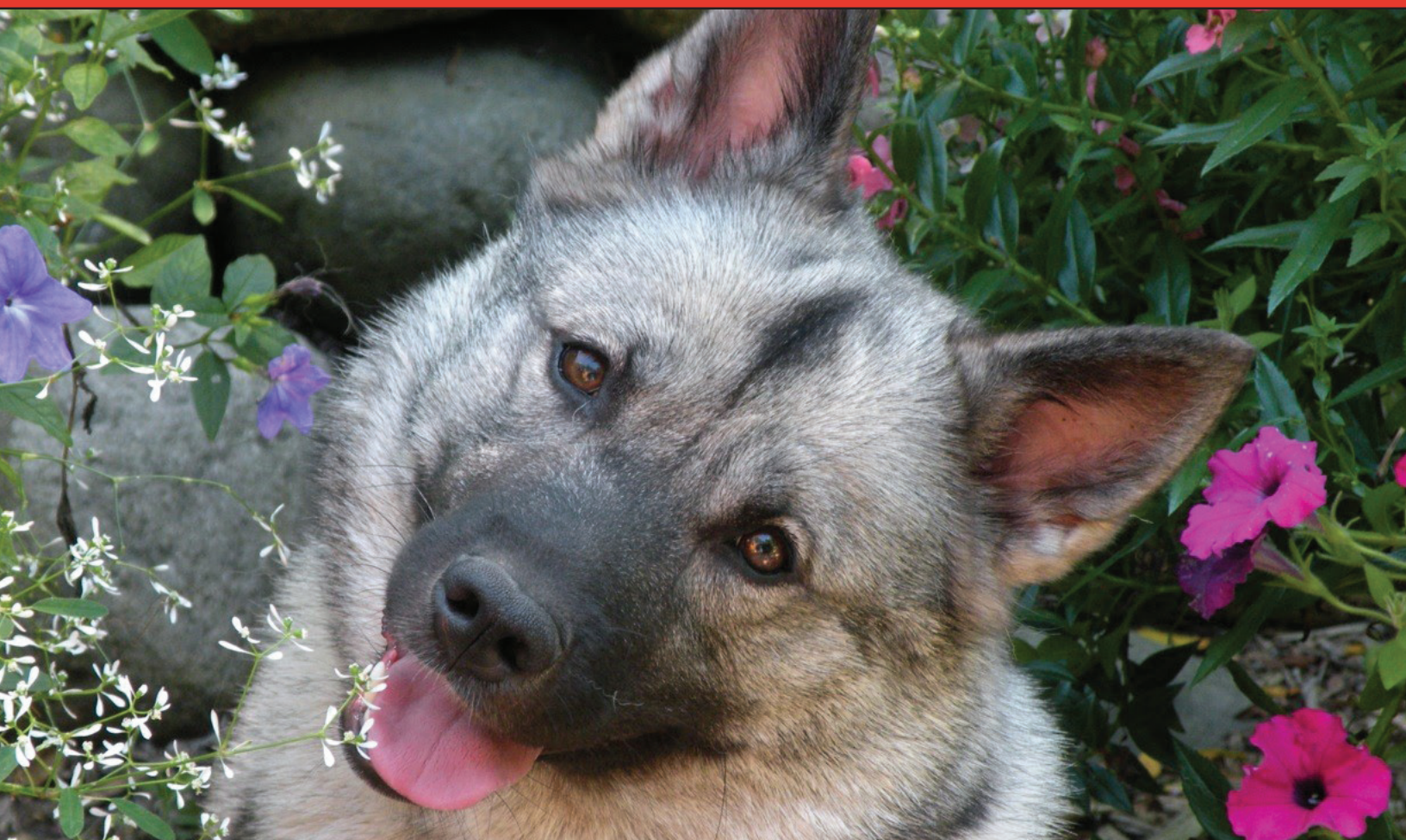




AMERICAN KENNEL CLUB
**CANINE HEALTH
FOUNDATION®**
PREVENT TREAT & CURE®
SINCE 1995

2019 Research Grants Portfolio

Volume 3



Dear Fellow Dog Lover,

Enclosed within these pages you will find the currently active research being funded through the AKC Canine Health Foundation (CHF). Since 1995 the CHF has addressed the important health needs of our closest companions. Working 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 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 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. We embrace 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, CHF considers areas of unmet health needs and areas of immediate opportunity for impact, while applying recent advancements in science and technology to canine health research.

Recent CHF research initiatives to address canine cancer, tick-borne diseases and epilepsy are reflected in this portfolio, and include publication outcomes and educational resources available at the following weblinks, akcchf.org/hemangiosarcoma, akcchf.org/ticks and akcchf.org/epilepsy. CHF is also bringing novel approaches to canine cancer including hemangiosarcoma through research initiatives to find solutions for this devastating disease. Currently funded research in the areas of oncology, infectious and zoonotic diseases, heartworm disease, neurology, Addison's disease and across all CHF research program areas is contained within this portfolio, and both current and past research and publication outcomes can also be found online at akcchf.org/research/our-research/

The Foundation is dedicated to educating the next generation of scientists for canine health research with grants through the CHF Clinician-Scientist Fellowship Program (akcchf.org/about-us/who_we_are/Fellows/), and through the Theriogenology Residency Program (akcchf.org/research/therio-residency/). Through outreach to breeders, veterinarians and the general public, we provide resources on outcomes of research and important topics for canine health. (akcchf.org/research)

As you review the contents of this portfolio, please do so knowing these studies are selected to achieve a better understanding of canine health concerns and to advance the diagnosis, prevention and treatment of canine diseases. To discuss a study or to learn about sponsoring research, please contact us at chfgrants@akcchf.org. We want to hear from you. Together, we are moving canine health research forward, benefiting the dogs who so enrich peoples' lives.

Thanks to the support of our partners at the American Kennel Club, Nestlé Purina, Elanco Animal Health, Orthopedic Foundation for Animals and the many breed clubs, foundations and private donors whose support we value, we continue to increase programs and research to benefit the health of all dogs.

Thank you for your passion and generosity, from the CHF Board of Directors and staff, and from the dogs whose lives are positively impacted by this work.

Sincerely,



Diane Brown, DVM, PhD, DACVP
Chief Executive Officer/Chief Scientific Officer



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02518

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 - 4/30/2020

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.

