Period: 2/1/2019 - 1/31/2021

Project Abstract: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) in the Boxer dog is an adult onset, familial disease characterized by the presence of ventricular arrhythmias, fainting and sudden death. The investigators have identified a causative mutation in the cardiac Striatin gene that is highly associated with the development of Boxer ARVC, and have demonstrated that some Boxer dogs with the mutation have a more severe form of the disease and will become quite sick while others will remain free of clinical signs. The reason for the variability in clinical signs is unknown but is thought to be associated with concurrent factors for an individual dog which could include a role for chronic infections, as well as genetics, hormonal levels, or other external factors including diet or exercise. The range of disease manifestation of Bartonella infection in dogs is broad, but has been shown to infiltrate the heart muscle, and has also been identified in human beings with ARVC. The investigators hypothesize that chronic Bartonella spp. infection may lead to the development of a more severe form of Boxer ARVC. Understanding the role of this, and other infectious diseases, in the severity of ARVC may greatly improve the ability to manage this common and sometimes fatal heart disease.
Circulating Cortisol Concentrations in Canine Congestive Heart Failure

Principal Investigator: Jessica Ward, DVM; Iowa State University
Total Grant Amount: $35,474
Grant Period: 12/1/2019 - 5/31/2022

Project Abstract: Congestive heart failure (CHF) is a common disease in dogs. A major contributor to disease progression is the renin-angiotensin-aldosterone system (RAAS), whose end-product aldosterone binds to mineralocorticoid receptors (MRs) and causes negative effects on the heart and blood vessels. RAAS activation is associated with a worse prognosis in humans and dogs with CHF. The stress hormone cortisol can also bind MRs. In healthy individuals, cortisol occupies the MR without activating it, while in disease states, bound cortisol can activate MRs just like aldosterone. In people with CHF, higher blood cortisol levels are associated with a higher risk of death. However, in the subset of patients treated with drugs that block MRs, cortisol is not associated with outcome. These findings suggest that the benefit of MR-blocking drugs may have more to do with blocking cortisol than with blocking aldosterone. The role of cortisol in dogs with CHF remains unknown. The purpose of this study is to determine the prognostic value of blood cortisol in dogs with CHF. Results of this study will help veterinarians better predict outcome for dogs with CHF and may suggest that MR-blocking drugs are indicated in treatment.
Canine Chagas Disease: Characterizing Cardiac Disease and Developing Screening Recommendations for Asymptomatic Dogs Seropositive for *Trypanosoma cruzi*

**Principal Investigator:** Ashley Saunders, DVM; Texas A&M AgriLife Research  
**Total Grant Amount:** $65,691  
**Grant Period:** 6/1/2019 - 5/31/2022

**Project Abstract:** Chagas disease (Trypanosomiasis) is caused by a parasite that infects the heart of humans and dogs in the United States causing heart disease and acute death. It is transmitted by kissing bugs, and there is no vaccination or approved treatment. Dogs in the Southern U.S. have a higher risk of parasite infection, and while all dog breeds can be affected, non-sporting, toy and herding breed groups are over-represented. Currently, there is only one commercially available test for Chagas disease in dogs and not all dogs with a positive test will develop clinical signs of disease. Characterization of the heart disease and recommendations for screening naturally infected dogs do not exist and veterinarians and owners are forced to make decisions about the health of their dog based on the currently available test results. This study will evaluate asymptomatic dogs with a positive Chagas test to characterize the presence of heart disease using electrocardiography ultrasound of the heart, and cardiac troponin I, a non-invasive biomarker of heart injury. Additionally, other Chagas tests will be evaluated as potential additional tests to confirm Chagas disease. Results will provide useful information to help owners and veterinarians screening dogs for evidence of heart problems associated with Chagas disease and will expand knowledge of the natural history of this disease in dogs.
Three-dimensional Echocardiographic Determinants of the Age of Onset of Myxomatous Mitral Valve Disease in Cavalier King Charles Spaniels

Principal Investigator: Michele Borgarelli, DVM, PhD; Virginia-Maryland Regional College of Veterinary Medicine

Total Grant Amount: $149,657

Grant Period: 5/1/2019 - 10/31/2022

Project Abstract: Myxomatous mitral valve disease (MMVD) represents a major health issue in Cavalier King Charles Spaniels (CKCSs). The disease appears at an earlier age, compared to other breeds, and has a genetic, heritable basis. The cause of the disease is unknown, but the role of altered stresses on the mitral valve (MV) has been proposed as one of the triggers for developing the disease. Three-dimensional echocardiography (RT–3DTTE) is a non-invasive technique that allows for characterization of the morphology of the MV. The investigator’s preliminary studies using RT–3DTTE found that some CKCSs have a MV of a different shape compared to other breeds. This altered shape of the MV could impose abnormal forces on the valve and predispose the breed for early development of the disease. This study will determine whether the shape of the MV is linked to the age of onset of MMVD in CKCSs, and, if so, the shape of the MV could be used as a screening method, and for directing breeding decisions in order to lower the prevalence of MMVD in CKCSs.
Investigation into Diet-Associated Dilated Cardiomyopathy in Dogs

Principal Investigator: Darcy Adin, DVM; University of Florida
Co-Investigators: Lisa Freeman, DVM, PhD and John Rush, DVM, MS, Tufts University; Rebecca Stepien, DVM, MS, University of Wisconsin, Madison; Amara Estrada, DVM and Margaret Sleeper, VMD, University of Florida; Joshua Stern, DVM, PhD, University of California, Davis
Total Grant Amount: $211,521
Grant Period: 4/1/2019 - 3/31/2021

Project Abstract: Dilated cardiomyopathy (DCM) is a serious disease of the heart muscle whereby the heart becomes enlarged with weak contractions. DCM can result in abnormal heart rhythms, congestive heart failure or sudden death. In dogs, DCM most often occurs in large- and giant-breeds, such as Doberman Pinschers, Boxers, Irish Wolfhounds, and Great Danes; in these dogs, survival time after diagnosis is often only months, even with aggressive medical therapy. Recently, veterinary cardiologists have recognized DCM more frequently in all breeds of dogs including mixed breeds, and even those not usually associated with DCM. There is suspicion that the disease in some dogs is associated with boutique, exotic ingredient, or grain-free (BEG) diets. Some affected dogs on such diets have shown reversal or improvement of their disease after changing their diet, supporting a potential association between consumption of a BEG diet and development of DCM. A specific cause, however, has not been identified, despite extensive nutritional testing of the dog foods and the canine patients. Moreover, the extent of the problem is unknown because only dogs that are symptomatic for DCM have been reported. It is possible that more dogs may be affected but not yet showing signs of heart disease. To investigate the extent of diet-associated heart problems in dogs, this multi-institutional team of veterinary cardiologists and nutritionists will prospectively screen a large population of apparently healthy dogs for DCM and compare important cardiac disease measures, including ultrasound of the heart, blood biomarker and taurine concentrations, and the frequency of DCM in dogs eating BEG versus non-BEG diets.
 Identification of a Second Genetic Risk Allele(s) Associated with the Development of Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer Dog

**Principal Investigator:** Kathryn Meurs, DVM, PhD; North Carolina State University  
**Total Grant Amount:** $115,474  
**Grant Period:** 5/1/2020 - 4/30/2022

**Project Abstract:** Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited heart disease diagnosed most commonly in the Boxer dog. Investigators previously identified the first known causative mutation for ARVC in the dog in the striatin gene. However, this mutation does not explain all affected canine cases. As in the human form of ARVC, there appears to be more than one genetic cause of this disease in the Boxer dog. To identify a second causative variant, DNA samples from Boxer dogs with confirmed Boxer ARVC that are negative for the striatin mutation will be whole genome sequenced to find a second genetic variant that is causative for the development of ARVC in the Boxer dog. The investigators previously used a similar approach to successfully identify a second causative mutation for dilated cardiomyopathy in the Doberman Pinscher. Ultimately, this information will improve understanding of the pathophysiology of ARVC, help improve treatment modalities, and provide information to develop a strategy to gradually reduce the prevalence of the additional variant and this disease.

*Funding for the research is provided through the collaborative efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Molecular Epidemiology of Methicillin-resistant *Staphylococcus pseudintermedius* in
the United States

**Principal Investigator:** Stephen Kania, PhD; University of Tennessee  
**Total Grant Amount:** $47,082  
**Grant Period:** 5/1/2019 - 4/30/2021

**Project Abstract:** The bacterium *Staphylococcus pseudintermedius* is the most common cause of canine skin infections as well as other important canine diseases. Disfigurement caused by skin infections and treatment failures is an important problem. Resistance to antibiotics is becoming increasingly widespread with few or no antibiotic options left for some cases. Alternative therapeutic approaches being investigated include vaccines, small molecule virulence factor inhibitors and bacteriophage lytic enzymes. In order for new products to be effective against the broadest spectrum of wildtype bacterial strains as possible, it is important to determine which strains of *S. pseudintermedius* clinically predominate in the United States today. A genetic typing method for *S. pseudintermedius* was previously developed by the research team along with a survey of bacterial strains in the United States in which they sequenced the genomes of the most common strains. This analysis provided a snapshot of predominant strains and suggested a potential for emergence of new, highly antibiotic resistant organisms. Identifying the current strains in the U.S. and sequencing their genomes will provide a basis for developing the next generation of treatments as well as important information about changes that occur in the bacterial population in response to selective pressures.
Discovery of Novel Biomarkers of Canine Atopic Dermatitis through Lipid Profiling

Principal Investigator: Harm HogenEsch, DVM, PhD; Purdue University
Total Grant Amount: $99,105
Grant Period: 5/1/2019 - 10/31/2020

Project Abstract: Canine atopic dermatitis (CAD) is a common allergic skin disease of dogs with a strong genetic basis. CAD can severely affect the health and well-being of dogs and current diagnosis of CAD requires time-consuming and expensive procedures for the owner. Furthermore, the molecular mechanisms underlying this condition are not well understood. Evidence from human studies suggests that several variants of atopic dermatitis (AD) exist with different mechanisms and responses to treatment. Therefore, new approaches to identify molecular markers that can help with better diagnosis and management are warranted. CAD and human AD are associated with changes in the composition of lipids in the epidermis which may precede the inflammation or result from the inflammation. The investigators will analyze the lipid composition of the epidermis and blood of healthy dogs in comparison to dogs with CAD using a novel analytical method developed by their interdisciplinary team. The results of this work could lead to new, minimally-invasive tests for the diagnosis of CAD and for the prediction and monitoring of the response of CAD patients to treatment.
Evaluation of the Serum and Cutaneous Levels of Chemokines in Atopic Dogs

**Principal Investigator:** Domenico Santoro, DVM, MS, DrSc, PhD; University of Florida

**Total Grant Amount:** $14,967

**Grant Period:** 2/1/2019 - 1/31/2021

**Project Abstract:** Atopic dermatitis (AD) is very common in dogs and children. AD is affected by complex and yet incompletely understood interactions between many factors such as environment, different types of white blood cells, and immunological factors. Chemokines are one of the factors that are used to modulate the immune system, leading to AD. Specific inflammatory chemokines were chosen for this study based on their relevance to AD from previously published studies in human and veterinary medicine. This study will evaluate the levels of these chemokines in blood, exosomes (a small pouch from cells that is used for communication between cells via blood), and skin of dogs with AD. In addition, the investigators will look for a correlation between the levels of these chemokines and severity of AD with a long-term goal to find a potential tool for monitoring and treating AD in dogs and humans.
Searching for the Cause for Alopecia X by Whole Genome Sequencing

**Principal Investigator:** Gary Johnson, DVM, PhD; University of Missouri

**Total Grant Amount:** $10,000

**Grant Period:** 10/1/2019 – 3/31/2021

**Project Abstract:** This study will use whole genome sequencing to identify a molecular genetic cause for a hair cycle deficiency known as Alopecia X. While the focus on the research is on the disease in Pomeranians, the results will be pertinent to other affected breeds including Alaskan Malamutes, Chow Chows, Keeshonds, Samoyeds, Schipperkes, and Siberian Husky dogs. If successful, the proposed research may lead to the creation of a DNA test that will enable dog breeders to selectively reduce risk for Alopecia X in their dogs.

*Funding for the research is provided through the collaborative efforts and generosity of the American Pomeranian Club, Inc. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Investigation on the Molecular Crosstalk between Canine Atopic Skin and Microbes: Unraveling Potential Pathomechanisms for Chronic Recurrent Skin Infections

Principal Investigator: Domenico Santoro, DVM, MS, DrSc, PhD; University of Florida
Total Grant Amount: $79,369
Grant Period: 5/1/2020 - 4/30/2021

Project Abstract: Environmental allergy is extremely common in dogs. Alterations of the skin barrier may lead to an altered inflammatory signal in allergic skin cells that perpetuates the inflammatory response and alters the interaction between skin cells and the external environment. Microorganisms have been shown to be more adherent on allergic compared with healthy skin. This increased adhesion on allergic skin cells has been associated with an increased susceptibility of allergic dogs to skin infections. Furthermore, an altered expression of natural defenses has been shown in allergic compared to healthy canine skin. How the interaction between microorganism and canine skin occurs and what this interaction activates in the host (canine skin) and the microorganisms is incompletely understood. Understanding which genes are activated in the host and the microbes in the early stage of adhesion is fundamental to better design treatments for skin infection in allergic dogs. The investigators will evaluate what occurs in the skin cells of allergic dogs and microbes (bacteria and yeasts) in the first hour of contact to increase our understanding of disease mechanisms in atopic dogs.
Identifying the Disease-Defining Autoantibodies in Canine Addison's Disease

**Principal Investigator:** Steven Friedenberg, DVM, PhD; University of Minnesota  
**Total Grant Amount:** $181,864  
**Grant Period:** 3/1/2018 - 8/31/2021

**Project Abstract:** Addison's disease is a common and life-threatening disorder in dogs in which the body's immune system destroys the outer layer of the adrenal glands. The adrenal glands produce hormones that are critical for energy metabolism, immune system function, intestinal health, and kidney function. Symptoms of Addison's disease can mimic other conditions, and as a result, many dogs remain undiagnosed for years. About one-third of dogs with Addison's disease are diagnosed only after suffering an acute adrenal crisis, which can cause a wide range of complications that require emergency stabilization and hospitalization. Today, there is no way to predict which dogs will develop Addison's disease before they become sick. If such a test were available, veterinarians would be able to evaluate high-risk dogs before they show signs, helping to prevent disease-related complications and potentially enabling earlier treatment. In this study, the investigator will use a novel approach combining gene and protein sequencing to identify the antibodies that target the adrenal glands in Standard Poodles, Portuguese Water Dogs, and English Cocker Spaniels with Addison's disease. These antibodies are produced by the immune system before the onset of clinical signs. The ability to identify these antibodies would therefore provide a test for early diagnosis. This research will contribute to progress in developing an important clinical test for Addison's disease that can help improve the lives of the many dogs at high risk of developing this life-threatening condition.
Addison's Disease and Symmetrical Lupoid Onychodystrophy in Bearded Collies Provide Common Ground for Identifying Susceptibility Loci Underlying Canine Autoimmune Disorders

Principal Investigator: Anita Oberbauer, PhD; University of California, Davis

Total Grant Amount: $118,458

Grant Period: 5/1/2018 - 12/31/2020

Project Abstract: Hypoadrenocorticism or Addison's disease (AD) is a life-threatening condition that afflicts multiple dog breeds and results from autoimmune destruction of the adrenal glands. Similarly, another canine autoimmune condition that causes pain and suffering is Symmetrical Lupoid Onychodystrophy (SLO). Both AD and SLO are postulated to be complexly inherited and preliminary data suggest a common set of susceptibility genes working in concert with additional genes that determine expression of either disease. For the study of AD and SLO the investigators will focus on the Bearded Collie breed due to its relatively high prevalence of both conditions and a genomic structure favorable for identifying variations in the DNA. The investigators will scan the entire canine genome using genetic markers coupled with whole genome sequencing to identify chromosomal regions that harbor genetic changes contributing to disease manifestation. The disease risk conferred by each of these genetic variants, or quantitative trait loci (QTL), will then be calculated to develop a tool for selecting sires and dams early in life, thereby allowing breeders to choose mating pairs that will produce offspring with a low likelihood of developing AD and SLO.
Breed Specific Reference Ranges for Canine Thyroid Testing

Principal Investigator: Brian Petroff, DVM, PhD; Michigan State University
Total Grant Amount: $139,975
Grant Period: 6/1/2019 - 5/31/2022

Project Abstract: Thyroid disease is common in dogs with the incidence of hypothyroidism approaching 30% in some breeds. Evaluation of thyroid function currently involves comparison of thyroid hormone concentrations in an individual patient with reference ranges generated from past testing of dogs of many breeds. However, while such all-breed reference ranges are generally accurate, they may not be optimal for some individual breeds, necessitating the generation of breed specific thyroid reference ranges. In thyroid testing specific for three breeds: Irish Setters, Rhodesian Ridgebacks and Whippets, dogs will be examined and tested sequentially to insure a healthy cohort for generation of a breed specific reference range for a panel of thyroid function assays. Once completed this study will generate breed specific thyroid testing reference ranges for three dog breeds. This work offers immediate and tangible improvements in canine health by refining thyroid testing interpretation in purebred dogs.
Pattern of Thyroid Function Tests during Recovery from Acute Nonthyroidal Illness

Principal Investigator: Timothy Bolton, DVM; Virginia-Maryland Regional College of Veterinary Medicine

Total Grant Amount: $13,792

Grant Period: 1/1/2020 - 6/30/2021

Project Abstract: Hypothyroidism is the most common endocrine disease in dogs. A diagnosis of hypothyroidism relies on finding both appropriate clinical signs and low thyroid hormone levels. Unfortunately, other illnesses can suppress thyroid hormone levels and result in a misdiagnosis. This phenomenon of low thyroid hormone levels caused by a disease not involving the thyroid gland is known as nonthyroidal illness or euthyroid sick syndrome. It is important to distinguish between nonthyroidal illness and hypothyroidism as the treatment for each is different. Historically, the recommendation for a dog with nonthyroidal illness has been to resolve the underlying disease, followed by a recheck of thyroid hormone levels thereafter. However, the duration of time after resolution of the nonthyroidal illness necessary to perform accurate thyroid hormone level testing is unknown. This study will provide information about thyroid hormone levels during the course of nonthyroidal illness, and also establish the approximate duration of time for recovery of thyroid hormone levels to normal following illness resolution. These results will correlate clinically with more concrete recommendations for thyroid hormone level testing following resolution of nonthyroidal illness.
Efficacy of Cannabidiol (CBD) for the Treatment of Canine Epilepsy

Principal Investigator: Stephanie McGrath, DVM, MS; Colorado State University
Total Grant Amount: $356,022
Grant Period: 12/1/2017 - 5/31/2021

Project Abstract: Epilepsy is the most common neurologic condition in dogs. Approximately 20-30% of dogs receiving standard therapy remain uncontrolled for their seizures. Additionally, the side effects of the antiepileptic drugs (AED) are often unacceptable. Thus, there is a need for an AED that is efficacious with minimal side effects. Cannabidiol (CBD), a prominent non-psychotropic component of the Cannabis sativa plant, has been shown to have anti-convulsant properties. While CBD offers promise as a treatment for canine epilepsy, controlled studies are needed to prove its effectiveness. In this randomized, double-blinded, placebo-controlled, crossover clinical trial, client-owned dogs with uncontrolled epilepsy will be enrolled following a full seizure evaluation, including bloodwork and magnetic resonance imaging. The canine patients will first receive either a placebo or CBD in addition to their standard AED protocol and then the opposite drug in this crossover designed study. Seizure frequency and medication side effects will be monitored by owners using a seizure log and questionnaire. Regular CBD plasma concentrations, routine bloodwork and serial physical examinations will be monitored by the investigator. The primary goal of the study is to determine the efficacy of CBD in the treatment of canine epilepsy. If CBD is effective in decreasing seizure frequency, it has the potential to improve the quality and length of life for dogs with uncontrolled epilepsy, and add a much-needed tool for veterinarians in the treatment of canine epilepsy.
Is Gut Dysbiosis Associated with Canine Idiopathic Epilepsy?

**Principal Investigator:** Karen Muñana, DVM, MS; North Carolina State University  
**Total Grant Amount:** $104,453  
**Grant Period:** 2/1/2019 - 1/31/2022

**Project Abstract:** Idiopathic epilepsy is the most common chronic nervous system disorder of dogs. Its cause is poorly understood but is believed to involve genetic and environmental factors. Treatment with anti-seizure drugs remains the standard of care. However, approximately one-third of dogs fail to achieve satisfactory seizure control, highlighting the need to investigate factors that may influence disease course. An association between epilepsy and inflammatory gastrointestinal disease is well documented in humans, and several other nervous system disorders have been linked to alterations in gut microbial populations, with considerable attention focused on the bacteria *Helicobacter* and *Lactobacilli*. The aim of this study is to determine whether dogs with idiopathic epilepsy have shifts in the gastrointestinal environment that may influence disease course. The researchers hypothesize that dogs with idiopathic epilepsy have alterations in the gut microbial population characterized by the presence of *Helicobacter*, a decrease in *Lactobacillus*, and resulting inflammation that are associated with epilepsy development and outcome. The investigators will collect and study paired fecal samples from untreated and phenobarbital treated epileptic dogs and including an unaffected dog from the same household. The occurrence of *Helicobacter* and *Lactobacillus* species will be analyzed using molecular genetic techniques and specific biomarkers of inflammation and evaluated for associations with disease onset and outcome. In exploring the association between the gut microbial population and canine epilepsy, this study has the potential to improve our understanding of epilepsy, and ultimately guide the development of more effective therapies for this disorder.
Genetics of Idiopathic Epilepsy in Labrador Retrievers

Principal Investigator: Hannes Lohi, PhD; The Folkhälsan Institute of Genetics

Total Grant Amount: $108,000

Grant Period: 5/1/2019 - 4/30/2021

Project Abstract: Epilepsy is the most common neurological disease in dogs and affects most breeds. Prevalence estimates vary from 1% up to 20% depending on the breed, suggesting a genetic contribution. Despite several gene discoveries that have been made in both symptomatic and idiopathic epilepsies, the genetic background in most dog breeds remains unknown, hampering progress in diagnostics, treatment and prevention. Challenges remain in incomplete clinical diagnostics to distinguish specific syndromes and to identify true cases and controls for genetic analyses. This study will develop a multilingual user-friendly mobile application for a validated epilepsy questionnaire to harmonize global data collection of epilepsies in different breeds. The app will enable automatic categorization of the epileptic dogs based on the reported symptoms, easy data sharing and regular follow-up of the affected dogs. It will also provide an opportunity for online consultation with registered neurologists for additional seizure information and treatment options, and aid recruitment of cases and controls for genetic studies. To specifically address the genetics of epilepsy in Labrador Retrievers (LR), the investigators will analyze the genomes of >300 dogs with a very high-density genotyping array (712K SNPs) to map the epilepsy loci, and will combine this information with whole genome sequencing data. The team has set up a global research collaboration to maximize the number of epileptic and non-epileptic LR samples to further confirm promising findings from the association studies. If successful, the study will provide new tools for epilepsy diagnostics and management in LRs and potentially other breeds.
Do Dogs Get Temporal Lobe Epilepsy? Clinical Signs, Magnetic Resonance Imaging and Pathological Findings in Epileptic Dogs

Principal Investigator: Starr Cameron, BVM; University of Wisconsin, Madison
Total Grant Amount: $14,555
Grant Period: 7/1/2020 - 6/30/2021

Project Abstract: Thirty percent of dogs with idiopathic epilepsy have poor seizure control and are considered by their caregivers to have a poor quality of life despite appropriate medical therapy. Temporal lobe epilepsy (TLE) is the most common type of epilepsy in humans, and has been well described in other species, including cats. Many epileptic dogs have a seizure presentation that is very similar to that described in humans with TLE including: excessive salivation, staring off, dilated pupils and facial twitching. Even with these similarities present, the actual anatomical changes within the brain have not been confirmed in dogs. Approximately forty percent of humans with TLE have poor seizure control, and additional treatment options, including surgery and laser ablation, result in the majority of patients becoming seizure-free long-term. The goal of this study is to further evaluate dogs for TLE, with the overall objective of better understanding the causes of canine epilepsy. Magnetic resonance imaging (MRI) findings and detailed anatomical changes from epileptic dogs with a history of TLE-like seizures will be studied. The hippocampus, which is the part of the brain implicated in TLE, will be extensively evaluated based on criteria established for TLE in humans and multiple other species. This project has the potential to further our understanding of epilepsy in dogs, broadening treatment options and ultimately leading to improved seizure control. Additionally, the results from this study will provide the foundation to explore other treatment options routinely recommended in humans with TLE for dogs with drug resistant seizures.
Identifying the Genetic Basis of Protein Losing Enteropathy in Yorkshire Terriers

Principal Investigator: Kenneth Simpson, BVMS, PhD; Cornell University

Total Grant Amount: $46,440

Grant Period: 3/1/2018 - 2/28/2021

Project Abstract: Chronic intestinal disease associated with the loss of protein into the gut, termed protein losing enteropathy (PLE), is a severe, life threatening condition that affects many dog breeds, including the Yorkshire Terrier, Soft-Coated Wheaten Terrier, Basenji, Norwegian Lundehund, and Chinese Shar-Pei. The syndrome of PLE is most common in Yorkshire Terriers (4.2-10 fold relative risk), and affected dogs frequently suffer from severe weight loss, accumulation of fluid within tissues and body cavities, diarrhea, low levels of circulating proteins, increased risk for abnormal clotting, and derangements in vitamin and mineral homeostasis. The microscopic appearance of the small intestine of Yorkshire Terriers with PLE (YT-PLE) is distinct from PLE in other breeds, suggesting it is caused by a breed-specific genetic abnormality. Despite aggressive treatment, remission is variably achieved and relapse is common. Long-term survival is infrequent with recent studies indicating treatment failure in approximately 50% of Yorkshire Terriers with PLE. The high morbidity and mortality of YT-PLE indicates the desire to eradicate this disease through breeding practices. The investigators are seeking to identify genetic regions and genes associated with YT-PLE to enable prevention of this disease, provide insights into the development of PLE across species, and facilitate the discovery of more specific and effective therapies. Preliminary studies in their laboratory have linked several genetic regions to YT-PLE but additional genotyping of DNA samples from YT with and without PLE is required to enable definitive identification of causal abnormalities.

Funding for the research is provided through the efforts and generosity of the Yorkshire Terrier Club of America and the Yorkshire Terrier Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Evaluation of Serum Zonulin as a Non-invasive Biomarker and Therapeutic Target in Dogs with Chronic Canine Enteropathy

Principal Investigator: Jamie Kopper, DVM, PhD; Iowa State University
Total Grant Amount: $12,085
Grant Period: 3/1/2020 - 2/28/2021

Project Abstract: Canine chronic enteropathy (CE) is the most common cause of gastrointestinal (GI) disease in dogs. The exact mechanisms causing CE are unknown, however, disruption of the inner lining of the GI tract is believed to play a significant role resulting in a "leaky" GI tract, leading to absorption of GI contents and overstimulation of the immune system. Unfortunately, treatment for CE currently requires life-long management such as food elimination diets which can be expensive and labor intensive for owners and/or require the use of medications which carry the risk for significant systemic side effects. Diagnosis and monitoring for disease relapse rely upon owner reported clinical signs and invasive diagnostic testing such as endoscopic intestinal biopsies. Thus, non-invasive diagnostics as well as specific treatments are needed. Zonulin, a protein found in animals and humans, plays an integral role in maintenance of intestinal barrier function. Humans and other animals with inflammatory bowel disease (IBD) have elevations in serum zonulin which can serve as a non-invasive biomarker for intestinal permeability or "leakiness" and disease severity as well as a therapeutic target. Zonulin has not been evaluated in dogs, therefore, the objective of this research is to determine if serum zonulin is elevated in dogs with CE.
Identification of Genetic Risk Factors Contributing to Gastrointestinal Motility Disorders

Principal Investigator: Leigh Anne Clark, PhD; Clemson University

Total Grant Amount: $57,930

Grant Period: 2/1/2020 - 1/31/2022

Project Abstract: Gastrointestinal motility disorders affect the nerves and muscles of the esophagus, stomach, and/or the intestines, causing digestive disturbances. Congenital idiopathic megaesophagus (CIM) is an esophageal motility disorder of dogs wherein contractility is reduced and leads to an enlargement of the esophagus. Affected puppies regurgitate after eating and survivors are susceptible to life-threatening complications. The highest incidences of CIM occur in the Great Dane and German Shepherd Dog breeds. Gastric dilatation-volvulus (GDV or bloat) is characterized by dilatation and twisting of the stomach, cutting off blood and oxygen to the organs. Based on a previous study for CIM in Great Danes, the investigators will 1) study a narrow region of chromosome 6, shown to be a major risk factor for CIM; 2) seek additional genomic regions that contribute to CIM, and 3) determine association between CIM and GDV based on shared genetic risk factors that impact gastrointestinal motility. The investigators hope to establish a pattern of transmission and develop a genetic test to reduce the incidence of CIM, and potentially GDV, in Great Danes.
Assessing Microvasculature for Intestinal Viability in Obstructed Small Intestines and Effects of Resection and Anastomosis Techniques

Principal Investigator: Penny Regier, DVM, MS; University of Florida
Total Grant Amount: $8,677
Grant Period: 1/1/2020 - 12/31/2021

Project Abstract: Intestinal foreign body ingestion is one of the most common causes for emergency surgery in dogs. Frequently, the foreign material causes damage to the intestines requiring surgical removal (resection) of the dead portion of intestine and surgical connection or re-attachment of the remaining intestine ends (anastomosis). At present, assessment of the need to resect and anastomose bowel is subjective and there may be areas of intestine with questionable health or viability. Recently, a hand-held, non-invasive device, GlycoCheck™, capable of imaging the smallest blood vessels (microvasculature) of tissues has been extensively studied in human medicine for quantification of vascular health. This study will use the GlycoCheck™ to assess areas of questionable intestinal health in dogs with foreign body obstruction and establish reference ranges that will aid the surgeon’s ability to assess small intestinal viability intra-operatively. This study has the potential to aid in reducing complications associated with foreign body surgery.
Analysis of the Health, Behavioral, and Longevity Data Collected in the 9/11 Medical Surveillance Longitudinal Study

Principal Investigator: Cynthia Otto, DVM, PhD; University of Pennsylvania
Total Grant Amount: $37,672
Grant Period: 2/1/2017 - 1/31/2021

Project Abstract: Following the attacks of September 11, 2001 on the World Trade Center and Pentagon, the AKC Canine Health Foundation awarded funds to the only lifetime longitudinal study tracking the medical and behavioral impacts of a major national disaster on the health and behavior of search & rescue (SAR) dogs. On June 6, 2016, the last study dog was laid to rest and data collection for the 9/11 Medical Surveillance Study was concluded. With 15 years of data, including annual radiographs, bloodwork, and handler surveys (health, performance, and behavior), the opportunity for in-depth analysis and discovery of new best practices and protocols for SAR dogs has never been greater. Data collected from deployed dogs will be compared to data collected from control SAR dogs that underwent similar training and careers, but did not deploy to 9/11. The investigators will explore three key areas of data: behavior, occupational hazards, and longevity related to health and work. Critical information gleaned from this study will have major implications applicable to the development, training, and care of our nation's SAR dogs, other working canines, and even companion dogs. Results will improve our understanding of traits of successful SAR dogs and thus influence dog selection. Importantly, following characterization of trait heritability, this data could be critical to a focused breeding program. The complete analysis of the occupational hazards of SAR dogs will shape preventive practices to allow these dogs to safely and effectively fulfill their mission of saving human lives.
Effect of Periodontal Treatment on Glycemic Control in Canine Diabetic Patients: A Prospective, Clinical Study

Principal Investigator: Michal Mazaki-Tovi, DVM; The Hebrew University of Jerusalem
Total Grant Amount: $14,970
Grant Period: 5/1/2018 - 9/30/2020

Project Abstract: Diabetes mellitus (DM) is a common endocrine disorder in dogs, with a strong breed disposition. The disease is associated with significant morbidity and death when left untreated, and tight control of blood glucose levels is crucial in avoiding the harmful effects of long-standing hyperglycemia. Insulin administration, appropriate diet, and treatment of concurrent diseases which interfere with insulin actions constitute the cornerstones of treatment. Among the various diseases in humans which affect treatment success, periodontal disease (PD) adversely affects glycemic control, and periodontal treatment leads to improvement in diabetic control. Periodontal disease is a multi-factorial, bacterial disease of dental supporting tissues. A common occurrence in dogs, its incidence increases with age, and most dogs over the age of five are afflicted by PD to variable extent. Beyond the local consequences of PD on dental and gingival health, PD induces a systemic inflammatory reaction, which purportedly accounts for its detrimental effects on diabetic control. In veterinary medicine, only few case reports and small experimental studies, involving 1 to 4 dogs, investigated the role of periodontal treatment (PT) on diabetic control. This study will investigate the effects of PT on diabetic control in a larger cohort of dogs through a prospective, clinical study. The investigators will also examine possible associations between PT, diabetic control and markers of systemic inflammation to elucidate possible mechanisms which may shed light on the relationship between the two conditions.
Understanding the Genetics of Adverse Drug Reactions in Sighthounds: Phase II

Principal Investigator: Michael Court, BVSc, PhD; Washington State University

Total Grant Amount: $172,765

Grant Period: 6/1/2018 - 11/30/2020

Project Abstract: Life-threatening unanticipated reactions to drugs with a narrow margin of safety, such as those used for anesthesia and to treat cancer, are a common yet serious concern for dog owners and veterinarians. Investigators at Washington State University have been conducting research to identify the cause of extremely slow recovery from anesthesia in a high proportion of Greyhounds, as well as in other sighthound breed dogs, including Italian Greyhounds, Scottish Deerhounds, Borzois, Irish Wolfhounds, Salukis, Afghan Hounds, and Whippets (among others). In previous work funded by the AKC Canine Health Foundation (#02242), the investigators discovered several mutations that were shown by cell-based testing to significantly decrease the function of genes responsible for breaking down (metabolizing) commonly used anesthetic drugs, as well as many other drugs used in dogs. The goal of this next phase of research is to develop a novel drug sensitivity test using saliva, blood or urine samples to identify dogs within a breed (or specific breeds) that metabolize drugs very slowly, thus creating a “personalized” or individual dog approach to drug selection. This test will then be used to confirm that the identified gene mutations are the cause of slow drug metabolism in sighthound dog breeds – as well as identify other breeds and individual dogs that could suffer from similar adverse drug reactions.
Evaluation of the Transversus Abdominis Plane Block to Control Pain Associated with Abdominal Surgery in Dogs

Principal Investigator: Alonso Guedes, DVM, MS, PhD; University of Minnesota
Total Grant Amount: $14,999
Grant Period: 3/1/2019 - 2/28/2021

Project Abstract: Abdominal surgery is common in veterinary practice, and opioids are the mainstay of pain management. Although effective painkillers, opioids are not free of adverse effects, and challenges stemming from the opioid epidemic in humans increased the urgency for developing alternative pain control strategies. In dogs, local nerve blocks are well-described for limb surgery, but comparatively little information exists for abdominal surgery. This study will determine whether surgical abdominal pain in dogs can be effectively and safely managed with a nerve block technique known as transversus abdominis plane (TAP) block; assessors will be blinded to treatment groups. The investigators will also examine whether a new long-acting form of the local anesthetic bupivacaine can provide long-lasting pain control for abdominal surgery. The results will advance canine health by providing evidence-based information of an alternative strategy to manage surgical abdominal pain in dogs.
Validation of Fine Needle Aspiration as a Minimally Invasive Sampling Method for Gene Expression Quantification of Pharmacogenetic Targets

Principal Investigator: Jennifer Reinhart, DVM, PhD; University of Illinois

Total Grant Amount: $5,940

Grant Period: 3/1/2019 - 8/31/2020

Project Abstract: Gene expression is the process in which genes are activated and perform their action through the creation of proteins. Measuring gene expression in different organs improves our understanding of disease because it detects what has become dysregulated in the body. Gene expression is also important in pharmacogenetics: the study of how genetics influences the body’s response to drugs. Drugs are most commonly metabolized in the liver, so measuring the expression of genes in the liver helps us understand how an individual animal’s genetics determine the way they will handle a drug. Usually, measuring gene expression requires a biopsy sample, which is an invasive procedure requiring anesthesia. A different sampling technique, fine needle aspiration (FNA), is safer, less painful, and may be preferred over surgically-obtained samples if FNA can be demonstrated to yield consistent, accurate results. FNA samples have been used to examine liver gene expression before, but it has not been determined if results differ between locations within the organ. Despite its potential advantages as a diagnostic tool, the FNA technique must be shown to yield consistent results before it can be recommended for routine clinical use. Therefore, the purpose of this study is to determine whether gene expression in liver FNA samples is affected by sampling site. The investigators will compare the expression of three pharmacologically important genes between various locations within the canine liver. If validated, FNA would be a valuable, low-risk tool for evaluating gene expression with many applications in pharmacogenetics and the study of disease.
Diagnostic Accuracy of Point of Care Analysis of Canine Urine and Plasma in Marijuana Toxicosis

Principal Investigator: Joel Weltman, DVM; Caspary Research Institute of the Animal Medical Center

Total Grant Amount: $14,450
Grant Period: 2/1/2020 - 7/31/2021

Project Abstract: Given the increase in availability of marijuana in the United States, a higher number of presumed marijuana exposures have been reported in veterinary emergency clinics. Since the clinical signs of marijuana ingestion are non-specific and may be observed in several disorders, an accurate canine bedside diagnostic test may alleviate the need for expensive and invasive diagnostic procedures in canine patients. To date, no studies have evaluated the accuracy of urine drug screening tests using non-invasive urine or blood samples in dogs. The purpose of this study is to determine the best method to diagnose marijuana toxicity in dogs in a point of care emergency setting.
Scientific and Clinical Assessment of Fecal Microbiota Transplant in Obese Dogs: SLIM Study

Principal Investigator: Jenessa Winston, DVM, PhD; The Ohio State University

Total Grant Amount: $94,989

Grant Period: 6/1/2020 - 5/31/2022

Project Abstract: Obesity is a growing epidemic in companion animals. Obesity results from a prolonged positive energy balance leading to excessive fat accumulation, which promotes dysregulation of metabolic, hormonal, and inflammatory responses. Ultimately these changes lead to physical impairment, comorbidities, and reduced quality of life. Evidence is mounting that the intestinal microbiota (collection of microorganisms that live in the intestines) contributes to obesity, and rational manipulation of this ecosystem may confer a health benefit. This study will provide a comprehensive scientific and clinical assessment of the efficacy of fecal microbiota transplantation (FMT) as an adjunctive therapy for canine obesity management. The investigators hypothesize that FMT (the transfer of feces from a healthy, lean donor dog into an obese dog) will amplify weight loss in obese dogs compared to the use of standard dietary obesity management. A randomized, placebo controlled clinical trial in client-owned obese dogs consisting of three groups: diet alone, diet + FMT, diet + placebo will provide data on weight loss and characterize the intestinal microbiota and metabolic function. Success of this study will benefit obese dogs by providing a microbial intervention to augment current strategies for canine obesity management aimed at promoting weight loss, normalizing metabolic status, and improving quality of life.
Do Dog Breeds Differ in Pain Sensitivity?