Blood Disorders

02348

Whole Blood Transcriptome Profiling of Dogs with Immune-Mediated Hemolytic Anemia (IMHA)**Principal Investigator:** Steven Friedenber, DVM, PhD; University of Minnesota**Total Grant Amount:** \$53,471**Grant Period:** 4/1/2018 - 3/31/2020

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.

02515-A

Investigating the Role of Interleukin-17-producing Cells in the Pathophysiology of Canine Immune Mediated Hemolytic Anemia

Principal Investigator: Shauna Blois, DVM, DVSc; University of Guelph

Total Grant Amount: \$8,690

Grant Period: 4/1/2018 - 7/31/2019

Project Abstract: Canine primary immune-mediated hemolytic anemia (IMHA) is an acute and severe disease of dogs with a mortality rate ranging up to 70%. IMHA is caused when the immune system produces abnormal antibodies that attack and destroy the dog's own red blood cells. It is not known how or why these abnormal antibodies form in the body. Increased levels of certain inflammatory cytokines (small proteins that affect cells) could cause the production of abnormal antibodies leading to IMHA, and many cells in the body, most notably the white blood cells, produce these cytokines. Autoimmune hemolytic anemia (AIHA) is a disease of humans that shares similarities to canine IMHA. As the causes of human AIHA are better understood, novel treatments are being discovered. Increases of a particular cytokine, interleukin (IL)-17, were recently found in people with AIHA. Additionally, targeted therapy to reduce IL-17 levels improved disease condition in AIHA models. The investigators recently identified increased IL-17 in blood of dogs with IMHA and will study its role in the cause of this disease. This study will specifically identify and measure the types of white blood cell(s) in the body that produce IL-17 which could lead to further understanding of the cause(s) of IMHA in dogs and help uncover new treatment targets for this disease.

02536-MOU

Immunoprofiling to Combat Canine Immune Thrombocytopenia

Principal Investigator: Marjory Brooks, DVM; Cornell University and Dana LeVine, DVM, PhD; Iowa State University

Total Grant Amount: \$16,106

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

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 reports.*

02637-A

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 - 1/31/2020

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.

New

01760-T

One Health

Use of Gene Therapy to Treat Dilated Cardiomyopathy

Principal Investigator: Margaret Sleeper, VMD; University of Florida

Total Grant Amount: \$146,774

Grant Period: 9/1/2016 - 2/28/2020

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.

2327-MOU

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 - 9/30/2019

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 reports.*

02368

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 - 7/31/2019

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 - 8/31/2019

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 reports.*

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 reports.*

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 - 9/30/2019

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.

Predicting Disease Stage and Diuretic Responsiveness in Dogs with Acquired Heart Disease

Principal Investigator: Mark Papich, DVM, MS; North Carolina State University

Total Grant Amount: \$41,731

Grant Period: 5/1/2018 - 10/31/2019

Project Abstract: Congestive heart failure (CHF) causes difficulty breathing because of fluid accumulation in the lungs. It is an important and common clinical problem. Mitral valve regurgitation and dilated cardiomyopathy are common causes of CHF in dogs, which can develop as these conditions progress in severity. Because there currently is no cure for these heart diseases, the treatment focus has been on prolongation of the time to CHF development, relieving signs of fluid retention when CHF occurs, and supporting the function of a failing heart. Diuretic medications ("water pills") cause increased urination after removal of fluid from the lungs and are the most effective treatment for CHF. Most dogs respond to diuretics initially, but over time, progression of heart disease and maladaptive mechanisms result in less urine production and return of CHF signs with potential for suffering, death, or euthanasia. Loss of responsiveness to diuretic medications may be multifactorial, and so identification of the underlying reason could guide medical interventions to restore urine production in response to diuretics and improve quality of life for dogs. The investigators have identified several candidate blood and urine variables that correlate with urine production in dogs and may be useful to indicate responsiveness to diuretic medications. This study will evaluate these variables in dogs with progressive stages of naturally occurring heart disease to identify those that are poorly responsive to diuretic medications and determine underlying causes for improved patient outcomes.

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 - 1/31/2020

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 reports.*

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 - 1/31/2020

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 reports.*

02531

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 - 5/31/2020

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.*

02550

The Role of *Bartonella* spp. Exposure and Cardiac Genetic Variation on the Clinical Expression of Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer Dog

Principal Investigators: Edward Breitschwerdt, DVM and Kathryn Meurs, DVM, PhD; North Carolina State University

Total Grant Amount: \$63,105

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

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.

New

One Health

02631

Genetic and Metabolic Determinants of Dilated Cardiomyopathy and their Relationship to Cardiac Arrhythmia in Doberman Pinschers

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

Total Grant Amount: \$56,592

Grant Period: 5/1/2019 - 4/30/2020

Project Abstract: Dilated cardiomyopathy (DCM) is a common inherited disease in Doberman Pinschers that can lead to heart failure. The genetic background is not known and an international research project has been established to discover genetic risk variants that predispose dogs to DCM, and to study how cardiac arrhythmias are connected to DCM. Nearly 600 dogs will be studied with cardiological examinations to determine the health and function of the dog's heart using electrocardiogram, echocardiography and Holter monitoring. Genetic studies have identified a novel disease locus in chromosome 5 and the investigators will perform the additional analyses to identify the causative gene and variant(s). If successful, the genetic findings in this study will have a broad impact on the health of Doberman Pinschers and potentially other dog breeds.

New

02632

New

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.

02649

New

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 - 4/30/2022

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.

02661

New

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: \$202,181

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.

Dermatology and Allergic Disease

02241

One Health

The City Dog Study: Dermatologic and Respiratory Disease among Inner-City Dogs Living in the Homes of Children with Asthma

Principal Investigator: Meghan Davis, DVM, MPH, PhD; Johns Hopkins University

Total Grant Amount: \$158,367

Grant Period: 2/1/2016 - 7/31/2019

Project Abstract: Children who live in inner-city households of low economic means suffer disproportionately from skin and lung diseases, including asthma. This study will evaluate the burden of skin and respiratory disease among the dogs who live with them. These dogs often can be hard to study because their owners may not have the means or access to take them to the veterinarian. As an adjunct to a funded public health research effort targeting 200 children with asthma, Dr. Davis and her team will enroll 100 dogs and follow their health at three home visits over six months, and perform two additional evaluations. First, they will study the microbial (bacterial) communities on the dogs to determine how these change over time, and if the changes are associated with skin or respiratory diseases in the dogs. Then, the investigators will look at how the children and dogs share bacteria (i.e. microbiome). Early life exposures to dogs may protect children against the development of asthma; next steps are to investigate if dogs also have a beneficial impact when the children are older and have existing disease. This study will provide knowledge needed to help understand disease in underserved dogs in urban neighborhoods, providing data to support keeping dogs and keeping them healthy to benefit both dogs and their owners.