**Principal Investigator:** Margaret Gruen, DVM, PhD; North Carolina State University

**Total Grant Amount:** $104,147

**Grant Period:** 3/1/2020 - 2/28/2022

**Project Abstract:** The investigators’ recent comprehensive survey found that both veterinarians and members of the public believe that dog breeds differ in their sensitivity to pain, yet this has never been fully investigated. Beliefs about breed differences in pain sensitivity could negatively impact clinical recognition and treatment of pain in dogs and result in unnecessary pain, particularly for breeds viewed as less sensitive to pain. The investigators hypothesize that dogs have similar pain sensitivity thresholds, regardless of breed, but that human perceptions about breed-based differences in pain sensitivity affect the clinical recognition and treatment of pain. This study will endeavor to answer whether dog breeds differ in pain sensitivity, and whether breed affects veterinarians’ treatment of pain in dogs. If breed differences in pain sensitivity exist, future work would be performed to understand genetic associations, and advance our understanding of effectively treating pain in a breed-specific manner. If no differences exist, then the impact of the human perception of breed differences must be understood to ensure that dogs of every breed receive appropriate pain management.
Genetics of Adverse Reactions to Anesthetic and Sedative Drugs in Chow-Chows

Principal Investigator: Michael Court, BVSc, PhD; Washington State University

Total Grant Amount: $16,924

Grant Period: 3/1/2020 - 2/28/2021

Project Abstract: Moderate to severe adverse drug reactions, including unexpected effects, slow recovery, and even death have been reported following administration of anesthetic/sedative drugs by owners in some Chow Chow dog. Problematic drugs included butorphanol, acepromazine, trazodone, hydromorphone, ketamine and midazolam. In preliminary studies we have excluded a role for the MDR-1 deletion mutation found in herding dog breeds, as well as the CYP2B11/POR mutations found in sighthound breed dogs. Gene capture sequencing of DNA from representative Chow Chows identified a novel mutation in the CYP2B11 gene that is predicted to cause a damaging change in the amino acid sequence (CYP2B11-F182). This study will determine if CYP2B11-F182 mutation is responsible for decreased CYP2B11 enzyme function leading to excessive drug exposure and subsequent adverse effects in affected dogs. Previous studies have identified CYP2B11 as the primary enzyme metabolizing ketamine and midazolam. However, the identities of CYPs metabolizing the other problematic drugs are currently unknown. This study aims to ascertain the role of CYP2B11 in metabolism of the implicated drugs, confirm the deleterious effect of the CYP2B11-F182 mutation on enzyme function in vitro, determine the prevalence of the CYP2B11-F182 mutation across the Chow Chow breed, and identify other breeds with this mutation. Evidence from this study will be used to examine the effect of the CYP2B11-F182 mutation in future studies on drug pharmacokinetics and pharmacodynamics in genotyped dogs.

Funding for the research is provided through the collaborative efforts and generosity of the Chow Chow Club, Inc. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Profiling the Metabolic and Lipid Imbalances that are Causative of Gallbladder Disease in Dogs

Principal Investigator: Jody Gookin, DVM, PhD; North Carolina State University
Total Grant Amount: $135,354
Grant Period: 1/1/2014 - 6/30/2020

Project Abstract: The gallbladder mucocele (GBM) is one of the most common, poorly understood and deadliest biliary diseases of dogs. A GBM develops when the gallbladder secretes abnormal mucus that eventually obstructs or ruptures the gallbladder. GBM formation afflicts all dogs, but especially Shetland Sheepdogs, Miniature Schnauzers and Cocker Spaniels, and in general, dogs with disorders of steroid hormone or lipid metabolism. By the time a diagnosis of GBM is made, emergency surgery to remove the gallbladder is often required. After surgery, only 22-50% of dogs survive to be discharged from the hospital. There is a critical need to determine why dogs form a GBM, so we can prevent the high cost and lost lives of these dogs. Based on the breeds and diseases that predispose to GBM, the investigator hypothesizes these dogs have a unique disturbance in cholesterol or lipid metabolism. If the cause of this disturbance can be identified then the investigators will be able to understand why GBM form, develop tests for early diagnosis and design diets or drugs to prevent GBM formation.
Understanding the Genetics of Hepatic Copper Toxicosis in the Dalmatian

Principal Investigator: Andrew Mason, PhD; University of Alberta

Total Grant Amount: $100,000

Grant Period: 3/1/2017 - 8/31/2020

Project Abstract: Copper toxicosis, leading to early death from liver disease, was first described in Bedlington Terriers in 1975, with similar diseases described in other dog breeds including the Labrador Retriever, West Highland White Terrier, Skye Terrier, and Doberman Pinscher. Genes have been linked to copper toxicosis in the Bedlington Terrier and the Labrador Retriever, but the genes differ by breed. In most breeds the genes are not known. Copper toxicosis was considered rare in the Dalmatian but may be more common than previously believed. Symptomatic dogs may be misdiagnosed as having other liver diseases, never appropriately diagnosed or only diagnosed with copper overload at a terminal stage. The investigators aim to identify the faulty gene(s) in Dalmatians using an advanced whole genome sequencing strategy to obtain the genome sequences of carefully selected members of an affected Dalmatian pedigree. Identification of the problem gene is the first step towards genetic testing and to improved breeding practices necessary to eradicate hepatic copper toxicosis from the Dalmatian breed. Gene identification will help raise awareness of copper toxicosis in the Dalmatian breed, lead to more rapid diagnosis of the condition, and support the search for the most effective therapy.

Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America and Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Medical Resolution of Gallbladder Mucocele Formation in Dogs

Principal Investigator: Jody Gookin, DVM, PhD; North Carolina State University

Total Grant Amount: $220,333

Grant Period: 10/1/2019 - 9/30/2022

Project Abstract: Gallbladder mucocele formation is a disorder of the gallbladder where excess secretion of abnormally thick mucus results in obstruction to the normal flow of bile or rupture of the gallbladder contents into the abdominal cavity. The disease has a breed predisposition for Shetland Sheepdogs, Border Terriers, Cocker Spaniels, Schnauzers, Pomeranians, Bichons Frises, Chihuahuas, Pugs, and Beagles and uncommonly affects mixed breed dogs. The only curative treatment for the disease is a costly surgery to remove the gallbladder and on average, 27% of dogs will die from post-operative complications. This objective of this study is to establish whether the course of mucocele formation can be reversed by correcting metabolic disturbances documented in affected dogs. Recent published data, generated by support from the AKC Canine Health Foundation (Grant #01986), demonstrated that dogs with mucocele formation are relatively deficient in essential dietary compounds that play key roles in normal metabolism and/or whose biological activity may help to promote normal secretory function of the gallbladder epithelium. This study will determine whether supplementation with such dietary factors will arrest and reverse the course of mucocele formation in dogs. If successful, this research will have an important positive impact by providing an immediate benefit to dogs with this disease.
**Evaluation of Gallbladder Motility in Dogs with Hyperlipidemia**  
**Principal Investigator:** Stefanie DeMonaco, DVM, MS; Virginia-Maryland Regional College of Veterinary Medicine  
**Total Grant Amount:** $9,148  
**Grant Period:** 2/1/2019 - 1/31/2021

**Project Abstract:** Gallbladder (GB) diseases are frequently recognized in dogs as a significant cause of illness and potentially death. In particular, gallbladder mucoceles (GBM), the distention of the GB with mucus, can rupture and cause a critical condition that can quickly lead to death if not addressed immediately. Currently, the cause of GBM is unknown making treatment and preventative strategies difficult. Dogs with GBM have poor GB motility and often increased lipid levels, such as cholesterol and triglycerides. Impaired GB motility occurs in people and rodents with increased lipid levels suggesting that this may also occur in dogs, therefore, it is possible that increased lipid levels may lead to abnormal GB motility and eventually GBM formation in dogs. Breeds with inherited disorders resulting in increased lipid levels, such as Shetland Sheepdogs and Miniature Schnauzers, are the same breeds that have the highest risk for GBM formation. However, it has yet to be determined if increased lipid levels are associated with impaired GB motility in dogs. The investigators will utilize ultrasound to compare GB motility between healthy dogs and those with increased lipid levels in an attempt to ascertain an association between increased lipid levels and abnormal GB motility. If this is established, then diets and medications aimed to reduce lipid levels in conjunction with vigilant monitoring for the development of GB disease may prove beneficial to prevent or reduce disease severity and risk of death, particularly in predisposed breeds.
Treatment of Idiopathic Chronic Hepatitis and Copper Associated Hepatopathy in Dogs

Principal Investigator: Sarah Shropshire, DVM, PhD; Colorado State University
Total Grant Amount: $15,000
Grant Period: 1/1/2020 - 12/31/2020

Project Abstract: This study will evaluate treatment regimens for two common and important liver diseases in dogs: idiopathic chronic hepatitis (ICH) and copper associated hepatopathy (CAH). Treatment of these diseases is essential to prevent progression to liver failure and death. At present, there are no standardized treatments for ICH or CAH in dogs. Dogs will be treated for ICH and CAH with two separate therapeutic regimens. The investigators will evaluate treatment efficacy by monitoring several hepatic parameters, including clinical signs, liver values, serum drug levels and copper levels. These parameters will be correlated to remission or relapse of disease to identify factors associated with treatment response. The findings of this project may significantly improve veterinarians’ ability to treat dogs with ICH and CAH.
The Impact of Lidocaine Administration on Natural Killer Cell Populations in Canine Sepsis

Principal Investigator: Mandy Wallace, DVM, MS; University of Georgia
Total Grant Amount: $14,896
Grant Period: 11/1/2017 – 10/31/2020

Project Abstract: Sepsis is a life-threatening condition that results from an excessive systemic inflammatory response to infection. This can occur due to infections in various parts of the body including the chest, abdomen, or bloodstream. Dogs and humans with sepsis have up to a 50% mortality rate, with most dying from organ system failure. This high mortality rate has been linked to the dysfunction of several types of immune cells. One of these cell types, Natural Killer (NK) cells, plays a critical role in the killing of bacteria within the body, but their role has not been evaluated in dogs with sepsis. Administration of the local anesthetic lidocaine, a drug that can decrease pain and correct cardiac arrhythmias, has been shown to increase survival in dogs with sepsis. This study seeks: 1) to determine the relationship between NK cell numbers and phenotype in the blood and disease severity in dogs with abdominal sepsis; and 2) to evaluate if the administration of lidocaine during surgery changes NK cell numbers or affects survival rates in dogs with sepsis from abdominal infection.
Predicting the Outcome of Coccidioidomycosis in Naturally Infected Dogs

Principal Investigator: Lisa Shubitz, DVM; University of Arizona
Total Grant Amount: $37,129
Grant Period: 3/1/2018 - 8/31/2020

Project Abstract: Coccidioidomycosis (Valley Fever) is a systemic fungal infection endemic to the desert southwestern United States. Dogs are affected, with an estimated $60 million per year in diagnostic and treatment costs. Valley Fever has a variable clinical picture, ranging from subclinical infections to mild disease to severe, uncontrolled disease. Development of a vaccine to prevent, or reduce, illness in dogs is currently underway. T-cells are a type of immune system cell called lymphocytes. It has been demonstrated that a robust T-cell mediated immune response is needed to control the infection in mice and humans. Exploratory work suggests this is also true in dogs. The investigators plan to develop an assay of canine T-cells, from dogs with variable clinical responses to naturally-occurring infections, that will allow them to correlate T-cell responses with the severity of clinical disease. This information will allow better prediction of the clinical course of disease in dogs, resulting in improved treatment recommendations. This assay will also assess the protective response to the vaccine by mimicking the T-cell mediated response seen in dogs with coccidioidomycosis, and will also be applicable to future studies of immune responses to other canine infectious diseases.
Canine Chagas Disease: Characterizing Cardiac Abnormalities, Vector Infection and Control Strategies, and Parasite Strains in Kennel Environments

**Principal Investigator:** Sarah Hamer, DVM, PhD; Texas A&M AgriLife Research

**Total Grant Amount:** $160,407

**Grant Period:** 1/1/2018 - 6/30/2020

**Project Abstract:** Chagas disease is a parasitic infection that can cause acute death and chronic heart disease in any breed of dog, and there is no vaccination or approved treatment. There is currently an unprecedented recognition for canine Chagas disease in the southern U.S., where infected kissing bug vectors occur. The disease is well-studied in Latin America but the current lack of knowledge about canine infection in the U.S. hinders our ability to protect canine health. Infected dogs occur across the range of kissing bugs in the southern half of the U.S., and Texas is a particular hotspot for infection due to the diversity of kissing bugs and high parasite infection prevalence. The investigators will establish a network of AKC breeding kennels in four key areas representing range limits of different vector species to: (1) characterize heart abnormalities of infected dogs using ECG and cardiac troponin I, a non-invasive biomarker of cardiac injury; (2) collect kissing bugs from kennel environments using complementary methods including a trained bug scent detection dog to determine vector infection prevalence and blood meal sources; and (3) characterize parasite strains in dogs and vectors because different genetic variants of the parasite are associated with different disease outcomes. Importantly, because this zoonotic disease is an emerging public health threat to canine owners and the veterinary community, the discoveries made will help to simultaneously advance both canine and human health initiatives.
Validation and Diagnostic Performance of a Novel Monoclonal Antibody based Histoplasma Urine Immunoassay in Dogs with Histoplasmosis

Principal Investigator: Andrew Hanzlicek, DVM, MS; Oklahoma State University
Total Grant Amount: $17,088
Grant Period: 3/1/2019 - 8/31/2020

Project Abstract: Histoplasmosis is a severe disease caused by the fungus Histoplasma capsulatum that can be fatal to dogs. The fungus is found in soil and dust around the world and most commonly in the Midwestern, Southern, and Southeastern U.S. Dogs contract the disease when they inhale spores produced by the fungus in the environment. The most common method of diagnosis is by finding the fungal organism in tissue or body fluid samples. Unfortunately, collecting these samples can be invasive and is not always feasible, depending on the location of the infection and the severity of illness. A commercial urine test for diagnosis in dogs, cats, and humans to aid diagnosis, is of limited availability. The current cost of testing, especially when repeated, can be prohibitive for some pet-owners. There is a need for an affordable test that is more widely available for dogs. This study aims to develop and describe the performance of a non-invasive, in-house Histoplasma urine test for dogs to address this important disease.
Analysis of Canine Herpesvirus Isolates Using Next-Generation Sequencing

Principal Investigator: Andrew Lewin, BVM&S; Louisiana State University

Total Grant Amount: $13,775

Grant Period: 1/1/2020 - 12/31/2020

Project Abstract: Canine herpesvirus (CHV-1) is a common and serious disease of puppies and adult dogs. It is often fatal in puppies and can cause serious illness such as ocular disease, upper respiratory disease and vaginitis in adult dogs. This study will use cutting edge technology to determine the DNA sequence of canine herpesvirus isolates collected from dogs in the U.S. Sequenced DNA will be analyzed to study the virus at a genomic level and to highlight differences in viral genomes based on geographic location. This level of characterization will represent the largest work for CHV-1 worldwide to help prevent disease and inform novel therapeutic targets for treatment.
Characterization of Renal Disease in American Boxer Dogs

**Principal Investigator:** Jessica Hokamp, DVM, PhD; The Ohio State University  
**Total Grant Amount:** $56,694  
**Grant Period:** 3/1/2018 - 2/28/2021

**Project Abstract:** Chronic kidney disease (CKD) is often a progressive and fatal disease in dogs. Boxer dogs appear to have a predisposition for development of CKD, suggesting that kidney disease in this breed might be heritable. Studies in Europe report an increased frequency of Boxers with kidney and urinary tract maldevelopments leading to CKD, termed "juvenile nephropathy". The investigators’ International Veterinary Renal Pathology Service (IVRPS) recently found that juvenile nephropathies are a main underlying cause of CKD in young Boxer dogs; however, there are no published studies that have determined the predominant cause(s) of CKD in Boxer dogs in the United States. The investigators hypothesize that pedigreed Boxers in the U.S. may be afflicted by several causes of CKD, including but not exclusive to juvenile nephropathies. To assess the most common causes of CKD in Boxers, the investigators will perform detailed examination of medical records and archived tissue samples to retrospectively reveal the predominant cause(s) and prevalence of kidney disease in Boxers and will also prospectively collect and analyze tissue and fluid samples from pedigreed families of Boxers afflicted by the predominant types of kidney diseases. This work will determine if certain types of kidney disease in Boxers follow a heritable pattern and might be related to genetic mutations, allowing for future studies on genetic analysis if an inheritance pattern of disease is determined.

*Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Characterization of Renal Disease in Greyhound Dogs

Principal Investigator: Rachel Cianciolo, VMD, PhD; The Ohio State University
Total Grant Amount: $36,182
Grant Period: 6/1/2020 - 5/31/2022

Project Abstract: Kidney disease is common in dogs, and some dog breeds seem to be more predisposed to development of kidney disease than other breeds. Greyhounds appear to be predisposed to proteinuric renal diseases; however, a complete characterization of the most common types of kidney diseases in this breed has not been performed to date, and potential genetic causes of kidney diseases in Greyhounds remain unknown. Preliminary data based on evaluation of cases through the International Veterinary Renal Pathology Service and Ohio State University has revealed that kidney disease in Greyhounds is likely from a variety of causes; including primary glomerular diseases and glomerular damage secondary to hypertension. For this study, samples will be prospectively collected to identify Greyhounds with kidney disease, determine which are proteinuric, localize the origin of proteinuria (glomerular versus tubulointerstitial), and identify dogs for further evaluations and monitoring. Prospective examination of kidney samples from pedigreed Greyhounds using advanced techniques (transmission electron microscopy and immunofluorescence) will ensure accurate diagnosis of renal injury. Detailed review of archived samples from Greyhounds will allow identification of common renal lesions. DNA will also be banked for future genomic studies if a hereditary component to kidney disease is detected in the breed.

Funding for the research is provided through the collaborative efforts and generosity of the Greyhound Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Characterizing Developmental Lung Disease as a Cause of Sudden Death in the Norwich Terrier

Principal Investigator: Kurt Williams, DVM, PhD; Michigan State University
Total Grant Amount: $116,076
Grant Period: 3/1/2018 - 2/28/2021

Project Abstract: Neonatal respiratory distress syndrome has been attributed to more than 60% of deaths early in life in puppies. The underlying cause(s) of this apparently common problem is poorly understood. Despite the high frequency of respiratory-related mortality in neonatal puppies, there are no reports describing the underlying lung pathology in affected individuals. In human medicine the classification, management and evaluation of diffuse interstitial lung diseases in infants are well described. The most severe neonatal lung diseases in humans develop as a result of abnormal development of the lung, and often result in death soon after delivery. The investigators recently documented microscopic evidence of striking abnormal lung development in puppies of various breeds who died suddenly, suggesting that developmental lung disease

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Assessment of Circulating Inflammatory Mediators in Dogs with Tracheal Collapse

**Principal Investigator:** Tekla Lee-Fowler, DVM, MS; Auburn University  
**Total Grant Amount:** $7,984  
**Grant Period:** 11/1/2019 - 10/31/2020

**Project Abstract:** This study investigates whether dogs with tracheal collapse have increased levels of blood inflammatory markers. Dogs with tracheal collapse can experience significant airway narrowing and thus airflow limitation. This can lead to mild or intermittent changes in oxygenation which may stimulate inflammation throughout the body. The research team aims to determine if inflammation occurs in dogs with tracheal collapse, and whether markers of inflammation could be used in the future to provide information about disease progression or response to therapy.
Diagnostic Utility of Thoracoscopy for Localization of Pulmonary Bullae in Dogs with Spontaneous Pneumothorax

Principal Investigator: Valery Scharf, DVM, MS; North Carolina State University
Total Grant Amount: $13,829
Grant Period: 1/1/2020 - 12/31/2022

Project Abstract: Primary spontaneous pneumothorax is defined as the presence of air in the space around the lungs without an obvious precipitating factor. This disease presents as a life-threatening emergency causing shortness of breath, exercise intolerance, and possible collapse or sudden death. The diagnosis of these lesions that cause spontaneous pneumothorax in dogs (known as pulmonary bullae) remains challenging. The accuracy of advanced imaging such as computed tomography (CT) for identifying bulla in dogs with spontaneous pneumothorax is limited. Currently, thorough exploration of the chest through an open surgical approach is the diagnostic standard for primary spontaneous pneumothorax. This strategy, however, requires an invasive surgical approach and weeks of post-operative recovery. In contrast, video-assisted scoping (thoracoscopy) of the chest, known as VATS, is preferred to open surgery for the treatment of spontaneous pneumothorax in human medicine. VATS is associated with fewer complications and reduced post-operative pain, making it a desirable alternative to the current standard in veterinary medicine, but its reliability in correctly identifying pulmonary bullae associated with spontaneous pneumothorax in dogs has not yet been proven. This study aims to prospectively evaluate the ability of thoracoscopy to identify and localize pulmonary bullae in dogs with primary spontaneous pneumothorax, thus facilitating minimally invasive treatment options for dogs with this disease.
The Pathologic Link between Lung and Gut: Diagnosis of Aerodigestive Disorders in Dogs

**Principal Investigator:** Carol Reinero, DVM, PhD; University of Missouri

**Total Grant Amount:** $83,801

**Grant Period:** 7/1/2020 - 6/30/2022

**Project Abstract:** Chronic unintentional inhalation (aspiration) of small amounts of gastrointestinal contents into the respiratory tract can cause or worsen respiratory disease in dogs. Gastroesophageal reflux (GER) is reported in up to 90% of people with certain respiratory diseases but is under-recognized and therefore, not treated in dogs in large part because they cannot report signs of heartburn. The investigators will use an advanced imaging technique, fluoroscopy, in dogs with respiratory disease in order to document GER and other swallowing abnormalities. Results may provide new avenues of treatment for canine respiratory disease by targeting underlying GER/swallowing abnormalities.
Approach to Identification of a Genetic Risk Allele(s) Associated with the Development of Tracheal Collapse in the Pomeranian

Principal Investigator: Kathryn Meurs, DVM, PhD; North Carolina State University
Total Grant Amount: $19,440
Grant Period: 12/1/2019 - 11/30/2020

Project Abstract: Tracheal collapse is a debilitating disease of the trachea and bronchi observed most commonly in small dogs. The Pomeranian is one of the more commonly affected breeds of dogs. Although some dogs can be managed with medical therapy, severely affected patients develop respiratory distress and some dogs do not survive. The frequency of tracheal collapse in small dogs, including the Pomeranian, suggests a genetic component to the disease. Investigation of the genetic basis of tracheal collapse could lead to development of improved diagnostic testing and alteration of breeding practices to reduce disease prevalence. Additionally, an improved understanding of the underlying cause of tracheal collapse could lead to improved development of medical management plans for affected dogs.

Funding for the research is provided through the collaborative efforts and generosity of the American Pomeranian Club, Inc. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Searching for a Genetic Risk Factor for Idiopathic Chylothorax in Afghan Hounds

Principal Investigator: Gary Johnson, DVM, PhD; University of Missouri
Total Grant Amount: $15,000
Grant Period: 2/1/2020 - 1/31/2021

Project Abstract: Chylothorax is a disease in which lymph leaks into the thorax causing coughing, difficulty breathing, a weakened immune system and/or severe metabolic disorders. Previous publications report that some Afghan Hounds are more likely to develop chylothorax. The reason for the greater susceptibility of some Afghan Hounds is unknown, but many authorities have suggested a mutation as a yet unidentified gene may be responsible. The investigators will compare the DNA of affected and healthy Afghan Hounds, in an effort to discover a mutation that increases susceptibility for developing chylothorax in some Afghan Hounds.

Funding for the research is provided through the collaborative efforts and generosity of Afghan Hound Club of America and William Dean III Charitable Trust. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Landmark Clinical Trial to Establish the Evidence-Based Use of Regenerative Medicine to Treat Tendon Injury in Dogs

**Principal Investigator:** Jennifer Barrett, DVM, PhD; Virginia-Maryland Regional College of Veterinary Medicine  
**Total Grant Amount:** $254,509  
**Grant Period:** 7/1/2014 - 11/30/2021

**Project Abstract:** This study will evaluate the effectiveness of Platelet-Rich Plasma (PRP) and stem cells in the treatment of the most common sporting injury in dogs: supraspinatus tendinopathy (similar to the rotator cuff injury in humans). Tendon injuries in dogs often progress undiagnosed and result in chronic lameness and pain. Ultimately, unassisted tendon healing results in scar formation and reduced function of the joint and surrounding muscle tissue. PRP and stem cell therapies aim to accelerate and promote healing through tissue regeneration and reduced scarring. The investigators will conduct a randomized, placebo-controlled clinical trial evaluating the effectiveness of PRP, adipose-derived, cultured stem cells (ASC) and commonly used stromal vascular fraction (SVF) cells to directly compare efficacy of intratendinous injection of ASC versus SVF, both of which are currently commercially available despite having limited scientific evidence of efficacy. The investigators hope to identify an effective treatment to supraspinatus tendon injury.
Basis of Dwarfism in Great Pyrenees

Principal Investigator: James Mickelson, PhD; University of Minnesota

Total Grant Amount: $18,745

Grant Period: 1/1/2018 - 6/30/2020

Project Abstract: Great Pyrenees dwarfism is not fatal, but is a chondrodysplasia first scientifically described in the mid-1990s. Pups appeared normal at birth, but within two weeks were shorter and smaller than their non-dwarf littermates. This form of dwarfism is not due to hormonal imbalances. Pedigree analysis suggests that it is inherited in an autosomal recessive fashion, and is potentially caused by a single gene. Dogs suspected to be carriers for this condition have normal proportions. The specific underlying genetic cause and the true prevalence of this condition within the breed is unknown. The investigators hypothesize that dwarfism in Great Pyrenees dogs has a genetic basis in which whole genome scans with DNA markers can identify a small chromosomal region that will contain a dwarfism-associated gene, and that high-throughput DNA sequencing will identify the causative mutation(s). The goal is to determine the frequency of the DNA variant in the breed, and to develop and provide a genetic test to inform breeding decisions, and eventually aid in eradicating this disorder from the breed.

Funding for the research is provided through the efforts and generosity of the Great Pyrenees Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.
The Role of Motilin Signaling in Canine Osteoarthritis

Principal Investigator: Li Zeng, PhD; Tufts University
Total Grant Amount: $15,000
Grant Period: 3/1/2019 – 8/31/2020

Project Abstract: Osteoarthritis is a devastating disease characterized by joint pain and immobility and while it is highly prevalent in dogs, there is no optimal treatment for this disease. The goal of this study is to design strategies to prevent osteoarthritis progression and improve the quality of life for dogs. A central feature for osteoarthritis is the destruction of joint cartilage, a tissue that normally serves as a cushion between bones. Without this cushion, there is increased friction at the joint, causing mechanical stress and accelerating joint degeneration. One treatment strategy is to combat inflammation, because inflammation results in joint cartilage loss and is a key component in the pathogenesis of osteoarthritis. In preliminary studies, the investigators found that the hormone motilin has an anti-inflammatory activity that has not been previously reported. Their hypothesis is that motilin protects the canine joint against inflammation and improves the health of the cartilage in osteoarthritis. Outcomes of this research may benefit both dogs and humans suffering from osteoarthritis.
Embracing Polygenicity of Common Complex Disease in Dogs: Genome-wide Association of Cruciate Ligament Rupture

Principal Investigator: Peter Muir, BVSc, PhD; University of Wisconsin, Madison
Total Grant Amount: $154,116
Grant Period: 5/1/2019 - 4/30/2022

Project Abstract: Cruciate ligament rupture (CR) is a common disabling, degenerative condition of the knee. It places a large financial burden on the American public. Inflammation of the stifle and fraying of cruciate ligament fibers, particularly in the cranial cruciate ligament, eventually leads to ligament rupture with associated stifle instability in affected dogs. CR is a moderately heritable, complex disease with genetic and environmental risk. CR is common in certain breeds, such as the Labrador Retriever, and rare in other breeds. There is a critical gap in knowledge regarding the genetic contribution to CR, as the number of genes influencing disease risk has never been studied in detail. Our main goal is to comprehensively analyze the genetic features of the disease across the genome and use this knowledge to develop a genetic test for CR disease risk using genomic prediction. We aim to robustly estimate heritability, analyze the genetic architecture of CR, and advance genetic testing using genomic prediction in the Labrador Retriever, the most common purebred dog breed. The rationale for this work is that detailed knowledge of the genetic features of CR will advance development of a genetic test for CR risk using genomic prediction. This work will fundamentally advance knowledge of the genetic architecture of CR, a very common canine disease. Consequently, such knowledge will provide an invaluable guide to future research into other canine complex diseases. CR genetic testing would enable early identification of at-risk dogs for precision medical care, and selective breeding to reduce the disease burden.
The Effect of a Modified Approach on Early Weight Bearing in Dogs Following a Tibial Plateau Leveling Osteotomy for Cranial Cruciate Ligament Rupture

**Principal Investigator:** Dominique Sawyere Hansford, BVSc, MS; Virginia-Maryland Regional College of Veterinary Medicine

**Total Grant Amount:** $14,939

**Grant Period:** 1/1/2020 - 6/30/2021

**Project Abstract:** A tibial plateau leveling osteotomy (TPLO) is a common procedure performed to address stifle (knee) instability secondary to cranial cruciate ligament rupture in dogs. During the surgical approach for a TPLO, some of the tendons of muscles attaching to the inside of the tibia are cut. These tendons are referred to as the medial crural fascia. The medial crural fascia is important for the normal function of the dog’s stifle. As opposed to the rapid gain in wound strength displayed in skin and the GI tract, restoration of fascia integrity is relatively prolonged. In the first week of healing, fascia incisions have no inherent strength; therefore, the repair is entirely dependent on the suture material, making it prone to inadequate healing. The clinical implication of this on early weight bearing and limb use following TPLO surgery is unknown. Additionally, tendons only reach 50-80% of their original strength at one year following reconstruction. In humans, deficiency in the repair of the medial crural fascia has been associated with decreased rotational stability, increased meniscal injury, and continued knee instability following surgery for cranial cruciate ligament rupture. If these findings are consistent in dogs, lack of attention to medial crural reconstruction and its inability to return to the original strength may contribute to continued subluxation of tibia and latent meniscal injury. In this study, dogs who undergo a modified approach to a TPLO will be evaluated to determine normalization of gait parameters and thigh circumference as compared to dogs who undergo a standard approach to a TPLO. Results from this study may change the approach to TPLO surgery in the future and provide canine patients with improved short- and long-term outcomes.
Identification of Biomarkers and Therapeutic Targets for Canine Degenerative Myelopathy: The Search for A Cure

Principal Investigator: Joan Coates, DVM, MS; University of Missouri, Columbia

Total Grant Amount: $154,077

Grant Period: 1/1/2015 - 6/30/2020

Project Abstract: Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that converts superoxide to water and hydrogen peroxide, superoxide dismutase 1 (SOD1), have been linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig's disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. Dr. Coates proposes developing a test that would assay the blood and cerebrospinal fluid (CSF) for proteins that are exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. The investigators will correlate the concentrations of neurofilament proteins in CSF and blood with disease stage and anticipate that neurofilament protein concentration in blood and CSF will increase as disease progresses. Such a test will allow for minimally invasive monitoring of disease. Furthermore, such a diagnostic test could be used to measure the success of therapy, which may be underway in a cohort of DM-affected dogs [Boxers and Pembroke Welsh Corgis (PWC)] (funded by NIH/NINDS). This work will complement the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. These are functional disease markers that are also being studied in ALS patients.

Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.
Targeting the T Helper Inflammatory Pathway in Meningoencephalomyelitis of Unknown Origin (MUO)

Principal Investigator: Renee Barber, DVM, PhD; University of Georgia

Total Grant Amount: $8,845

Grant Period: 1/1/2018 - 6/30/2020

Project Abstract: Meningoencephalomyelitis of unknown origin (MUO) is a common neurological disorder of dogs that results in inflammation of the brain and/or spinal cord causing depression, seizures, blindness, difficulty walking, and death. All dogs can be affected but young to middle aged small and toy breed dogs (such as the Chihuahua, Maltese, Pug, and Yorkshire Terrier) are more frequently affected. Currently, brain biopsy is the only means of definitive diagnosis prior to death and the ideal treatment is not known. There is a critical need to improve diagnosis and treatment of MUO. The investigators will identify changes in the immune system associated with inflammation that occurs in the brains and spinal cords of affected dogs, looking for specific products of the immune response, such as interferon-gamma and interleukin 17, in blood and cerebrospinal fluid. Identification of these products could lead to development of new diagnostic tests, strategies for more effective treatment, and improved prognosis prediction.
Clinical and Molecular Genetic Analysis of Juvenile-Onset Laryngeal Paralysis in American Staffordshire Terriers

Principal Investigator: Gary Johnson, DVM, PhD; University of Missouri

Total Grant Amount: $15,000

Grant Period: 7/1/2018 - 6/30/2020

Project Abstract: In this study, the investigators will examine a newly recognized, fatal, neurologic disease referred to as American Staffordshire Terrier juvenile laryngeal paralysis and polyneuropathy (AST-JLPP). This project has two objectives: 1) to conduct thorough neurologic and pathology examinations of affected American Staffordshire Terrier puppies, and 2) to identify the molecular genetic cause for the disease. In the first objective, the neurologic examination will include characterization of the nature and degree of neurological deficits by a board-certified veterinary neurologist. Electromyography (EMG) and various nerve conduction velocities will be measured and recorded, and a laryngeal exam will be performed. Examination of affected nerves and muscle tissue as well as systemic gross and histopathological examination will be performed. A summary of the findings will be published in a scientific veterinary journal so that veterinarians around the world will be able to recognize and diagnose this new disease. To accomplish the second objective, the investigators will perform whole genome sequencing for puppies with AST-JLPP. A genome-wide association study will be used to map the AST-JLPP. Successful discovery of the causal mutation would provide a basis for DNA tests that could be used to confirm a diagnosis of AST-JLPP and aid breeders for marker-based breeding strategies.

Funding for the research is provided through the collaborative efforts and generosity of the Staffordshire Terrier Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Genetic Basis of Exercise-Induced Collapse in Border Collie Related Breeds

Principal Investigator: James Mickelson, PhD; University of Minnesota  
Total Grant Amount: $56,456  
Grant Period: 1/1/2019 - 6/30/2020

Project Abstract: An episodic nervous system disorder triggered by strenuous exercise, termed Border Collie collapse (BCC), exists in Border Collies, mixes, and related breeds, including Australian Shepherds, Kelpies, Bearded Collies, Shetland Sheepdogs, and Whippets. BCC is recognized throughout the world and is observed in dogs used for working stock, participating in agility and fly-ball competitions, or repeatedly retrieving a ball. Based on work with breed associations, field trial groups, and at competitions, the investigators estimate 5 - 10% prevalence of BCC in working Border Collies, and a somewhat lower frequency in Australian Shepherds. The research team has characterized the clinical and physiological signs of BCC to enable accurate phenotyping and the inclusion and exclusion of cases and control dogs from both breed. This study’s hypothesis is that BCC is a moderately heritable polygenic disorder, and the objectives are to define its underlying genetic architecture, heritability, and potentially genomic loci, through computational analyses of dense whole-genome DNA marker genotyping data. Knowledge of the fraction of the BCC phenotype determined by genetics, as opposed to environment and genotype x environment interaction, and whether major gene mutations are likely to exist, will inform veterinarians and working/stock dog communities of the true nature of this condition. Future research strategies would be the acquisition and genotyping of validation cohorts, and the identification of a panel of markers to predict risk in susceptible Border Collies, Australian Shepherds, related breeds, and their crosses.