02472-A

Effect of Lokivetmab on Tissue Biomarkers of Canine Atopic Dermatitis using RNA Sequencing

Principal Investigator: Frane Banovic, DVM, PhD; University of Georgia

Total Grant Amount: \$9,747

Grant Period: 12/1/2017 - 9/30/2019

Project Abstract: Atopic dermatitis (AD) is the most common, chronic, inflammatory and pruritic allergic skin disease that affects dogs worldwide. Treatment of canine AD has a high unmet need for effective and safe therapeutics. The transcriptome investigation of human AD tissues before and after treatment modalities has revolutionized the understanding of the molecular fingerprint of AD, further defining pathogenic immune pathways and identifying disease-specific biomarkers. In the early-phase trial, lokivetmab, a caninized monoclonal antibody targeting interleukin-31 (IL-31) cytokine, markedly improved disease activity, but the effect of IL-31 blockade on AD at the genomic level has not been characterized. The investigators will evaluate lokivetmab modulation of the canine AD transcriptome (defined as differentially expressed genes between lesional and non-lesional skin) using next-generation RNA sequencing (RNA-seq). Findings may suggest that inhibition of a single target has the potential to reverse AD pathomechanisms, opening the door for new targeted treatment for this common and debilitating inflammatory skin disease. Furthermore, transcriptome analysis using RNA-seq may identify novel pathogenic pathways of inflammatory biomarkers as canine AD disease drivers, with potential for development of novel targeted therapeutics.

02597

New

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.

02651

New

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 - 4/30/2020

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.

02653-A

New

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 - 1/31/2020

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.

One Health

Endocrinology

02428

Identifying the Disease-Defining Autoantibodies in Canine Addison's Disease

Principal Investigator: Steven Friedenber, DVM, PhD; University of Minnesota

Total Grant Amount: \$181,864

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

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.

02488

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 - 4/30/2020

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.

02659

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.

New

Epilepsy Initiative

02252

Investigating a Ketogenic Medium-Chain Triglyceride (MCT) Supplement for the Treatment of Drug-Resistant Canine Idiopathic Epilepsy and Its Behavioral Comorbidities

Principal Investigator: Holger Volk, DVM, PhD; Royal Veterinary College, University of London

Total Grant Amount: \$107,697

Grant Period: 5/1/2016 - 9/30/2019

Project Abstract: Canine epilepsy is a chronic neurological condition, often requiring lifelong medication with anti-epileptic drugs (AEDs). Despite appropriate treatment with available AEDs, seizure freedom may not always be achievable. Indeed, over two thirds of dogs with epilepsy continue to have seizures long-term and around 20-30% remain poorly controlled on standard AEDs. The hardest to treat dogs are termed 'refractory' or 'drug-resistant' patients. There is an urgent need to develop alternative treatments to improve the quality of life (QoL) of drug-resistant patients. The ketogenic diet, originally characterized as high in fat and low in carbohydrates, has been a successful treatment in children with epilepsy for several decades, decreasing seizure activity and even leading to seizure freedom in drug-resistant patients. Recent research has identified that a component of the ketogenic diet, a medium-chain fatty acid (MCT) called C10 has direct anti-seizure effects on the brain. The investigators will assess whether dietary supplementation with ACT oil containing C10 for dogs with drug-resistant epilepsy will reduce seizure frequency and/or severity. As epilepsy has multiple impacts on QoL beyond seizure frequency, the researchers will also investigate whether the MCT supplement alters the side effect profile of AEDs, improves behavioral problems associated with epilepsy (e.g. anxiety) and cognition, and improves the stress levels of the affected dog. If successful, MCT supplements could provide a new tool for canine epilepsy treatment.

02323

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 - 11/30/2020

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.

02561

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.

New

02566

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.

New

01935-B

Abnormalities in the Stomach's Ability to Contract Predisposes Large-Breed Dogs to Bloat

Principal Investigator: Bryden Stanley, BVMS, MVetSc.; Michigan State University

Total Grant Amount: \$233,774

Grant Period: 1/1/2014 - 6/30/2019

Project Abstract: Gastric dilatation-volvulus (GDV), or bloat, is a devastating disease common in large and giant-breed dogs. Occurring most frequently in older dogs with a close relative who has also suffered the condition, the stomach becomes both displaced and distended with air. Without emergency medical stabilization and surgical intervention, affected dogs quickly experience shock, damage to the stomach wall, and death. Most of the research relating to GDV has described risk factors for the disease, determinants of outcome with treatment, and the effectiveness of preventive surgery (gastropexy). However, the underlying cause of GDV remains unknown. Abnormalities in the ability of the stomach to contract have been documented in dogs after naturally-occurring GDV. An analogous stomach condition in cattle, left-sided displacement of the abomasum (LDA) has been shown to, in some instances, be associated with abnormalities in the motilin gene. Motilin is an important driver of stomach contraction. This suggests that LDA and potentially GDV may be primarily caused by a stomach that does not properly contract, and that this condition may be inherited. This study will help to determine the relationship between abnormal stomach contraction and GDV, and to define the biochemical and genetic alterations that may be associated with these stomach abnormalities. The long-term goal is to develop a test to identify dogs at high-risk for GDV. This would allow for early detection and offer selective breeding as an option to eliminate the condition and determine best preventive therapies.

02338

The Genetics of Bloat in German Shepherd Dogs: The Roles of Immune System Genes and the Gut Microbiome

Principal Investigator: Michael Harkey, PhD; Fred Hutchinson Cancer Research Center

Total Grant Amount: \$152,270

Grant Period: 6/1/2017 - 11/30/2019

Project Abstract: While gastric dilatation volvulus (GDV), or bloat, is a serious problem for many large canine breeds, little is known about the causes of this deadly disease. The most significant factors may be genetic, since certain breeds are more susceptible than others, and strong familial predispositions are seen within breeds. The investigators have recently shown a significant association of three immune genes with bloat in Great Danes. For each of the three genes, one allele (variant) is found at unusually high frequency in dogs that have been treated for bloat, and the presence of any one of these "risk" alleles triples the chance that the dog will experience bloat at some time in its life. The research team also showed that the bacterial population living in the gut (the gut microbiome) is altered in dogs with bloat, and in dogs that carry these "risk" alleles, which may predispose these dogs to bloat. It is not known if other breeds show this same association of genetics and microbiome with bloat. The team will investigate whether bloat in German Shepherd Dogs is associated with the same risk alleles and the same microbiome profiles as were seen in Great Danes. The results of this work could lead to genetic tests for at-risk dogs, as well as dietary or probiotic therapies to prevent bloat.