This research is co-funded through the collaborative efforts of the Border Collie Society of America and AKC Canine Health Foundation.
Genetic Basis of Canine Spinal Abnormalities

Principal Investigator: Kari Ekenstedt, DVM, PhD; Purdue University

Total Grant Amount: $112,993

Grant Period: 4/1/2019 - 3/31/2021

Project Abstract: This study will identify potential genes and risk alleles to better understand the genetic basis of canine spinal abnormalities using comparisons between affected and unaffected dogs. The identification of these genes and risk alleles will advance knowledge with an ultimate goal to develop genetic tests and/or a genetic risk model to help predict healthy spines for good health in breeds with tightly curled tails such as Pugs, French Bulldogs, English Bulldogs, Boston Terriers and Basenjis.
Clinical, Pathologic, and Molecular Genetics Investigations of Canine Lysosomal Storage Diseases and Related Diseases

Principal Investigator: Gary Johnson, DVM, PhD; University of Missouri
Total Grant Amount: $16,000
Grant Period: 4/1/2019 - 3/31/2021

Project Abstract: Lysosomes are organelles within cells that contain enzymes to breakdown biomolecules as part of normal cellular function. Lysosomal storage diseases (LSDs) occur when genetic defects render lysosomes unable to completely degrade complex biochemicals and partially degraded biochemicals then accumulate within the lysosomes of cells. These abnormal lysosomes can be detected by light and/or electron microscopy. This group of disorders occur in many species, including humans, cats and dogs. The team of investigators has identified the likely causes for 17 different canine LSDs in the last 15 years, many described in dogs for the first time with both purebred and mixed breed dogs identified. Because of these successes, the laboratory receives blood samples from suspected canine LSD cases and is asked to help diagnose these dogs. This work will provide dog breed clubs with a mechanism that allows them to participate in ongoing and future research into novel canine LSDs, thus contributing to the health of their breed. Genetic tests for LSDs help breeders make sound breeding decisions for the health of their breeds, and help veterinarians diagnose these rare but important diseases.
Characterization of Sensory Neuronal and Muscle Pathology in Canine Degenerative Myelopathy to Identify Targets for Therapeutic Intervention

**Principal Investigator:** Joan Coates, DVM,MS; University of Missouri  
**Total Grant Amount:** $153,360  
**Grant Period:** 6/1/2019 - 5/31/2021

**Project Abstract:** Many dog breeds, including mixed breeds, carry genetic mutations for degenerative myelopathy (DM), a late adult-onset disease that begins with loss of coordination and progressive hind limb paralysis. The disease is particularly prevalent in Boxers and Pembroke Welsh Corgis, and is similar to amyotrophic lateral sclerosis (ALS) in people. Approximately two to three years after first signs of DM appear in dogs, loss of muscle function spreads, resulting in complete paralysis. Although the investigators have found that almost all cases of DM in dogs are associated with mutations in a gene called SOD1, it is not understood how these mutations lead to the progressive paralysis that characterizes DM. Ultimately, the research team hopes to develop a treatment that will prevent the onset and progression of disease. In order to do so, a better understanding of the earliest pathology in the muscles and nerves of affected dogs, and how this pathology spreads over time, is needed. This will enable the identification of targets for therapeutic intervention. In this study, the research team hopes to identify the earliest biochemical and structural changes in the central nervous system, muscles and nerves of dogs, and to characterize these changes as the disease progresses.
Characterization of the Fecal Microbiome in Dogs with Spinal Cord Injury Secondary to Intervertebral Disc Disease (IVDD)

Principal Investigator: Kari Foss, DVM, MS; University of Illinois
Total Grant Amount: $14,958
Grant Period: 4/1/2020 - 3/31/2022

Project Abstract: Intervertebral disc disease (IVDD) is a common cause of spinal cord injury (SCI) in dogs and can significantly impact quality of life in this patient population. Surgery is the current standard of care and focuses on relieving the actual spinal cord compression. In addition to compression, the spinal cord also suffers from contusive injury for which there are not established treatments. As such, even with surgery, the contusive injury can lead to progressive damage of the spinal cord. Studies in mice and people have shown that gut dysbiosis (bacterial imbalance in the gut) occurs as a result of SCI but can also contribute to further injury and damage. This is because the dysbiosis is thought to cause further inflammation within the spinal cord tissue. Not only is the dysbiosis a result of the SCI, but it further contributes to the injury in a vicious cycle. Studies in dogs have shown that spinal cord inflammation contributes to significant injury to the spinal cord secondary to disc disease. Therefore, targeting gut dysbiosis could play an important role in the management of SCI. This study will focus on determining the presence of gut dysbiosis in dogs with SCI secondary to IVDD when compared to healthy dogs.
**Neurofilament Light Chain Concentration in Dogs with Meningoencephalitis (MUE)**

**Principal Investigator:** Christopher Mariani, DVM, PhD; North Carolina State University  
**Total Grant Amount:** $9,473  
**Grant Period:** 2/1/2020 - 1/31/2021

**Project Abstract:** Meningoencephalitis of unknown etiology (MUE) is a common and devastating disorder that is most prevalent in small and toy breed dogs such as Pugs, Maltese and Chihuahuas. Although dogs frequently respond to anti-inflammatory or immunosuppressive therapy, many dogs suffer relapses or worsen in the face of such therapy, and this condition is ultimately fatal in most cases. Currently available diagnostic tests including magnetic resonance imaging (MRI) and spinal fluid (CSF) analysis are necessary to make a diagnosis of MUE but are not helpful in predicting the course of disease or likelihood of survival. In addition, these tests are expensive and their role in monitoring the response to therapy is uncertain. There is a critical need for novel biomarkers that will help predict responses to therapy and to monitor ongoing therapy, ideally using a blood sample. Neurofilament light chain (NF-L) is a protein found in neurons and released into the CSF and blood after injury to the central nervous system. NF-L has emerged as a promising biomarker of brain inflammation in humans, largely due to the development of a sensitive assay that can detect very small concentrations of this protein. This study will measure NF-L within the CSF and serum of dogs with MUE and compare these concentrations with control samples. The investigators will evaluate the utility of NF-L to predict patient response to therapy and prognosis.
Defining the Effect of Genotype, Breed and Age on the Risk of Developing Canine Degenerative Myelopathy and Investigating the Molecular Mechanisms Underlying That Risk

Principal Investigator: Gary Johnson, DVM, PhD; University of Missouri
Total Grant Amount: $108,000
Grant Period: 4/1/2020 - 3/31/2021

Project Abstract: Canine degenerative myelopathy (DM) is a progressive and inevitably fatal neurological disease affecting members of different dog breeds and mixes. It is an inherited disease with an age-related penetrance. The risk of developing the disease when dogs are homozygous for the causal SOD1 variant allele is currently unknown but of great concern to dog breeders and owners. The proposed research will further define the risk for developing DM in genetically at-risk dogs with a health survey distributed to dog owners whose dogs have been tested for the risk factor allele. This work will also examine the molecular mechanisms responsible for disease onset and spread by comparing single-nucleus RNA expression patterns in specific cell types in dorsal root ganglia from normal dogs and from affected dogs at various stages of the disease.
Clinical Trial of *Prevotella histicola* Supplementation to Ameliorate Meningoencephalomyelitis of Unknown Origin (MUO)

**Principal Investigator:** Nick Jeffery, BVSc, PhD; Texas A&M AgriLife Research  
**Total Grant Amount:** $40,180  
**Grant Period:** 3/1/2020 - 2/28/2023

**Project Abstract:** Meningoencephalomyelitis of unknown origin (MUO), also known by a number of other abbreviations such as MUE, MUA and, sometimes, GME (granulomatous meningoencephalomyelitis), is the name given to a group of closely-related inflammatory diseases of the brain and spinal cord. These conditions are common, about 25% or more of the neurologic cases treated by veterinary neurologists, and are severe and often fatal. MUO is considered an ‘autoimmune’ disease, in which the immune system attacks part of the body, in this case the nervous system, resulting in neurologic signs including seizures, loss of balance and inability to walk steadily. Current treatment relies on immunosuppressive drugs, such as corticosteroids, cyclosporine, cytarabine, azathioprine and others, many of which have detrimental side effects. A large proportion of affected dogs will die despite treatment or suffer long-term neurologic impairments. MUO has striking similarities to multiple sclerosis in people and a disease called ‘EAE’ in rodents. It is now known that the immune system is regulated by bacteria in the gastrointestinal (GI) tract. GI bacteria in people with multiple sclerosis, rodents with EAE and dogs with MUO are different from those in unaffected individuals. Recent evidence suggests altering bacteria in the GI tract of mice with EAE prevents or reduces severity of disease. In this study, the investigators will test whether giving an oral supplement of a specific harmless bacteria to dogs will reduce the severity of MUO. If successful, this could improve treatment to control disease and reduce reliance on immunosuppressive drugs.
Clinical Trial of Procaspe-3 Activator (PAC-1) in Combination with Hydroxyurea for Treatment of Canine Meningioma

Principal Investigator: Timothy Fan, DVM, PhD; University of Illinois
Total Grant Amount: $55,375
Grant Period: 2/1/2017 - 1/31/2021

Project Abstract: Primary brain tumors are a significant cause of illness and death in pet dogs, with meningioma accounting for approximately half of the cases seen by veterinary neurologists and oncologists. Although surgery remains the best treatment for dogs with meningioma, some dogs are not good candidates for this approach based on their tumor size and/or location. Dogs also may experience tumor regrowth after an attempt is made to surgically remove the tumor. In these situations, effective treatment options are limited. Thus, new treatments that are both safe and effective are needed for dogs with meningioma.

A team of investigators from the National Cancer Institute's Comparative Oncology Program (NCI-COP) and selected veterinary academic centers will work together using state-of-the art imaging and a novel therapeutic approach for dogs with meningioma that are good surgical candidates. Dogs enrolled in this study will receive an investigational combination of chemotherapy agents (PAC-1 + hydroxyurea) and will be monitored with magnetic resonance and non-invasive molecular imaging techniques. Dogs will then undergo tumor removal and tissue analysis. This approach is the first to validate and advance a new therapy that is directly applicable to dogs, and potentially also to humans, with advanced, locally-recurrent, and/or non-resectable meningioma.
Development of Genetic Biomarkers to Improve Diagnosis and Treatment of Canine Histiocytic Sarcoma

Principal Investigator: Benoit Hédan, DVM, PhD; CNRS - University of Rennes
Total Grant Amount: $138,107
Grant Period: 5/1/2018 - 4/30/2021

Project Abstract: Several breeds of dog, including Retrievers, Bernese Mountain Dogs and Rottweilers, are known to present elevated risks of cancers including histiocytic sarcoma (HS), lymphoma, and hemangiosarcoma. HS may be misdiagnosed due to clinical presentation shared with these other cancers. Due to the aggressiveness of HS and its late diagnosis, there is no known effective treatment. With different prognostic and therapeutic options, an early and accurate diagnosis of cancer is important to select appropriate therapies to improve outcomes for affected dogs, while still being cost effective. There is a need for the development of biomarkers for early and precise detection of such cancers. The research team has identified tumoral DNA alterations specific to HS and will use these unique alterations to improve early diagnosis of HS and to develop more specific therapies. Moreover, the investigators have been able to detect these biomarkers, already used in their lab to discriminate HS, in the blood of affected dogs. The objectives of this study are to develop a non-invasive diagnostic blood test using genetic biomarkers to accurately diagnose HS, and to explore earlier diagnosis to improve treatment outcomes through the selection of targeted therapies.
The Impact of Intravenous Anesthetic Agents on Canine Natural Killer Cell Cytotoxic Function: The Achilles Heel in Cancer Diagnosis and Surgery?

**Principal Investigator:** Oliver Garden, BVetMed, PhD; University of Pennsylvania

**Total Grant Amount:** $13,655

**Grant Period:** 1/1/2018 - 6/30/2020

**Project Abstract:** Dogs are often placed under general anesthesia for diagnostic and surgical procedures. Aside from the well-known risks of anesthesia, such as heart or lung depression, anesthetic agents can also suppress immune function. This poorly understood phenomenon is especially important in dogs that may already suffer from immune compromise, such as those with critical illness or cancer. The role of commonly used anesthetic agents, such as ketamine and propofol, on immune function in patients with cancer is being investigated in laboratory animals and humans, with ketamine increasing the spread of cancer to the lungs in rats compared to propofol. Unfortunately, there is no current research in dogs comparing these two anesthetic agents. Additionally, a newer anesthetic agent, alfaxalone, is gaining popularity for use in both healthy and critically ill dogs, but there is no research available on the effects of alfaxalone on immune function in dogs. Given the lack of information of the immune effects of these three anesthetic agents, the objective of this study is to compare the effects of ketamine, propofol and alfaxalone on a type of immune cell that is important in preventing cancer spread (metastasis). Based on the outcome of this research project and further studies, the investigators plan to develop immune-sparing anesthetic protocols to improve outcomes of dogs with cancer undergoing anesthesia for diagnostic procedures or surgery.
OX40 Checkpoint Molecule Targeted Antibodies for Cancer Immunotherapy in Dogs

Principal Investigator: Steven Dow, DVM PhD; Colorado State University
Total Grant Amount: $168,905
Grant Period: 3/1/2018 - 2/28/2021

Project Abstract: Checkpoint molecules play a key role in regulating T cell immunity against cancer (T cells are one type of immune cell called lymphocytes). Clinical trials of antibody therapeutics that target checkpoint molecules such as PD-1 in human oncology (e.g., Opdiva, Keytruda) have demonstrated remarkable results in inducing tumor regressions and cures, against a variety of different cancer types. This new era of cancer immunotherapy also has tremendous potential for treatment of cancer in dogs. The investigators will begin development of a new, second-generation immunotherapy targeting the canine checkpoint molecule OX40 (CD134). Development of the first generation PD-1 antibodies for canine oncology is already underway, and the investigator's laboratory has been involved in evaluating immune responses to these antibodies. Studies in rodent models indicate that targeting the OX40 checkpoint molecule may be more effective than PD-1 for cancer immunotherapy. The investigators will use antibodies generated in their lab against the canine OX40 checkpoint molecule to investigate its role in regulating cancer immunity in dogs, as a first step in advancing OX40 antibodies to clinical trials in dogs with cancer. In this project, they will characterize canine OX40 antibodies, determine which immune cells express OX40 in dogs, determine how OX40 antibodies activate effector T cells in dogs, and how these antibodies trigger immune activation in tumor tissues to help accelerate development of OX40 checkpoint molecule targeted antibodies as next generation cancer immunotherapeutics for dogs.
Tumor-permissive Collagen Signatures in Canine Mammary Gland Tumors: Development of Prognostic Markers and Targeted Therapies for Improved Outcomes

Principal Investigator: Susan Volk, VMD, PhD; University of Pennsylvania

Total Grant Amount: $162,700

Grant Period: 3/1/2018 - 8/31/2020

Project Abstract: Mammary gland tumors (MGT) are the most common malignancies in intact female dogs, and the resulting premature death and morbidity in this sub-population of dogs represents a significant health problem. While genetic alterations within tumor cells can promote their uncontrolled growth and ability to spread to distant sites, recent work indicates that normal, non-malignant cells and extracellular matrix (ECM) within the surrounding tumor stroma also regulate the growth and spread of cancer. The investigators have identified cancer-associated stromal (collagen) signatures in canine MGT biopsy samples that predict clinical outcome better than commonly used markers. These predictive markers may improve the veterinary oncologist’s ability to accurately predict which dogs truly need aggressive treatment from those that do not. Notably, their laboratories have shown that inhibition of a collagen-degrading enzyme (Fibroblast Activation Protein (FAP)) and increasing a tumor-suppressive collagen (type III collagen (Col3)) prevent the formation of these tumor-inciting signatures in other species (mouse and human). This work suggests that if these novel targets can suppress tumor-permissive collagen signatures in the dog, we can treat canine MGT more effectively. The goals of this project are 1) to identify additional collagen signatures which predict clinical outcome in dogs, 2) determine how they direct tumor cell behavior and 3) develop therapies that prevent formation of tumor-inciting collagen signatures in canine MGT. Based on the investigators’ published and preliminary data, they predict that identifying and targeting tumor-inciting collagen signatures will lead to improvements in both diagnosis and treatment of dogs with malignant MGT.
**Immune Targeting of the V600E B-Raf Neoantigen in Canine Urothelial Carcinoma**

**Principal Investigator:** Nicola Mason, BVetMed, PhD; University of Pennsylvania  
**Total Grant Amount:** $183,146  
**Grant Period:** 2/1/2018 - 1/31/2021

**Project Abstract:** Bladder cancer or urothelial carcinoma (UC) affects approximately 40,000 dogs per year in the U.S. with specific breeds including Scottish Terriers, West Highland White Terriers, Shetland Sheepdogs, Beagles, and Parson Russell Terriers being over-represented. Affected dogs usually display lower urinary tract clinical signs including bloody urine, frequent urination, difficulty and pain on urinating, and urinary outflow tract obstructions. Standard of care consists of anti-inflammatory drugs either alone or in combination with chemotherapy or radiation therapy. While these treatments can lead to stable disease for 6-12 months, they rarely lead to a cure, and most dogs eventually succumb to their disease. In human medicine, urinary bladder tumors have been shown to exhibit a high gene mutational burden which directly correlates with a favorable response to immune therapies. Canine UC exhibits a similar mutational load suggesting that the disease in dogs may also be immune responsive. In this study, the investigators will evaluate the safety and effectiveness of a novel targeted, immune therapy that aims to promote a powerful immune response against a specific gene mutation (V600E B-Raf) recently identified in up to 87% of dogs with UC. The investigators hypothesize that vaccine-induced anti-tumor immune responses will lead to tumor regression and that such favorable responses will correlate with the baseline mutational burden of the tumor. The investigators will use standard immunological methods and advanced genetic sequencing technology to study systemic and intra-tumoral immune responses to identify biomarkers that may predict immunological and clinical response in dogs.