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 - 2/29/2020

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 reports.*

General Canine Health

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 - 1/31/2020

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.

02434-A

Characterization of the Anal Sac Microbiota in Dogs with Sacculitis

Principal Investigator: Marcio Costa, DVM, PhD; University of Montreal

Total Grant Amount: \$14,708

Grant Period: 12/1/2017 - 11/30/2019

Project Abstract: Anal sacs are two small cavities found adjacent to the anus in dogs and accumulate secretions from the ad-anal glands. Inflammation of the anal sac (sacculitis) is a frequent condition affecting up to 12% of dogs and is mainly caused by bacterial infection. Therefore, treatment of this disease requires antibiotics, but reoccurrence can occur and often culminates with surgery. During the last decades, the development of new methods for DNA sequencing has allowed a better characterization of bacterial communities, since only the minority of those organisms grow in culture media. Imbalances of the normal populations are related to predisposition to certain diseases. Risk factors for sacculitis in dogs are still uncertain, but studies investigating the role of bacteria in this disease are rare. The investigators will characterize the microbiota present in the anal sac of dogs affected by sacculitis and compare it to the healthy contra-lateral sac using next generation DNA sequencing (NGS). In addition, factors such as antibiotic use, severity of inflammation and clinical response to treatment will be followed. Understanding the physiopathology of sacculitis in dogs may lead to increased success rates following conservative treatment, reducing the need for invasive surgery.

02475-A

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 - 10/31/2019

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.

02529

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 - 5/31/2020

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.

02593-A

New

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 - 2/29/2020

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.

02614-A

New

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 - 2/29/2020

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.

Hepatic Disease

01986

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 - 12/31/2019

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 – 8/31/2019

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 reports.*

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.

Immunology and Infectious Disease

Estimating Prevalence and Identifying Risk Factors for Canine Leptospirosis in North America

Principal Investigators: Thomas Wittum, MS, PhD; Ohio State University and Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,990

Grant Period: 5/1/2017 – 10/31/2019

Project Abstract: Leptospirosis is an important and re-emerging disease of dogs, humans and other species that is transmitted by contact with infected urine. Infected dogs can develop severe illness, including death. Despite being recognized as a disease that appears to be increasing in frequency in dogs across the United States and Canada, many areas important to dog health are unknown. Regions of greatest canine leptospirosis risk, dog factors that increase risk and the most important prevention methods remain unclear. The investigators will use an existing large international database of dogs to determine the occurrence and changes over time and region of this disease. Current "hot spots" for canine leptospirosis will be determined. These "hot spots" will be further evaluated in detail by enrolling dogs and their owners in a follow-up study component to identify key behaviors and practices that can be used to successfully reduce the risk of leptospirosis in dogs. Maps will be created for use by dog owners and veterinarians to identify areas of greatest risk and concern for this disease. Together, maps and risk reduction data will allow for targeted education to individuals with dogs living or traveling to higher-risk areas to protect dogs against leptospirosis.

02404-A

One
Health

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 - 10/31/2019

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.

02407-A

One
Health

In vitro Efficacy of Nano-sulfur Against Planktonic and Biofilm State of Resistant Bacteria

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

Total Grant Amount: \$14,958

Grant Period: 5/1/2018 - 10/31/2019

Project Abstract: Antibiotic resistance and biofilm are emerging problems in both human and veterinary medicine. The inappropriate use of antibiotics helps selecting for resistant strains. Biofilms have an increased resistance pattern due to the presence of a shield that hinders penetration of antibiotics. Currently few antimicrobial options are available for resistant bacteria and biofilm causing major concerns for post-surgical patients. Over the past years, the increased development of nanotechnologies has made the fight against bacteria easier and safer due to the use of lower antimicrobial doses, reduced side effects, and increased antimicrobial efficacy. The most commonly used nano-antimicrobial is nano-silver. However, despite its efficacy, worries persist regarding its safety profile and environmental toxicity. Another emerging nano-antimicrobial is nano-sulfur; widely used in the agricultural industry. Sulfur has been a well-known and safe antimicrobial for centuries, however, its efficacy as nano-particles against biofilm formation/disruption is unknown. The investigators will evaluate the efficacy of nano-sulfur against resistant bacteria and in preventing and/or disrupting biofilm with on multidrug-resistant *Staphylococci* (*S. aureus* and *S. pseudintermedius*) and *Pseudomonas aeruginosa*. This study will determine: 1) whether nano-sulfur is effective against bacterial growth and biofilm adhesion/formation/disruption; 2) if nano-sulfur is cytotoxic at antimicrobial concentrations. If proven effective, nano-sulfur will provide a more cost-effective and safer treatment for antibiotic-resistance and biofilms.

02408

One
Health

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 - 2/29/2020

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.

02441

One
Health**Evaluation of a New Vaccine for Canine Brucellosis****Principal Investigator:** Angela Arenas, DVM, PhD; Texas A&M AgriLife Research**Total Grant Amount:** \$67,524**Grant Period:** 3/1/2018 - 8/31/2019

Project Abstract: Canine infection by *Brucella spp.* constitutes a serious problem for dog breeders and pet owners, leading to the economic burden associated with reproductive loss and veterinary care. Canine brucellosis is also considered a public health concern because of its potential to be transmitted to humans. Within the U.S., the disease has reemerged due to the chronic persistence of the organism, low dose for infection, low sensitivity and specificity of the current diagnostic tests, and most importantly, the lack of a protective vaccine for dogs. Historically in the U.S., brucellosis control efforts for cattle, sheep, goats and domestic pigs have been successful mainly due to the availability of protective and efficacious vaccines. The goal of the proposed research is to develop a brucellosis vaccine that is safe, stable, free of side effects and efficacious for dogs. Previous AKC CHF funding (Grant #02275-A) has permitted the investigators to successfully engineer a promising live attenuated vaccine candidate denominated *B. canis* RM666ΔvjbR. This study will further investigate the ability of the vaccine candidate to induce appropriate immunity prior to its testing in dogs and will also develop a diagnostic assay capable of differentiating naturally infected vs vaccinated animals, necessary for mass vaccination. The development of a safe and highly protective brucellosis vaccine for dogs, will significantly impact owners, breeders and human health by limiting the spread of the disease.

02448

One
Health**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 - 12/31/2019

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.

02458-A

A Laboratory Test for Detecting Drug Resistance in Canine Heartworm Disease**Principal Investigator:** Matt Brewer, DVM, PhD; Iowa State University**Total Grant Amount:** \$15,000**Grant Period:** 2/1/2018 - 1/31/2020

Project Abstract: *Dirofilaria immitis* is the nematode parasite that causes heartworm disease in the United States. Heartworm infection causes severe pathology and suffering in dogs and cats. Until recently, heartworm infection was a preventable disease due to the availability of effective monthly preventative treatments. A recent development shows drug-resistant heartworms have emerged in the United States. The scope of the resistance issue has not yet been characterized because there is a critical need to develop a test that can discriminate drug-susceptible and drug-resistant parasites. Recent research assessed computer-aided motility studies of the parasite in the presence of drugs, however, there are no motility differences among parasite isolates in these assays. The investigators have developed biochemical stains and measurements that can quantify parasite killing in the presence of anti-parasitic drugs. In this study, the investigators will evaluate various metabolic assays and staining procedures to compare drug-susceptible and drug-resistant heartworm isolates in an effort to identify the best assay for detecting heartworm killing, and thereby creating a tool to rapidly identify resistant infections in dogs.

02532-A

Canine Influenza: Occurrence, Spatial and Temporal Trends and Identifying Modifiable Factors to Reduce Transmission at Events in the United States

Principal Investigators: J. Scott Weese, DVM; University of Guelph and Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,040

Grant Period: 6/1/2018 - 8/31/2019

Project Abstract: Canine influenza is an important disease affecting dogs, especially in situations where many dogs come together (e.g., boarding, dog shows, doggie daycare). Several recent outbreaks of canine influenza have been reported in the United States with anecdotally high levels of dog-dog transmission of canine influenza virus (CIV), resulting in dog illness and death as well as disruption or cancellation of shows and other events. Despite the importance of this disease, little is known of modifiable factors linked to CIV spread in dogs. Work to address this research gap is greatly needed in order to answer key questions about CIV and future control and prevention needs. The investigators will utilize an existing database of dogs tested for CIV to determine any recent changes over time and region (outbreaks) of CIV in the United States. Surveys of dog show participants will also be used to collect information on dog, owner/handler, and canine event factors related to CIV spread. Results will be used to develop and pilot a voluntary surveillance network to serve as an early warning mechanism to identify disease outbreaks (CIV and others) linked to dog events. Findings from this work will allow for targeted prevention strategies to reduce CIV spread in the United States which could be applied to other canine infectious diseases.

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 - 2/29/2020

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.

02633

New

One Health

Investigation of Cytokine Biomarkers for the Diagnosis of Canine Tuberculosis

Principal Investigator: Conor O'Halloran, BVSc; R(D)SVS and Roslin Institute, University of Edinburgh

Total Grant Amount: \$15,000

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

Project Abstract: Tuberculosis (TB) is a global disease which affects both humans and animals. As our most commonly kept companion animals, domestic dogs can be the source or recipient of human TB infections. The pathogen *Mycobacterium* (*M. bovis* is one of the organisms capable of causing TB in a very broad range of potential host animals in both the USA and the United Kingdom (UK), including many species of deer, cattle and camelids but also pet cats, dogs and humans. Data from the U.S. Centers for Disease Control indicate that ~2% of human TB cases in the USA are *M. bovis* infections. Historically, canine TB cases have only been reported in small numbers of individual animals. Between 2016 and 2017 the investigators studied a prolonged outbreak of *M. bovis* TB in a kennel of dogs in the UK. Over half of the animals were positive for *M. bovis*, and all dogs with bacterial isolates had the same strain. The researchers will test these samples for markers of inflammation to improve the accuracy of diagnostic testing for the emergent infectious disease.

02647-A

New

One Health

01844

Treatment of Urinary Incontinence with Multipotent Muscle Cells: A Regenerative Medicine Approach to a Common Canine Health Problem

Principal Investigator: Shelly Vaden, DVM, PhD; North Carolina State University

Total Grant Amount: \$116,184

Grant Period: 1/1/2013 - 12/31/2019

Project Abstract: Urinary incontinence affects more than 20% of spayed female dogs, with medium and large breeds more commonly affected. In the majority of the cases urinary incontinence is caused by dysfunction of the muscles controlling the urethral sphincter. This results in uncontrolled loss of urine and can lead to serious bladder and kidney infections, in addition to irritation and/or ulceration of the skin in contact with the urine. Treatment can include hormone therapy, drugs designed to strengthen the muscle tone of the urethral sphincter, collagen injections, or surgery. Recently, Dr. Vaden's lab has reported that injection of muscle progenitor cells into damaged urethral sphincters can restore normal function in dogs. The purpose of this project is to extend those observations and examine the usefulness of cultured muscle cells for the restoration of function of the urethral sphincter in dogs with naturally occurring urinary incontinence. The effects of the procedure will be determined by owner reported continence scoring, as well as urodynamic testing that will provide an objective measurement for how well the bladder, sphincters, and urethra are storing and releasing urine.

02066

Identification of Novel Biomarkers and Therapeutic Targets for Chronic Kidney Disease in Dogs

Principal Investigator: Mary Nabity, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$108,243

Grant Period: 1/1/2014 - 6/30/2019

Project Abstract: Chronic kidney disease is a significant cause of illness and death in dogs. Early treatment can prolong the lives of dogs with chronic kidney disease, but timely detection can be difficult. The outcome for each patient using current, early non-invasive testing is unpredictable. Therefore, improvements in tests to detect kidney damage at an earlier stage would allow veterinarians to provide dogs with appropriate treatments in a more timely fashion to slow disease progression and improve quality and length of life. Further, better treatments are needed to prevent disease progression. MicroRNAs (miRNAs) are small molecules that can regulate gene expression by up or down regulation of messenger RNA transcripts and proteins in target tissues. Many studies have found that increases or decreases in miRNAs can serve as biomarkers of diseases, including human chronic kidney disease. They also contribute to the development of diseases. Dr. Nabity will evaluate miRNAs in the serum and urine of dogs with chronic kidney disease to determine their use as biomarkers of kidney injury and their potential as targets for future therapeutics. They will evaluate kidney tissue, urine, and serum samples from dogs with a hereditary disease that causes early-onset chronic kidney disease, as well as serum and urine from dogs with a variety of other naturally occurring kidney diseases to identify miRNAs that may be useful as biomarkers of kidney damage. Gene and protein targets of altered miRNAs will also be evaluated to learn more about the mechanisms that contribute to the development of chronic kidney disease in dogs.