*Collaborative grant between the AKC Canine Health Foundation and the V Foundation for Cancer Research.*
Defining the Flow Cytometric Characteristics of Normal and Diseased Canine Spleen and Visceral Lymph Nodes

Principal Investigator: Courtney Johnson, DVM; University of Minnesota
Total Grant Amount: $14,903
Grant Period: 5/1/2019 - 4/30/2021

Project Abstract: The canine spleen and internal lymph nodes are frequently affected by blood-borne cancer. Flow cytometry (FC) can provide key diagnostic and prognostic information for canine cancer and is a rapid and objective tool while also minimally invasive to the patient. However, the methodology is currently limited by the lack of tissue-specific reference intervals (i.e., what is considered “normal”), and published data on the canine spleen and internal lymph nodes is lacking. In light of these knowledge gaps, the investigators will examine the benefits of flow cytometry in the evaluation of dogs with blood-borne cancer that commonly affects the spleen and internal lymph nodes. Performing flow cytometry on tissues from canine patients presenting to University of Minnesota Veterinary Medical Center will allow identification of tissue-specific reference intervals. The findings may provide for accurate and reliable diagnosis of blood-borne disease, including cancer, in dogs.
Development of RNA in-situ Hybridization to Identify T Regulatory Cells and their Function within the Tumor Microenvironment of Canine Oral Malignant Melanoma

Principal Investigator: Sandra Bechtel, DVM; University of Florida
Total Grant Amount: $15,000
Grant Period: 4/1/2019 - 9/30/2020

Project Abstract: Oral malignant melanomas (OMM) in dogs have a high potential to metastasize or spread. While OMM is responsive to immunotherapy, responses are varied and difficult to predict, and only a subset of patients respond to immunotherapy. Therefore, it is vital to identify dogs with the best chance of responding to immunotherapy, understand which dogs may not respond and why, and to discover new therapeutic targets to increase response rates. Current high throughput methods for profiling the immunology of the tumor microenvironment cannot define cells nor can they investigate cell functions that are critical for determining immunologic profiles. This study’s objective is to identify T regulatory cells, a type of lymphocyte, that suppress the immune response, within the tumor microenvironment of OMM. The investigators will concurrently determine cellular function by investigating intracellular cytokine production utilizing a highly sensitive and specific in situ hybridization technology known as RNAscope®. Unlike current methods of detection, this technology can detect multiple cell markers simultaneously, identifying the cells of interest. This technology has the potential to define prognostic and predictive factors for immunotherapy response to assist veterinarians and clients in determining the best treatment option for their dog.
Examination of the Effects of Cannabidiol on Canine Neoplastic Cell Apoptosis/Autophagy and Potential for Chemotherapy Resistance or Sensitivity

Principal Investigator: Joseph Wakshlag, DVM, PhD; Cornell University

Total Grant Amount: $14,580
Grant Period: 6/1/2019 - 11/30/2020

Project Abstract: Currently the use of cannabidiol (CBD) rich extracts for canine oncology patients is common, yet there is no data in canine oncology regarding the effects of CBD on canine cancer cells. Oncologists are wary of CBD use in their patients due to a lack of knowledge regarding the effects of CBD during chemotherapy. Initial studies on cytotoxicity by the research team show that CBD has cytotoxic activity on a variety of canine cancer cell lines at modest concentrations in the laboratory. These effects cause apoptosis, or programmed cell death, within a very short time frame, suggesting a discrete mechanism. The objective of this study is two-fold; 1) to determine if co-treatment of cancer cells with a common chemotherapeutic (doxorubicin) and CBD at varying concentrations affects chemotherapeutic cytotoxicity, and 2) to examine the molecular framework of the cell death response looking at the most commonly implicated pathways targeted in canine cancer treatment, including mechanisms of cell signaling and autophagy (removal of damaged cells).
**Comparative Brain Tumor Consortium (CBTC) Meningioma Pathology**

**Principal Investigators:** Amy LeBlanc, DVM; National Institutes of Health/National Cancer Institute/Center for Cancer Research/Comparative Oncology Program, Andrew Miller, DVM; Cornell University, Molly Church, MS, VMD, PhD; University of Pennsylvania

**Total Grant Amount:** $79,600  
**Grant Period:** 4/1/2019 - 9/30/2020

**Project Abstract:** Meningioma is the most common intracranial neoplasm in the dog representing up to 50% of all primary intracranial neoplasms. Dogs can suffer significant clinical signs and impact on quality of life depending on size, location, and degree of invasiveness of the tumor. Treatment typically consists of surgical excision, if the mass is accessible, followed by radiation and/or chemotherapeutics. Unfortunately, while surgical advances have been made for this tumor type, correlative data describing the gross and histopathologic findings with the dog’s post-surgical outcome has remained elusive and is in its infancy. Therefore, an unmet need exists for developing a standardized set of pathologic criteria that can be correlated with surgical outcome and be used to guide prognosis, therapeutic intervention, and identify novel biomarkers that will aid in both diagnosis and treatment efficacy. The Comparative Brain Tumor Consortium (CBTC) meningioma pathology board represents a collaboration of diagnostic and investigative experts with diagnostic, scientific, and clinical experience in canine and human meningiomas. For this project, expertise provided by veterinary and physician neuropathologists will be complemented by the prospective integration of clinical outcome data and molecular profiling analyses. This integrated platform will identify prognostic and therapeutic biomarkers for canine patients and will generate uniformity in diagnosis across institutions. A grading and classification scheme will also be developed for canine meningioma to help define prognostic outcome and prospectively integrate tumor morphology, immune cell infiltrate, and epigenetic profiles with genomic data obtained from a robust collection of canine tumors. This level of tumor characterization will allow specific parallels to be drawn between subsets of canine and human tumor subtypes, thus fostering comparative translational clinical trials to benefit both species.
Tumor-educated Platelets: A Novel Minimally Invasive Liquid Biopsy for Early Cancer Diagnosis

Principal Investigator: Unity Jeffery, VetMB, PhD; Texas A&M AgriLife Research

Total Grant Amount: $14,999

Grant Period: 1/1/2020 - 12/31/2020

Project Abstract: Platelets are a vital part of the blood clotting system and interact closely with tumor cells. These interactions promote tumor growth and spread, but also alter the RNA content of platelets. These altered platelets are described as tumor-educated platelets because they carry this tumor signature to distant sites as they circulate through the body. TRNA from platelets routinely collected in blood samples can be sequenced to identify the genes of origin. This platelet RNA profile can reliably distinguish human cancer patients with a wide variety of tumors from healthy people and patients with inflammatory disease. This study will perform RNA sequencing to determine the platelet RNA profile for dogs with several types of cancer versus healthy dogs and dogs with infectious disease. This will be a first step in developing a platelet-based minimally invasive cancer screening test.
Optical Coherence Tomography for Margin Evaluation of Canine Skin and Subcutaneous Neoplasms

**Principal Investigator:** Laura Selmic, BVetMed, MPH; Ohio State University Research Foundation

**Total Grant Amount:** $43,443

**Grant Period:** 3/1/2020 - 2/28/2022

**Project Abstract:** Skin cancer is common in older dogs and often requires surgery to treat. For these tumors, the best chance of cure is offered if the surgeon can fully remove both visible and microscopic traces of the tumor. Currently surgeons must rely on pathologist’s assessment of tissues after surgery and the success of the procedure will not be known until several days later. This result is important as residual cancer may need further surgery or other treatments like radiation therapy. Additional treatments such as these can result in further risk and discomfort for dogs as well as be an emotional and financial cost for owners. Optical coherence tomography is an emerging diagnostic imaging tool that uses light waves to generate real-time, high-resolution images of tissue at a microscopic level. These images can be used to evaluate for residual disease at the time of surgery giving immediate feedback to the surgeon. This study will focus on validating this technology for the imaging of surgical margins of canine skin and subcutaneous tumors. If successful, this technology could be used to assess for residual cancer intra-operatively to benefit patients by guiding accurate treatment recommendations.
Bladder Carcinogen Exposures in Pet Dogs

Principal Investigator: Lauren Trepanier, DVM, PhD; University of Wisconsin, Madison
Total Grant Amount: $149,145
Grant Period: 3/1/2020 - 2/28/2022

Project Abstract: Bladder cancer is an aggressive cancer that affects ~ 20,000 dogs per year, and often leads to euthanasia. Certain breeds have a higher incidence of bladder cancer but genetic studies even in the highest risk breeds have been inconclusive and still indicate influence from environmental exposures. The investigators propose that specific household environmental chemical exposures contribute to the risk of bladder cancer in dogs. In this study, they will measure urinary concentrations of five different chemicals that are known or suspected to be bladder carcinogens, in dogs with bladder cancer compared to unaffected dogs. The investigators will determine whether the presence of certain chemicals is associated with household exposures, based on owner questionnaires and household proximity to industrial sites. Finally, they will determine whether urinary chemical concentrations are linked to early DNA damage in the urinary cells of healthy dogs that do not have bladder cancer. The overall goal of this study is to provide veterinarians and dog owners with evidence-based bladder cancer prevention strategies.
Transcriptional Profiling of Canine Soft Tissue Sarcoma

Principal Investigator: Andrew Miller, DVM; Cornell University
Total Grant Amount: $132,759
Grant Period: 3/1/2020 - 2/28/2023

Project Abstract: Soft tissue sarcomas account for 10-15% of all skin and subcutaneous cancers in dogs. Traditionally, biopsy and subsequent histology have been the primary means of diagnosing these cancers. The histology is assigned to one of three grades ranging from low (grade I), intermediate (grade II), and high (grade III). Histologic grade is currently the key criterion for guiding treatment and determining patient outcome. However, in human medicine and pathology, soft tissue sarcomas are diagnosed with a hybrid approach that involves both histologic features and genetic analysis of the tumor sample. This genetic analysis guides further treatment, aids in developing accurate follow-up information, and has been shown to have a positive effect on patient outcome and survival. Despite how common soft tissue sarcomas are in the dog, current veterinary care still relies solely on the histologic grade, which is subjective at best, and does not incorporate genetic data into the diagnostic plan. This study will perform transcriptome analysis on 300 canine soft tissue sarcomas in order to establish the transcriptome profile of canine soft tissue sarcoma and correlate this transcriptome to patient follow-up. This will allow for the formation of a hybrid diagnostic approach that will provide more accurate information to inform the prognosis for dogs afflicted with soft tissue sarcoma.
Identification of Novel Synthetic Lethal Partners to Optimize PI3K Targeted Therapies in Canine Hemangiosarcoma

**Principal Investigator:** Cheryl London, DVM, PhD; Tufts University School of Medicine  
**Total Grant Amount:** $168,857  
**Grant Period:** 3/1/2018 - 2/28/2022

**Project Abstract:** Hemangiosarcoma (HSA) is a cancer of the cells lining the blood vessels that is very aggressive and has nearly always spread by the time it is diagnosed. HSA accounts for 5-7% of all cancers in dogs resulting in approximately 25,000-50,000 new cases per year. The treatment of choice is surgical removal followed by chemotherapy administration. Unfortunately, despite aggressive therapy, the majority of dogs diagnosed succumb to their disease within 6-8 months. Virtually no improvements in outcome for affected dogs have occurred in the past 30 years despite multiple clinical trials and research efforts. More recently a new therapy has been developed targeting two receptors on HSA cells. However, the majority of dogs still died by 10-12 months after treatment. The molecular pathway known as the PI3K/AKT/mTOR pathway has previously been implicated in the pathogenesis of many forms of cancer including HSA. Indeed, inhibitors of PI3K/AKT/mTOR pathway have some activity against HSA cell lines in the laboratory. The investigators have generated data showing that a subset of canine HSA tumors possess genetic mutations in PI3K that are known to activate the pathway in cancer cells. In this study, they will fully characterize the expression and function of PI3K in canine HSA tumor cell lines and tumor samples. This information will then be leveraged to identify new ways to block the PI3K/AKT/mTOR pathway using a combination of small molecule inhibitors that are most effective at killing tumor cells. These data will then be used to design future clinical trials in dogs with HSA.
Prevalence of *Bartonella* spp. Infection in Dogs with Cardiac and Splenic Hemangiosarcomas Within and Between Geographic Locations

**Principal Investigator:** Edward Breitschwerdt, DVM; North Carolina State University  
**Total Grant Amount:** $219,026  
**Grant Period:** 2/1/2018 - 1/31/2021

**Project Abstract:** Splenic masses comprise ~50% of all canine splenic disease. Despite advances in imaging and pathologic definition, the etiology and medical relevance of splenic lesions in dogs are often ambiguous. While some splenic tumors are benign, approximately two-thirds are highly malignant and carry a poor prognosis. Hemangiosarcoma (HSA) accounts for the majority of canine malignant splenic tumors and occurs in many large dog breeds, including mixed breeds. A less common site of HSA localization is the heart (cardiac HSA). Risk factors for both cardiac and splenic HSA remain unclear, confounding development of preventative strategies. The investigators recently reported a high prevalence of species of the bacterial genus *Bartonella* in dogs with HSA from North Carolina, suggesting a potential role in the initiation and/or progression of this cancer. *Bartonella* species exist worldwide and are transmitted by blood-sucking arthropods (e.g. ticks, fleas) and their presence in splenic tissue could potentially be explained by the fact that the spleen is primarily responsible for removal of blood-borne parasites from the systemic circulation. The investigators will perform a comprehensive examination of the potential association between *Bartonella* infection and HSA by comparing the prevalence of *Bartonella* DNA in tumor and blood samples from both splenic and cardiac HSA cases, and also within and between distant geographical locations in the U.S. Ultimately, demonstration of a robust association between *Bartonella* infection and the development of HSA may lead to new opportunities for improved diagnosis, treatment and prevention of this devastating cancer.
Clinical Trial for Evaluation of Propranolol and Doxorubicin in the Treatment of Canine Hemangiosarcoma

Principal Investigators: Erin Dickerson, PhD and Antonella Borgatti, DVM, MS; University of Minnesota
Co-Investigators: David R. Brown, PhD; University of Minnesota, Michael O. Childress, DVM, MS; Purdue University, Jennifer Mahoney, DVM and Pascale Salah, DVM, MS/DrPh II; University of Pennsylvania
Total Grant Amount: $310,970
Grant Period: 7/1/2019 - 6/30/2022

Project Abstract: Canine hemangiosarcoma is a largely incurable cancer in dogs, and treatment approaches to improve outcomes have remained relatively stagnant over the past few decades. Treatment remains a challenge partly because the cancer is frequently detected at an advanced stage and because these tumors are often resistant to chemotherapies. Recently published reports showed that propranolol, a drug used to treat heart disease in humans and dogs, substantially increased the survival time of human angiosarcoma patients when used in combination with standard of care treatments. Propranolol was also shown to sensitize hemangiosarcoma cells to doxorubicin, providing a more effective way to kill tumor cells. Because angiosarcoma is strikingly similar to canine hemangiosarcoma, this multi-institutional clinical trial has been designed to determine the efficacy of propranolol in dogs with hemangiosarcoma when used in combination with surgery and chemotherapy. The main goal of the study is to establish whether propranolol in combination with doxorubicin following surgery improves outcomes for dogs when compared to the use of chemotherapy and surgery alone. The investigators will also evaluate the plasma concentrations of propranolol achieved during dosing to assess whether the levels of propranolol correlate to survival times. If successful, the findings from this approach will be rapidly conveyed to the veterinary community, and the guidelines provided to clinicians for the use of propranolol and doxorubicin for the treatment of canine hemangiosarcoma.
Evaluation of Serum miRNA as a Diagnostic Tool for Canine Splenic Hemangiosarcoma

**Principal Investigator:** Janet Grimes, DVM, MS; University of Georgia  
**Total Grant Amount:** $15,000  
**Grant Period:** 3/1/2020 - 2/28/2021

**Project Abstract:** Cancer is the leading cause of death in adult dogs, with hemangiosarcoma (HSA) being the most common tumor of the spleen. Affecting predominantly large-breed dogs, HSA is associated with a nearly 100% death rate with most dogs surviving 3-6 months with treatment. Other splenic masses occur in dogs which may have better prognoses; however, there are not currently available methods to accurately differentiate HSA from other masses of the spleen prior to surgery and histopathology. There is a critical need to identify the presence of HSA earlier than is currently possible. MicroRNA are short segments of RNA that control gene expression and have been shown to be involved in cancer progression. Studies have shown that microRNA present in dogs with HSA are different than those present in normal dogs and dogs with other tumors. The objectives of this study are to identify microRNA present in the blood of dogs with HSA before and after removal of the spleen, and to determine a panel of microRNA that can discriminate dogs with HSA from dogs with other masses of the spleen. This will allow for earlier diagnosis, leading to improved prognosis, and also assist with more accurate monitoring for disease recurrence/progression.
Reprogramming the Tumor Immune Niche in Canine Hemangiosarcoma

**Principal Investigator:** Jong Hyuk Kim, DVM, PhD; University of Minnesota  
**Total Grant Amount:** $150,000  
**Grant Period:** 7/1/2020 - 6/30/2022

**Project Abstract:** Hemangiosarcoma (HSA) is a common, devastating disease of dogs. The malignant tumor is seen frequently in older Golden Retrievers, German Shepherd Dogs, Portuguese Water Dogs, Labrador Retrievers, and Schnauzers, but it can occur in any dog of any breed at any age. Survival times of dogs with the tumor are short, even with surgical removal and standard of care treatment. Inflammation within the tumor tissue is common in canine HSA, and the immune response may contribute to tumor heterogeneity and prognosis for the dog. Yet, the immunological features in the context of the HSA niche are virtually unknown. The investigators have found that HSA cells have a strong capacity to promote proliferation and differentiation of hematopoietic stem and progenitor cells, with increased inflammatory cytokines, suggesting a niche regulatory function of HSA cells. This study will focus on understanding the functional relationships between HSA cells and immune cells that contribute to the tumor niche to identify molecular mechanisms that regulate critical signaling pathways in canine HSA. This approach will improve our understanding of the tumor immunity and heterogeneity, as well as aid in patient selection for novel immunotherapies.
Targeting the Cancer Epigenome: The Effect of Specific Histone Lysine Methyltransferase Inhibition in Canine B-Cell Lymphoma

Principal Investigator: Angela McCleary-Wheeler, DVM, PhD; University of Missouri
Total Grant Amount: $78,029
Grant Period: 9/1/2018 - 12/31/2020