02152

Translation of MicroRNA into an Early Diagnostic Test for Chronic Kidney Disease

Principal Investigator: Mary Nabity, DVM, PhD; Texas A&M AgriLife Research

Total Grant Amount: \$26,988

Grant Period: 1/1/2015 - 6/30/2019

Project Abstract: Chronic kidney disease (CKD) is a significant cause of illness and death in dogs and is often due to glomerular diseases. Dogs with glomerular disease often have poor outcomes with standard therapy, and specific treatment recommendations are difficult without performing a kidney biopsy to determine the type of glomerular disease present, since treatment and outcome among these diseases differs substantially. Even then, there lacks an understanding of the mechanisms driving these diseases, limiting the ability to optimally treat these dogs. Therefore, tests to non-invasively diagnosis the type of glomerular disease would help veterinarians more appropriately treat these patients and provide insight into the mechanisms that cause the diseases. This could lead to better therapies that slow disease progression and improve quality and length of life in dogs with CKD. One area of emerging importance in CKD is the role of microRNAs (miRNAs) in disease pathogenesis and progression. miRNAs are small molecules that can regulate gene expression by up or down regulation of messenger RNA transcripts and proteins in target tissues. Many studies have found that increases or decreases in miRNAs can serve as biomarkers of diseases, including human CKD. They also contribute to the development of diseases. The goal of Dr. Nabity's study is to identify miRNAs in serum and urine of dogs that are specific for the three major causes of glomerular disease in this species. They also aim to identify miRNAs associated with disease progression for each of these diseases. Successful completion of these goals will support the translation of miRNAs into diagnostic tests and viable targets for future drug development.

Characterization of Kidney Disease in Dalmatians

Principal Investigator: Rachel Cianciolo, VMD, PhD; Ohio State University

Total Grant Amount: \$31,434

Grant Period: 5/1/2016 - 4/30/2020

Project Abstract: Chronic kidney disease is a significant progressive problem in dogs. Two different hereditary diseases of the urinary system are being studied in Dalmatian dogs: urinary stone formation (urolithiasis) and glomerular disease. These diseases cause distinct clinical signs: urolithiasis leads to urinary tract obstruction while glomerular disease results in protein loss into the urine (proteinuria). The genetic cause of urolithiasis is known while the genetic cause of glomerular disease has not yet been identified. Although one specific type of glomerular disease has been reported in the literature, preliminary investigations indicate that there may be multiple causes of proteinuria in Dalmatians. Evaluation of kidney tissue by the International Veterinary Renal Pathology Service has revealed diverse types of glomerular diseases in Dalmatians, at least 4 of which might be hereditary. Therefore, the most common disease type is unknown and must be identified and characterized. A detailed review of autopsy and biopsy sample archives previously obtained from Dalmatians with proteinuria will be performed. Next, prospective examination of select kidney samples using advanced techniques (electron microscopy and immunofluorescence) will ensure an accurate diagnosis of the glomerular disease. Ultimately, genetic analyses could be performed on related dogs that demonstrate similar glomerular lesions to identify candidate genes. *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 reports.*

Characterization of Renal Disease in American Boxer Dogs

Principal Investigator: Jessica Hokamp, DVM, PhD; Ohio State University

Total Grant Amount: \$56,693

Grant Period: 3/1/2018 - 2/29/2020

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 reports.*

Identification of the Molecular Genetic Cause for Cystinuria in Irish Terriers

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

Total Grant Amount: \$10,000

Grant Period: 12/1/2018 - 11/30/2019

Project Abstract: The goal of this study is to identify the molecular genetic cause for cystinuria in Irish Terriers. Preliminary data was obtained from DNA samples of Irish Terriers affected with cystinuria. The investigators generated and analyzed a whole genome sequence (WGS) from an affected Irish Terrier; however, no variants in cystinuria-associated genes were identified. Using additional dogs and WGS, the investigators will look for rare genetic variants in affected dogs using latest technologies, including an Oxford Nanopore sequencer to effectively detect potentially causal sequence variants. *Funding for the research is provided through the collaborative efforts and generosity of the Irish Terrier Club of America. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

Lung and Respiratory Disease

02507

One
Health

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 - 2/29/2020

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 of 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 (DLD) is an important and unrecognized cause of early death in young puppies. Breeders of Norwich Terriers (NT) report that sudden death of puppies early in life is common. Through preliminary studies, a high incidence of DLD in NT puppies associated with sudden death has been identified. The identification of a breed-association with DLD in the NT presents an opportunity to correlate the pathology and genetics to sudden death in NT puppies. Findings could lead to the development of preventive measures to reduce the incidence of DLD in the NT as well as other dog breeds and may also be applicable to similar developmental lung diseases in children.

Musculoskeletal Conditions and Disease

02107

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 - 6/30/2018; 7/1/2019 – 6/30/2021

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.

02610-A

New

One
Health

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 - 2/29/2020

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.

02624

New

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.

02646-A

New

Effect of Hyperthermia on Skeletal Muscle Energy Efficiency

Principal Investigator: Michael Davis, DVM, PhD; Oklahoma State University

Total Grant Amount: \$14,831

Grant Period: 3/1/2019 - 2/29/2020

Project Abstract: Working dogs are at risk for heat exhaustion and heat stroke due to the large amount of body heat they produce and the difficulties inherent in a dog's ability to dissipate heat. Preliminary data suggest that dogs that lack adequate fitness are at particular risk for hyperthermia due to inefficiency in their ability to burn cellular fuel to power their muscles. The investigators aim to confirm this observation and identify the mechanisms by which fitness improves energy efficiency in a dog's muscles, improving their well-being by allowing them to work harder in hot environments without overheating. Confirming the importance of physical conditioning of working dogs to avoid heat injury, will provide dog handlers, trainers, and veterinarians with an important tool to emphasize fitness training of working dogs.

Neurology

02157-MOU

Genomics of Deafness in the Dalmatian

Principal Investigator: Claire Wade, PhD; University of Sydney

Total Grant Amount: \$120,960

Grant Period: 1/1/2015 - 12/31/2019

Project Abstract: Congenital deafness is a health issue that has higher prevalence in certain breeds, including the Dalmatian. Other studies in this breed have found the trait to be inherited in a complex rather than simple Mendelian manner. Using a large number of samples from animals that have been tested for hearing status, investigators will employ the latest genomic technologies and computational analyses to conduct this study. The ultimate goal is to identify mutations underlying the trait of congenital deafness in the Dalmatian breed and work towards a genetic testing solution for the Dalmatian breeding community. *Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

Defining the Genetic Foundations of Chiari-Like Malformation and Syringomyelia as a Tool to Better Treat Neuropathic Pain in the Dog

Principal Investigator: Natasha Olby, VetMB, PhD; North Carolina State University

Total Grant Amount: \$78,786

Grant Period: 1/1/2015 - 6/30/2019

Project Abstract: Chiari-like malformations and syringomyelia (CM/SM) are a common problem in Cavalier King Charles Spaniels (CKCS) causing severe neuropathic pain. The morphometry of the skull has been examined in detail and the development of clinical signs and syringomyelia has been correlated to reduced caudal fossa to cranial cavity volume ratios and stenosis of the jugular foramen respectively. There is evidence this disorder is a complex hereditary trait but attempts to identify genetic causes have been hampered by assigning an affected or normal phenotype. Use of quantitative data from magnetic resonance imaging (MRI) will allow us to perform a more appropriate genetic analysis of this important and common disease. Quantification of neuropathic pain is challenging and while owners of affected CKCS frequently complain that their pet is experiencing significant pain, a routine evaluation by palpation does not always correlate well to their history. Humans with CM report increased sensitivity to touch and temperature. During case phenotyping for the genetic study, Dr. Olby will also investigate sensory thresholds in affected and normal CKCS to improve the ability to document and treat pain in these patients. This project will define the genetic etiology of this disease with the long-term aim of developing genetic tests for use by breeders and will quantify the sensory dysfunction experienced by these dogs to facilitate objective therapeutic trials. *Funding for the research is provided through the efforts and generosity of the American Cavalier King Charles Spaniel Club Charitable Trust. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

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 - 6/30/2019

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 - 6/30/2019

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, Columbia

Total Grant Amount: \$15,000

Grant Period: 7/1/2018 - 6/30/2019

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 reports.*

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 - 12/31/2019

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.*

02589

New

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.

02604

New

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.

02606

New

The Genetic Background of Lumbosacral Transitional Vertebrae in Dogs

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

Total Grant Amount: \$59,320

Grant Period: 4/1/2019 - 3/31/2020

Project Abstract: Dogs of medium and large size or breed can suffer from a condition called lumbosacral transitional vertebrae (LTV), which means that the dog has a malformed vertebra in the caudal end of the spinal cord. Different types of LTV exist and radiographic screening is used to determine the form of LTV in dogs. The disorder can be seen right after birth and it is hereditary. However, it is not known how the disease is inherited, or what genes may contribute to this abnormal development of the spinal vertebrae. LTV is common in German Shepherd Dogs and the disorder predisposes the dogs to cauda equina syndrome. Affected dogs may become increasingly painful or may develop paralysis of the hind legs. There is a need to clarify the genetic background of LTV. The investigators plan to use genetic analyses to identify and confirm genetic risk factors that bring about LTV in dogs. The researchers will both search for regions in the dog genome that associate with the disease and will also investigate the possible contribution of known LTV candidate genes discovered in other species.

02658

New

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.

Oncology - General

02321

One Health

Clinical Trial of Procaspace-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: \$51,191

Grant Period: 2/1/2017 - 1/31/2020

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.

02446

Development of Genetic Biomarkers to Improve Diagnosis and Treatment of Canine Histiocytic Sarcoma

Principal Investigator: Benoît Hédan, DVM, PhD; CNRS - University of Rennes

Total Grant Amount: \$138,107

Grant Period: 5/1/2018 - 4/30/2020

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.

02456-A

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: \$14,945

Grant Period: 1/1/2018 - 12/31/2019

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.

02487

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 - 2/29/2020

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.

One Health

02489

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 - 2/29/2020

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.

One Health

02500

One
Health**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 - 1/31/2020

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.*

02595-A

New

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 - 4/30/2020

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.

02636-A

New

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 - 3/31/2020

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.

02643-A

New

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: 5/1/2019 - 4/30/2020

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).

02663

New

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 - 3/31/2020

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.

Oncology - Hemangiosarcoma

02234-MOU

A Novel Approach for Prevention of Canine Hemangiosarcoma

Principal Investigator: Jaime Modiano, VMD, PhD; University of Minnesota

Total Grant Amount: \$432,000

Grant Period: 3/1/2016 - 8/31/2019

Project Abstract: Hemangiosarcoma, an aggressive form of cancer in dogs, is the cause of death for one out of every five Golden Retrievers in the United States. Portuguese Water Dogs and Boxers also have an especially high risk for this disease which is devastating for all dogs. Hemangiosarcoma is incurable partly because the cancer is detected at a very advanced stage when it is resistant to conventional therapies. Thus, an unconventional approach to improve outcomes for hemangiosarcoma patients will involve effective methods for early detection and for disease prevention. This project will pair two novel technologies consisting of a patented test to detect hemangiosarcoma cells in blood samples, and a treatment that attacks the cells that establish and maintain the disease. Three milestones will be met: first, will be to expand understanding of the performance and utility of the blood test for cancer in dogs with active disease; second will be to confirm the utility of the test to predict disease progression in treated dogs; and third will be to establish the performance of the test in the "early detection" setting (dogs at high risk without evidence of active cancer), and thus measure hemangiosarcoma prevention through eradication of the tumor initiating cells with the targeted, investigational drug. This project will create tools to guide further development, licensing and deployment of these paired technologies against cancer, specifically hemangiosarcoma, with an ultimate goal for disease prevention in all dogs. *Funding for the research is provided through the collaborative efforts and generosity of the American Boxer Charitable Foundation, Golden Retriever Foundation, and Portuguese Water Dog Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress reports.*

02510-T

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 - 2/28/2021

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.

02519

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 - 1/31/2020

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.

02534

Clinical Trial for Evaluation of Propranolol and Doxorubicin in the Treatment of Canine Hemangiosarcoma

Principal Investigators: Erin Dickerson, PhD and Brian Husbands, DVM; 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, 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.

New

One
Health

02309-T

One Health

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, Columbia

Total Grant Amount: \$78,069

Grant Period: 1/1/2017 - 12/31/2019

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.