Project Abstract: Canine lymphoma is one of the most common cancers in dogs. While some breeds appear more at risk than others, all can be affected. Although it is often treatable, canine lymphoma can rarely be cured. A continued understanding of the mechanisms causing lymphoma in dogs and identification of novel therapies are needed to improve survival in dogs with lymphoma. One area of research that has been actively explored and provided exciting breakthroughs for human lymphoma is epigenetics, or alterations in how genes are turned on and off independent of the DNA sequence. One way in which this occurs is due to modifications of the proteins that interact with DNA called histones. Various modifications to these histones can result in genes being turned on or off, leading to the development of cancer. One particular enzyme that modifies histones, EZH2, has been found to play a role in some human lymphomas. However, this has been unexplored in canine lymphoma. Given the striking similarities between human and canine lymphoma, the objective of this work is to characterize the function and role of EZH2 in canine lymphoma. The investigators will utilize an EZH2 inhibitor to study EZH2 in canine lymphoma cells. The information obtained from this study will help guide the future development of this targeted inhibitor for use as a novel therapy to treat canine lymphoma.
The Role of Complex Translocations Associated with TP53 Somatic Mutations for Aiding Prognosis of Canine Diffuse Large B-Cell Lymphoma

Principal Investigator: Matthew Breen, PhD; North Carolina State University
Total Grant Amount: $177,327
Grant Period: 1/1/2017 - 6/30/2020

Project Abstract: Lymphoma accounts for up to 24% of all cancers diagnosed in pet dogs. Among these cases diffuse large B-cell lymphoma (DLBCL) is the most common subtype. Despite continued advances in veterinary medicine, the response to treatment for canine lymphoma remains highly variable with no reliable means to predict response. Studies of lymphoma in people have identified characteristic genome changes that have both diagnostic and prognostic significance. In human DLBCL, mutations in the TP53 gene, and genome rearrangements involving the MYC, BCL2 and BCL6 genes have been shown to confer particularly poor prognosis in cases treated with standard of care multi-agent (CHOP-based) chemotherapy. The investigator’s previous CHF-funded studies have shown that canine cancers, including lymphoma, exhibit genomic changes that are conserved with those observed in the corresponding human cancers, and have identified MYC and BCL2 rearrangements and a high frequency of TP53 mutation in canine DLBCL. This research will screen a well-defined collection of over 450 pre-treatment, canine DLBCL samples to determine accurate frequencies of these genome changes. The researchers will investigate the correlation of these target aberrations with duration of first remission, and identify key genomic signatures that may aid prognosis of prospective canine lymphoma cases. The data generated should assist owners and veterinarians with decisions regarding treatment with CHOP. Patients with signatures predictive of poor response to conventional CHOP chemotherapy may benefit from more aggressive treatment at the outset to improve outcome.
**Precision Medicine for Canine Lymphoma**

**Principal Investigator:** Nicola Mason, BVetMed, PhD; University of Pennsylvania  
**Total Grant Amount:** $86,400  
**Grant Period:** 3/1/2018 - 2/28/2021

**Project Abstract:** The clinical response of dogs with lymphoma to multi-agent chemotherapy is highly variable. Although up to 85% of dogs respond initially, some relapse within weeks, while others enjoy remission times of two years. This heterogeneity in clinical response is in part explained by the recognition that "lymphoma" is not a single disease entity, but consists of different subtypes that can be characterized on a molecular level by mutations in specific genes. As in human medicine, it follows that different lymphoma subtypes, driven by different molecular mechanisms, may respond better to therapies that are specifically selected to inhibit the driver mechanisms within that patient’s tumor. Recent work using sophisticated genetic sequencing tools (next-generation sequencing (NGS)) has begun to shed light on the different molecular subtypes of canine B cell lymphoma, and specific therapies aimed at targeting patient-specific driver genes and pathways are being developed. To enable targeted therapies to move into the clinic, a personalized diagnostic tool must be developed that can rapidly and cost-effectively determine the mutational profile of a patient’s cancer allowing selection of the most effective drug for that patient. The investigators aim to develop a NGS diagnostic test that can be employed on standard biopsy samples to identify molecular drivers of a patient's lymphoma (personalized diagnostics), enabling the most appropriate targeted therapy to be selected for that patient. In addition, they aim to determine whether specific mutational profiles within canine lymphoma identified by their NGS panel are predictive of clinical outcome.
The Role of the Putative Tumor Suppressor Gene SETD2 in Canine Diffuse Large B-cell Lymphoma

Principal Investigator: Bonnie Harrington, DVM, PhD; Michigan State University
Total Grant Amount: $14,996
Grant Period: 2/1/2020 - 1/31/2022

Project Abstract: Lymphoma is a common, deadly cancer affecting both humans and dogs. Effective therapies without side effects are lacking. This study will investigate the role of a gene called SETD2 in the development of canine lymphoma. SETD2 is often disrupted in human cancers, including lymphoma, and preliminary data suggest a similar gene disruption in canine lymphoma. The work set forth will confirm alteration of this gene in dogs and evaluate whether and how it is related to clinical factors, including severity of disease, resistance to treatment, and dog breed. Overall, these studies will establish the significance of SETD2 dysfunction in canine lymphoma, laying the groundwork for future investigations to understand how this gene contributes to cancer development and how to more effectively treat canine lymphoma.
Luteinizing Hormone Receptor Activation Induces Migration and Adhesion in Neoplastic Canine Lymphocytes

**Principal Investigator:** Michelle Kutzler, DVM, PhD; Oregon State University

**Total Grant Amount:** $14,580

**Grant Period:** 2/1/2020 - 1/31/2021

**Project Abstract:** Luteinizing hormone (LH) is secreted from the brain (pituitary) in sexually intact dogs to stimulate synthesis of estrogen and testosterone in females and males, respectively. However, LH is secreted at concentrations up to 20 times higher following gonad removal with spaying or castration because hormonal negative feedback is lost. Although LH is considered to be a reproductive hormone, there are dozens of non-reproductive tissues in dogs that contain receptors for LH including immune system cells, specifically lymphocytes. Lymphoma is a common malignant cancer of dogs involving lymphocytes, and spayed/castrated dogs are reportedly 3-4 times more likely to develop lymphoma. Conventional chemotherapy results in remission in approximately 60-90% of cases with a median survival time of 6-12 months. Preliminary work has identified LH receptors in canine lymphoma tissue and demonstrated LH-receptor-induced proliferation of neoplastic lymphocytes in vitro. This study aims to determine if LH receptor activation induces adhesion and migration of neoplastic lymphocytes in vitro. Characterizing the role of LH receptor in neoplastic lymphocyte proliferation may help guide future lymphoma treatment options.
Identifying Early Stage Ultra-rare Mutations as Predictive Biomarkers of Lymphoma in High-risk versus Low-risk Breeds Within the Dog Aging Project

Principal Investigator: Daniel Promislow, PhD; University of Washington

Total Grant Amount: $75,600

Grant Period: 3/1/2020 - 2/28/2021

Project Abstract: The most common type of cancer in dogs is lymphoma, with ~80,000 cases diagnosed annually in the United States. Breeds vary in their risk of lymphoma, but it is unclear why there is variation despite considerable effort to identify the genetics of cancer risk and progression in dogs. Cancer typically arises from the accumulation of non-inherited (i.e. somatic) mutations. However, variation among breeds in cancer risk could be due to breed-specific variation in the types of mutations, the rate of accumulation of mutations, or the downstream effects of mutations in healthy dogs. This study will use novel sequencing technology to test the hypothesis that breed-specific lymphoma risk is due to variation in the frequency and type of rare precancerous mutations. Normally, measuring these low-frequency mutations has been beyond the range of standard sequencing technology, which is limited to detecting mutations present in >1% of cells. The new technology applied here represents a >10,000-fold improvement in accuracy, enabling the investigators to accurately detect a precancerous mutation present at a single site at a frequency of just one out of every 10 million DNA base pairs. By determining if mutation frequency in blood of healthy high-risk and low-risk dogs can predict lymphoma risk, this work could lead to the development of novel tests for the early diagnosis and prognosis of canine lymphoma. This work has the potential to shed light on the mechanisms that underlie breed-specific variation in lymphoma risk, and in the long term, could lead to the development of novel tests for the early diagnosis and prognosis of canine lymphoma.
Identifying the Genes That Confer Risk for Osteosarcoma

Principal Investigator: Carlos Alvarez, PhD; The Research Institute at Nationwide Children's Hospital

Total Grant Amount: $120,000

Grant Period: 1/1/2012 - 12/31/2020

Project Abstract: Osteosarcoma (OSA) is the most common cancer of the bone in both dogs and humans. A prime candidate for investigation of the genetic component of OSA is the Greyhound, which has the highest risk of OSA of any breed. However, despite significant effort, classical genetic approaches have not identified any Greyhound variant that accounts for most OSA cases in that breed. Dr. Alvarez proposes that Greyhound OSA variants have been directly or indirectly selected for in racing performance, consistent with the vastly elevated incidence in racing vs. show Greyhounds. If this is true and all racers carried an OSA mutation on both chromosomes, then this could not be detected using classical approaches (which require different genetic markers to distinguish cases v. controls). Here Dr. Alvarez proposes an innovative genetic approach that is impervious to the limitations described above, and enables genome-wide discovery of Greyhound variation with large effects on OSA risk. Such findings would lead to rapid development of therapies and clinical trials in dogs, and translation to human medicine.
NF-kappaB Inactivation Enhances Apoptosis in Canine Osteosarcoma Cells

**Principal Investigator:** Travis Laver, VMD, PhD; University of Georgia  
**Total Grant Amount:** $13,792  
**Grant Period:** 4/1/2019 – 9/30/2020

**Project Abstract:** Osteosarcoma (OSA) is the most common cancer originating in the bone in dogs. Current treatments for OSA range from quality of life focused care, such as pain management, to amputation and chemotherapy. Unfortunately, regardless of the path pursued, very few dogs are cured of this cancer. Quality and quantity of life are limited in patients with OSA due to significant destruction of normal bone, which puts patients at risk of fractures. Furthermore, OSA has a high rate of spread to other areas of the body (metastasis), most commonly to the lungs. The investigators recently identified abnormal activation of a protein transcription factor called NF-kappaB in both patient-derived tumor samples and in established OSA cell lines, and believe the increased activity of this pathway may be contributing to some of the aggressive characteristics of OSA in dogs. Recent information indicates that a drug called bortezomib may be able to limit or completely stop the activation of this protein. Bortezomib has recently been investigated in multiple cancer types in humans with some encouraging results. This study will investigate the role of NF-kappaB and bortezomib in canine OSA.
Defining the Functional Consequences and Therapeutic Vulnerability of Dystrophin Alterations in Canine Osteosarcoma

Principal Investigator: Cheryl London, DVM, PhD; Tufts University
Total Grant Amount: $94,605
Grant Period: 4/1/2020 - 3/31/2023

Project Abstract: Lay Abstract:
Osteosarcoma is the most common primary bone tumor in dogs, predominantly occurring in large and giant breed dogs such as the Great Dane, Irish Wolfhound, Rottweiler, Greyhound and Golden Retriever, among others. While surgery and chemotherapy help improve outcome for patients, over 90% of dogs will develop chemotherapy resistance and die due to disease progression within one year. Therefore, new treatment approaches are needed for dogs with osteosarcoma. The investigators previously performed whole genome sequencing of canine osteosarcoma tumors and identified large deletions in DMD, the gene that encodes the dystrophin protein. Loss of this protein is associated with more aggressive cancers in people, however virtually nothing is known about the role of dystrophin in canine osteosarcoma. This study will determine the incidence of DMD gene deletions across a larger number of osteosarcoma tumors and validate a targeted sequencing panel to rapidly identify these deletions in client-owned dogs with osteosarcoma. Additionally, the investigators will characterize the role of DMD deletions in tumor biology to determine the best way to treat osteosarcoma tumors with DMD deletions. This work will lay the groundwork for future prospective clinical trials targeting genetic mutations in dogs with osteosarcoma.
Histotripsy for Treatment of Canine Appendicular Osteosarcoma

Principal Investigator: Joanne Tuohy, DVM, PhD; Virginia-Maryland Regional College of Veterinary Medicine
Total Grant Amount: $35,975
Grant Period: 3/1/2020 - 2/28/2021

Project Abstract: Osteosarcoma (OS) is the most common bone cancer in dogs. Large and giant breeds such as Irish Wolfhound, Great Dane, Greyhound, Scottish Deerhound, Rottweiler, Boxer, Saint Bernard, and Irish Setter are most affected. OS is treated with a combination of surgical removal of the primary tumor and chemotherapy for metastatic disease. Surgical removal of the tumor usually involves limb amputation or limb salvage surgery, which can have high complication rates, and not all dogs are suitable for limb amputation. Even after surgical tumor removal and chemotherapy, the cancer often metastasizes and dogs usually die of metastatic disease within an average of 12 months after diagnosis. Survival times have not greatly improved over the last 30 years. Histotripsy is a precision non-thermal focused ultrasound method that mechanically breaks down tissues, can potentially induce immune activation towards an anti-OS immune response, and is an emerging modality for treating multiple cancers including liver and brain cancer. A non-surgical option for treatment of the primary tumor in OS will help patients preserve their limb and avoid complications of surgical limb-salvage. A therapy that stimulates an anti-tumor immune response may increase OS survival. This study aims to evaluate the efficacy of histotripsy to treat dogs with OS, to ultimately advance the development of histotripsy as a limb salvage treatment option for primary OS and an immunotherapy treatment against metastatic disease for OS.
Genetic Contribution to Early-onset Osteosarcoma

Principal Investigator: Susannah Sample, DVM, MS, PhD; University of Wisconsin, Madison
Total Grant Amount: $161,718
Grant Period: 3/1/2020 - 2/28/2023

Project Abstract: Osteosarcoma is a devastating disease that affects many dog breeds. Although osteosarcoma is typically a disease of older dogs, in some breeds, such as the Irish Wolfhound, dogs can be affected at a young age. This study will investigate the genetic basis of early-onset osteosarcoma in the Irish Wolfhound breed. Osteosarcoma is responsible for ~20% of deaths in the Irish Wolfhound breed, with many dogs being diagnosed before 5 years of age. Consequently, there is a critical need to advance understanding of the genetic basis of early-onset osteosarcoma in the Irish Wolfhound. State-of-the-art DNA sequencing will provide insight into an osteosarcoma-associated genetic variant that strongly influences disease risk in young Irish Wolfhounds. This discovery, with subsequent development of a genetic screening test, will contribute to selective breeding decisions to decrease osteosarcoma prevalence in the Irish Wolfhound breed. Findings can then be applied to other osteosarcoma-predisposed breeds. The genomic research approach will also have substantial impact in method development for other genetic studies of rare diseases in dogs or diseases in rare breeds.
**Genetics of Primary Angle Closure Glaucoma in American Cocker Spaniels**

**Principal Investigator:** Sara Thomasy, DVM, PhD; University of California, Davis  
**Total Grant Amount:** $40,000  
**Grant Period:** 5/1/2017 - 10/31/2020  

**Project Abstract:** Glaucoma is a leading cause of irreversible blindness and globe removal (enucleation) in dogs. Primary angle closure glaucoma (PACG) is the most common form of glaucoma in dogs whereby acute blockage of the iridocorneal angle leads to a rapid increase in intraocular pressure. Consequently, PACG is painful, demands immediate medical attention, and often causes incurable vision loss. The American Cocker Spaniel (ACS) has the highest reported prevalence of any canine breed for PACG. The investigators will study the genetics of PACG in the ACS to identify potential disease-causing loci and variants. Dogs will be extensively phenotyped as PACG cases or controls using advanced imaging equipment used to investigate glaucoma in human patients. Identification of genetic markers associated with PACG in ACSs will facilitate the development of a genetic test to inform breeding programs. Furthermore, identification of the molecular basis of PACG may help elucidate novel therapeutic or testing strategies in the management of this blinding disease that may be translatable to the human condition.
Microphthalmia and Delayed Growth Syndrome in the Portuguese Water Dog

Principal Investigator: Margret Casal, DVM, PhD; University of Pennsylvania

Total Grant Amount: $12,960

Grant Period: 11/1/2017 - 10/31/2020

Project Abstract: Microphthalmia and delayed growth syndrome (aka "puppy eye syndrome") has been reported by Portuguese Water Dog breeders dating as far back as 1986. However, there is no information in the scientific literature and the majority of data concerning this syndrome has been obtained from records of breeders, which have anecdotal reports of the disease and little, if any, medical diagnostics. Affected dogs present with microphthalmia of varying severity, other eye abnormalities, short stature and other findings. To date, the investigators have been able to collect DNA from 24 affected dogs. Males and females can be affected, although females predominate (about 70%). Preliminary pedigree studies suggest an autosomal recessive inheritance. Human literature reports numerous syndromes associated with microphthalmia, and many genes have been identified as having a causative role. The goals of this investigation are to better characterize the clinical syndrome seen in Portuguese Water Dogs, confirm a suspected mode of inheritance, obtain additional samples for investigation into the genetic mutation, and develop a mutation based, genetic test for breeders to eliminate this syndrome from the Portuguese Water Dog breed.

Funding for the research is provided through the collaborative efforts and generosity of the Portuguese Water Dog Foundation, Inc., and the Portuguese Water Dog Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.
Tears as a Source of Biomarkers for Dry Eye in the Dog

Principal Investigator: Francesca Capaldo, DVM; Animal Health Trust
Total Grant Amount: $13,837
Grant Period: 6/1/2018 - 5/31/2020

Project Abstract: Dry eye (DE) or keratoconjunctivitis sicca (KCS) is a painful disease in dogs and humans where insufficient tear production can cause pain, corneal ulceration and blindness. KCS in dogs is commonly immune-mediated, where the dog's immune system attacks the tear glands. However, the mechanism by which this occurs is not well understood. In humans, long term use of ocular medications containing the preservative Benzalkonium Chloride (BAC) may trigger DE. While no studies have been conducted to explore whether a correlation between BAC and DE exists in dogs, long term ocular treatment for dogs with BAC-containing drugs may cause ocular surface inflammation resembling KCS. The treatments available for KCS (immunomodulating and tear replacement drugs, and surgery) are often not completely effective. The investigators will look for and measure proteins in the tears of dogs affected by presumptive immune-mediated KCS, and the tears of dogs on long term ocular medications containing BAC. This work will help improve understanding of the pathogenesis of KCS and allow development of a non-invasive diagnostic test, which can also be used to monitor progression of the disease and response to treatment.
Genetics of Primary Angle Closure Glaucoma in the Siberian Husky

Principal Investigator: Gillian McLellan, BVMS, PhD; University of Wisconsin

Total Grant Amount: $121,740

Grant Period: 3/1/2018 - 2/28/2021

Project Abstract: Glaucoma is a very painful and rapidly blinding disease that leads to irreversible sight loss in many thousands of dogs in the USA and worldwide each year. Current medical and surgical treatments that target the damaging high pressure in the eyes of affected dogs are not able to cure the disease but only control it. In many dogs with glaucoma, surgical removal of both eyes is needed to control pain. Past research reveals that the Siberian Husky is one of the more commonly affected breeds in both North America and Europe. With improvements in canine DNA sequencing tools, it is now possible to carry out very detailed sequencing of DNA of individual dogs, and these techniques have identified mutated genes responsible for several dog diseases. The investigators in this study will analyze DNA from Siberian Huskies with glaucoma and compare it to DNA from dogs without glaucoma. The goal is to identify the DNA mutation (or mutations) that cause glaucoma and, in turn, develop a genetic test for the disease in this breed and possibly other affected breeds such as the Samoyed and Shiba Inu. A DNA test would provide an important tool in efforts to fight this disease as dog breeders could develop more informed breeding strategies, with a goal to ultimately help eliminate this disease from the dog population.
Development of a Polygenic Risk Model for Pigmentary Uveitis in Golden Retrievers

**Principal Investigator:** Wendy Townsend, DVM, MS; Purdue University

**Total Grant Amount:** $89,855

**Grant Period:** 3/1/2019 - 2/28/2021

**Project Abstract:** Pigmentary uveitis (PU) affects 10% of senior Golden Retrievers and often results in blindness due to cataracts and glaucoma. There are no current methods to prevent or reverse the disease. The best options to maintain vision are early detection through annual ophthalmic examinations and early initiation of topical anti-inflammatory therapy. The disease does not develop until eight years of age or older, thus, affected dogs may have already been bred before their PU status is known. Using previous AKC CHF funding, the investigators have established a bank of Golden Retriever DNA and, in an initial genetic analysis, determined that PU involves not just one but multiple genes. The research problem remains to identify involved genes and risk alleles that are associated with PU. The objective of this study is to identify these genes and alleles using genome-wide association studies and whole genome sequencing of severely affected dogs in conjunction with analysis of RNA expression within the iris and ciliary body of affected dogs. Identification of the involved genes and risk alleles will allow for creation of a genetic risk score to quantify an individual’s genetic risk for developing PU, allowing identification of high-risk individuals and intervention prior to the onset of clinical signs. In addition, breeders will have the necessary knowledge to decrease the prevalence of PU.

*Funding for the research is provided through the collaborative efforts and generosity of the Golden Retriever Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Characterization of Retinal Phenotypes and their Association with RPGRIP1 and Modifiers in English Springer Spaniels

**Principal Investigator:** Keiko Miyadera, DVM, PhD; University of Pennsylvania  
**Total Grant Amount:** $99,303  
**Grant Period:** 4/1/2019 - 3/31/2021

**Project Abstract:** Advances in molecular techniques have led to the identification of nearly 30 gene mutations that cause inherited retinal diseases in dogs, often leading to loss of vision. While an insert in the RPGRIP1 gene has been linked to a blinding retinal disease first found in Dachshunds, this same mutation is very common in English Springer Spaniels (ESSs). However, retinal diseases are rarely seen in this breed, raising the question as to whether the RPGRIP1 mutation by itself causes retinal disease. Notably, the research team has found similar mismatches between the mutation and the disease in Dachshunds, where the disease presentation varies greatly. In this breed, they found additional genetic factors or ‘modifiers’ that together with the RPGRIP1 mutation, are better able to predict the disease. This study will determine if these factors or additional factors yet to be identified also contribute to retinal disease severity in ESSs by 1) clinically characterize the spectrum of the retinal disease in ESSs, including functional tests to detect the earliest sign of disease in dogs with an apparently normal phenotype, and 2) study the relationship between the RPGRIP1 mutation and the disease status and then search for other genetic contributors specific to ESSs. By determining the role of the RPGRIP1 mutation in ESS retinal disease, a reliable DNA testing platform may be established.

*Funding for the research is provided through the collaborative efforts and generosity of the English Springer Spaniel Field Trial Association Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.*
Histologic characterization of Golden Retriever Pigmentary Uveitis

Principal Investigator: Wendy Townsend, DVM, MS; Purdue University
Total Grant Amount: $11,793
Grant Period: 2/1/2019 - 1/31/2021

Project Abstract: Pigmentary uveitis affects an estimated 10% of senior Golden Retrievers and often results in blindness due to cataracts and glaucoma. There are no current methods to prevent or reverse the disease. Clinically, a known risk factor for the development of glaucoma in dogs affected by pigmentary uveitis is the presence of an undefined, amorphous material in the eye. On histologic examination of affected eyes, the amorphous material has been noted within uveal cysts, surrounding uveal cysts, coating the lens, and free floating in the anterior chamber. The material blocks fluid flow within the eye resulting in glaucoma. Limited analysis has shown the material is unusual with features of both collagen and an acid. This amorphous material is considered to play a significant role in the pathology of pigmentary uveitis and associated glaucoma, but little is known about its chemical composition, structure, or tissue of origin. The objectives of this study are: 1) determine if all Golden Retrievers with pigmentary uveitis have this amorphous material within their eyes, or if only a specific subset; 2) define the chemical composition of the amorphous material; and 3) determine the ocular tissue producing the material. This information may play an important role to help develop preventative or therapeutic measures for pigmentary uveitis and define phenotype(s) for genetic studies.

This research is co-funded through the collaborative efforts of the Golden Retriever Foundation and the AKC Canine Health Foundation
Identification of Genetic Risk Factors for Primary Closed Angle Glaucoma and Pectinate Ligament Abnormality in the Basset Hound

Principal Investigator: Cathryn Mellersh, PhD; Animal Health Trust
Total Grant Amount: $29,750
Grant Period: 3/1/2019 - 2/28/2021

Project Abstract: Primary glaucoma is a painful and blinding disease associated with abnormally high intraocular pressure. Treatment in dogs is usually unsuccessful, and most affected dogs ultimately require removal of their eyes. The most common form of canine primary glaucoma is primary closed angle glaucoma (PCAG) which is significantly associated with pectinate ligament abnormality (PLA), also referred to as pectinate ligament dysplasia (PLD), an abnormality affecting the drainage angle of the eye. PCAG and PLA are prevalent in several breeds, and PLA is highly heritable. Not all dogs with PLA develop glaucoma, however, indicating that the inheritance of PCAG is complex. This complex inheritance and the progressive nature of PLA mean that breeding strategies based on ophthalmic examinations alone are unlikely to be sufficient to eliminate the disease. PCAG and PLA appear to be prevalent in the Basset Hound (BH) both in Europe and the U.S. Two genetic regions have been identified in the BH which are strongly associated with PCAG but not with PLA in European and USA BH dogs. This study will sequence the genomes of European and USA BH dogs with PCAG and PLA to identify variants that segregate with PCAG (and not PLA). Follow-up on PCAG candidate variants in large cohorts of European and USA BH will be performed to confirm association with disease in the breed. The ultimate aim is to develop DNA tests for PCAG in the BH that will reduce disease prevalence when used in parallel with breed-specific guidance for breeders while simultaneously allowing for breeding of BH with PLA that are not at risk of PCAG.
Efficacy and Safety of Netarsudil for Canine Corneal Endothelial Dystrophy

Principal Investigator: Sara Thomasy, DVM, PhD; University of California, Davis

Total Grant Amount: $116,640

Grant Period: 2/1/2020 - 1/31/2022

Project Abstract: The corneal endothelium is primarily responsible for maintenance of corneal dehydration and transparency, which is critical for normal vision. Corneal endothelial dystrophy (CED) is a late-onset disease in dogs whereby the endothelial cells prematurely degenerate resulting in progressive corneal swelling, vision loss and ocular pain due to corneal ulceration. Secondary corneal infection and perforation can occur necessitating eye removal. Currently, the only definitive treatment for CED and a similar disease in human patients, termed Fuchs´ endothelial corneal dystrophy (FECD), is corneal transplantation. However, corneal transplants are rarely performed in dogs due to the risk for graft rejection, lack of appropriate donor tissue, and expense. Alternative treatments for canine CED are urgently needed. Preliminary work demonstrated that a rho-associated kinase coiled-coil containing protein kinase (ROCK) inhibitor accelerated corneal endothelial regeneration. Netarsudil 0.02% ophthalmic solution (Rhopressa®) is a topical ROCK inhibitor and norepinephrine transport inhibitor recently approved by the Food and Drug Administration (FDA) for use in patients with glaucoma. Preliminary data suggest that netarsudil accelerates corneal endothelial recovery. This study will investigate the efficacy and safety of netarsudil for the treatment of early canine CED. If successful in dogs, netarsudil findings may translate to use for treatment of FECD in human patients.
Lipid Composition and Lipid Droplet Dynamics in Canine Pyometra Affected Endometria

Principal Investigator: Cordula Gabriel, PhD; University of Veterinary Medicine of Vienna
Total Grant Amount: $13,608
Grant Period: 10/1/2019 – 9/30/2021

Project Abstract: Pyometra is the most common uterine disease in intact bitches leading to potentially life-threatening complications. *Escherichia coli* (E.coli) are the most abundant isolated pathogens causing pyometra. Previous studies identified increased amounts of lipid droplets (LDs) in canine endometrial epithelial cells (cEECs) occurring in metestrus, the cyclic stage with the most common presence of pyometra. A specialized receptor relevant for lipid-uptake (SR-B1) to be expressed in cEECs and up-regulated in pyometra affected uteri was also identified. Lipids are attractive targets for pathogens to modulate host cell processes in order to allow pathogens’ survival and replication. A correlation of LD accumulation in cEECs with pyometra-related pathogenic *E. coli* infection is assumed. In this study, the lipid composition in the LDs and different members of LD-coating proteins of the cEECs will be investigated in healthy metestrous and pyometra affected uteri. Furthermore, the effects of bacterial infection on lipid composition and LD formation and function will be investigated. Understanding the regulation of lipid metabolism in pyometra etiology has important implications for exploring new therapeutic strategies for management and treatment of this serious uterine disease in intact bitches.
Surveillance of *Hepatozoon americanum* in Populations of the Gulf Coast Tick

**Principal Investigator:** Andrea Varela-Stokes, DVM, PhD; Mississippi State University  
**Total Grant Amount:** $12,960  
**Grant Period:** 2/1/2018 - 1/31/2021

**Project Abstract:** American Canine Hepatozoonosis is a debilitating tick-borne disease with poor prognosis and limited treatment options. Affected dogs usually experience fever, muscle pain, and body wasting, and some dogs may have a thickening of their long bones. While most tick-borne diseases occur after transmission of the disease agent during tick feeding, in American Canine Hepatozoonosis, dogs are infected by eating the tick vector carrying the disease agent. *Hepatozoon americanum* causes American Canine Hepatozoonosis. It is a protozoan parasite carried by the tick species, *Amblyomma maculatum*, also known as the Gulf Coast tick. The percentage of Gulf Coast ticks carrying *H. americanum* is unknown. The investigators will use an optimized test to perform active surveillance on Gulf Coast ticks collected in Mississippi during the summer seasons of 2018 and 2019, when adult Gulf Coast tick stages are active. Veterinary summer research students will also participate in the research each year. By involving veterinary students and obtaining active surveillance data on tick populations, the researchers will fill an important gap in the knowledge of American Canine Hepatozoonosis, and increase veterinary and public awareness of potential risk in canine patients.
Developing a Next Generation Sequencing Diagnostic Platform for Tick-Borne Diseases

Principal Investigator: Pedro Diniz, DVM, PhD; Western University of Health Sciences

Total Grant Amount: $120,983

Grant Period: 6/1/2018 - 11/30/2020

Project Abstract: Diagnostic tests based on the detection of DNA from harmful organisms in clinical samples have revolutionized veterinary medicine in the last decades. Currently, diagnostic panels for several vector-borne organisms are available through universities and private labs in the U.S. and abroad. However, the vast majority of results from sick dogs are negative, which frustrates veterinarians and dog owners trying to reach a definitive diagnosis. These panels are based on the detection of previously known DNA sequences of each pathogen, which limits their ability to detect novel organisms. In this study, the investigators will adapt high-throughput next-generation sequencing (NGS) to the detection of tick-borne bacteria in dog blood in an effort to overcome the limitations of current diagnostics for tick-borne diseases. If successful, increasing the capabilities of NGS to detect infected dogs and to accurately determine which bacteria are responsible for disease will support the development of a better diagnostic tool to simultaneously advance canine and human health. This work expands on Dr. Diniz's previous AKC CHF-funded study #02292.
Targeted Next Generation Sequencing Panel for Comprehensive Testing of Vector-borne Pathogens

Principal Investigator: Rebecca Wilkes, DVM, PhD; Purdue University
Total Grant Amount: $103,245
Grant Period: 2/1/2019 - 1/31/2021

Project Abstract: Diagnosing vector-borne disease (VBD) in dogs can be difficult for a number of reasons. First, there are many different disease-causing agents that can be transmitted from ticks/fleas, and the clinical signs caused by these agents in dogs can overlap. Additionally, because ticks/fleas can harbor more than one agent at a time, multiple pathogens may be passed to a dog with a single vector bite, resulting in co-infections. VBD infections can initially present with non-specific signs, such as fever, lethargy, vomiting, diarrhea, and/or respiratory signs. Severe cases can be associated with neurologic signs. These signs can be a diagnostic conundrum. While initial blood work can be helpful and suggest VBD, it does not determine the infecting agent. This study will develop a comprehensive next generation sequencing panel to detect and identify major VBD agents known to cause disease in dogs and to aid in diagnosis of active infections. Additionally, through parallel sequencing with this method, this panel will incorporate testing for additional infectious diseases that may cause GI, respiratory, or neurologic signs in dogs. The comprehensive nature of this sequencing panel should be a useful tool for surveillance of infectious diseases in the canine population for rapid identification of VBD in dogs and protection of pet owners from such zoonotic diseases.
The AKC Canine Health Foundation Clinician-Scientist Fellowship Program supports young scientists. Through this effort our mission to prevent, treat and cure canine disease will endure for years to come.

Recipients are selected based upon the following criteria for a resident/graduate student:
1) Enthusiasm for pursuing a career in canine health research,
2) Research aligns with CHF’s mission to advance the health of all dogs,
3) Research abides by CHF policies, including our Humane Use of Animals Policy.

2020 AKC Canine Health Foundation Clinician-Scientist Fellows

Shelby Gasson, DVM; Texas A&M University

Mentor: W. Brian Saunders, DVM, PhD, DACVS

Dr. Gasson received her DVM from Texas A&M University. She is continuing her work as the AKC Canine Health Foundation GCHP Hill Country's Let's Get Ready To Rumble “Rumble” Clinician-Scientist Fellow (akcchf.org/rumble). Dr. Gasson’s work focuses on the development of tissue engineering constructs for treatment of osteochondral defects. She will evaluate the growth and differentiation of canine mesenchymal stem cells on different tissue scaffolds.

This fellowship is generously sponsored by Rumble's owners, Carolyn and Gary Koch, breeders Kristy and Kevin Ratliff, and handler Esteban Farias.
Sarah Murphy; Clemson University

Ms. Murphy is a PhD candidate at Clemson University. Her work focuses on the genetics of congenital idiopathic megaesophagus (CIM) in German Shepherd Dogs and Great Danes. The goal of her study is to identify genetic markers and, where possible, the exact genetic variations underlying CIM in order to develop a genomic prediction tool. Understanding which genotypic combinations result in CIM will facilitate breeding choices that produce puppies at low risk for this disease without sacrificing genetic diversity.

This fellowship is generously sponsored by the Orthopedic Foundation for Animals (OFA).

Liza Crissiuma Gershony, DVM, PhD

Dr. Gershony earned her DVM and MS degrees from Fluminense Federal University in Brazil. She completed her PhD in Animal Biology at the University of California, Davis focusing on genetic susceptibility markers for complex canine autoimmune diseases. Dr. Gershony continues her research in the laboratory of Dr. Anita Oberbauer at the University of California, Davis on the Canine Genetic Analysis Project. She will collaborate to provide a review of the current state of genetic testing for dogs to inform disease pathogenesis and aid genetic test development. Her goal is to use genetic testing to improve the quality of life and reduce disease prevalence in dogs.

Pradeep Neupane, MS; North Carolina State University

Mr. Neupane is a doctoral candidate in the Intracellular Pathogens Research Laboratory at North Carolina State University. Under the mentorship of Dr. Edward Breitschwerdt, he is studying serodiagnostic testing options for infection with canine Bartonella spp. and evaluating the association between Bartonella infection and hemangiosarcoma in dogs.

This fellowship is generously sponsored by the American German Shepherd Dog Charitable Foundation, Inc. and Briard Club of America Health and Education Trust.

To support this program visit: akcchf.org/clinsci
This program is a collaboration between the American Kennel Club, the AKC Canine Health Foundation, and the Theriogenology Foundation to increase the number of trained practitioners in companion animal theriogenology and clinical genetics. Theriogenology is the branch of veterinary medicine concerned with reproduction, including the physiology and pathology of male and female reproductive systems, and the clinical practice of veterinary obstetrics, gynecology, and andrology.

2020 Theriogenology Residents

**Kelsey Martin, DVM**  
**Residency Coordinator:** Fiona Hollinshead, BVSc, PhD, DACT; Colorado State University  
**Total Grant Amount:** $100,000  
**Grant Period:** 7/1/2020 - 6/30/2023

Dr. Martin received her bachelor’s degree in Biology at the University of Louisiana-Lafayette. She returned to Colorado to earn her veterinary degree at Colorado State University. After graduation, she completed a clinical internship at a large animal private practice.

**Joanna Koilpillai, BVSc & AH**  
**Residency Coordinator:** Marco A. Coutinho da Silva, DVM, PhD; Ohio State University  
**Total Grant Amount:** $99,965  
**Grant Period:** 7/1/2020 - 6/30/2022

Dr. Koilpillai earned her veterinary degree from Madras Veterinary College in Chennai, India. After one year in mixed animal private practice in India, she completed a small animal internship at Veterinary Healthcare Associates in Florida. Her interests are small animal medicine and mixed animal reproductive medicine.
2018 Theriogenology Residents

Dr. Kate Withowski completed her veterinary degree at St. George's University School of Veterinary Medicine after receiving her bachelor of arts from Stony Brook University. Most recently, she spent a year in field service and completed a theriogenology internship at the University of Georgia. Dr. Withowski competes in dog showing and hunt testing with her Weimaraners.

Dr. Alyssa Helms attended the University of Tennessee for both her undergraduate degree in animal science (summa cum laude) and her veterinary degree. She has extensive experience in dog training and works with canine breeders to educate on the preservation of purpose-bred dogs and canine reproductive medicine. Dr. Helms competes in conformation, rally, herding, and Up Dog with her Australian Shepherd and Pembroke Welsh Corgi.

2019 Theriogenology Resident

Dr. Jamie Douglas received her DVM from Michigan State University College of Veterinary Medicine in 2014 and her master's degree in animal science (reproduction) from Southern Illinois University Carbondale's College of Agricultural Sciences in 2015. She returned to Michigan State University to complete a veterinary anesthesia internship in 2015.

To support this program visit: akcchf.org/therio


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