02317

One Health

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 - 6/30/2019

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.

02318

One
Health**Genetic and Environmental Risk for Lymphoma in Boxer Dogs****Principal Investigator:** Lauren Trepanier, DVM, PhD; University of Wisconsin, Madison**Total Grant Amount:** \$112,861**Grant Period:** 1/1/2017 - 6/30/2019

Project Abstract: Lymphoma is a fatal cancer of the blood cells that can occur in any dog. Lymphoma is more common in Boxers, Golden Retrievers, and several other purebreds, which suggests involvement of inherited genes. Recent research has focused on gene mutations in the tumors of dogs with lymphoma. However, we do not understand why these mutations accumulate in certain dogs, and this understanding is essential for disease prevention. Canine lymphoma resembles Non-Hodgkin Lymphoma (NHL) in humans, which is more common in industrialized countries and is associated with chemicals found in tobacco smoke, certain household products, pesticides, herbicides, and fungicides. Glutathione-S-transferases (GSTs) are enzymes that can break down toxic chemicals in the body and prevent tumor mutations. Inherited gene defects in the 3 major GST enzymes, GST-theta, GST-pi and GST-mu, each increase NHL risk, and simultaneous defects in more than one enzyme further increase NHL risk. The investigators have characterized two GST-theta enzymes in dogs, and both have defective gene variants. So far, their findings suggest one variant is a risk factor for lymphoma in dogs of varying breeds. However, the genes for canine GST-pi and GST-mu enzymes have not yet been explored. This research will determine whether defective GST genes along with certain household and yard chemicals are associated with lymphoma in dogs, with a focus on the high-risk Boxer breed. The overall goal of this study is to identify combinations of genes and environmental chemicals that contribute to the development of lymphoma in dogs, so that better cancer prevention strategies can be developed.

02502

One
Health**Precision Medicine for Canine Lymphoma****Principal Investigator:** Nicola Mason, BVetMed, PhD; University of Pennsylvania**Total Grant Amount:** \$86,400**Grant Period:** 3/1/2018 - 2/29/2020

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, known as 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.

Oncology - Osteosarcoma

01660

One
Health**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 - 12/31/2019

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.

02642-A

New

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 - 3/31/2020

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.

Ophthalmology

02164-MOU

Determining the Genetic Contribution to Boxer Corneal Ulcers**Principal Investigator:** Kathryn Meurs, DVM, PhD; North Carolina State University**Total Grant Amount:** \$68,053**Grant Period:** 1/1/2015 - 12/31/2019

Project Abstract: Spontaneous chronic corneal epithelial defects (SCCEDs) are chronic corneal ulcers that fail to undergo normal healing that are commonly observed in Boxers. The predilection for Boxers suggests that SCCEDs is inherited in this breed. Affected dogs develop spontaneous corneal ulcers that are often exceptionally painful and persist for weeks to months. Most dogs require surgical therapy to heal the corneal ulcer and experience corneal scarring as a result. The impact on the quality of life for dogs during episodes of ulceration has led to increased interest in disease prevention. However, since SCCED is an adult onset disease, many dogs are selected for breeding before they are diagnosed. A blood test that could identify affected animals before they are used for breeding would greatly decrease the prevalence of SCCEDs. In a previous study funded by the AKC Canine Health Foundation, Dr. Meurs and colleagues collected samples from adult Boxers with and without SCCED and performed a genome wide association study. In the study proposed here they will perform whole genome sequencing (GWAS) on a subset of affected and unaffected dogs and use the data from the GWAS to focus in on important variants. They will then more closely evaluate variants of interest to determine the gene and ultimately the causative genetic mutation. They hope that the identification of a genetic cause for SCCEDs in the Boxer can be used to reduce the prevalence of this disease in this breed but also to provide information for other affected breeds. *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.*

02336

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 - 4/30/2020

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 - 10/31/2019

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 reports.*

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 - 11/30/2019

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, Madison

Total Grant Amount: \$121,740

Grant Period: 3/1/2018 - 2/29/2020

Project Abstract: Glaucoma is a very painful and rapidly blinding disease that leads to irreversible sight loss in many thousands of dogs in the U.S. 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.

02569-MOU

New

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 reports.*

02572-MOU

New

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 reports.*

02590-A

New

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 - 1/31/2020

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.*

02608-A

New

02608-A: 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: \$14,750

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.

Reproductive Conditions

02409-A

02409-A: Targeting Bacterial Adhesion via Blocking the Scavenger Receptor Type B1 in Canine Pyometra

Principal Investigator: Cordula Gabriel, PhD; University of Veterinary Medicine of Vienna

Total Grant Amount: \$14,904

Grant Period: 1/1/2018 - 2/29/2020

Project Abstract: Pyometra is the most common uterine disease in intact bitches leading to potentially life-threatening complications via the systemic inflammatory response syndrome (SIRS). *Escherichia coli* (*E.coli*) is the most abundant isolated pathogen causing pyometra. In a previous study the investigators characterized endometrial epithelial foam cells (EEFCs) in the canine endometrial surface occurring in metestrus, the cyclic stage with the most common presence of pyometra. They identified a specialized receptor named scavenger receptor class B1 (SR-B1) expressed in EEFCs. SR-B1 is relevant for lipid-uptake and thereby involved in EEFC formation. SR-B1 is also a strong binding partner for *E.coli*, and a significant upregulation of SR-B1 in pyometra affected canine uteri was identified. The hypothesis in this study is that blocking of SR-B1 in EEFCs can be used as supportive non-invasive pyometra treatment. Binding capacity of an adherent pyometra-related *E.coli* strain will be tested in the presence of the functional SR-B1 and in cells in which the SR-B1 is blocked in vitro. The mechanisms behind SR-B1 upregulation will be investigated to gain more information about this pyometra-related target molecule. Multidisciplinary analyses will be applied to identify the effects of blocking SR-B1 on *E.coli* adherence and inflammatory cytokine release. The reduction of the inflammatory response via blocking the endometrial SR-B1 could be a further benefit of this novel therapeutic approach.

Tick-Borne Disease Initiative

01780

One Health

Defining the Mechanism by Which Ticks Locate Dogs in Order to Better Prevent Disease Transmission

Principal Investigator: Emma Weeks, PhD; University of Florida

Total Grant Amount: \$103,660

Grant Period: 3/1/2013 - 9/30/2019

Project Abstract: The brown dog tick (BDT) is common across the U.S. and is the most widely distributed tick in the world. BDT's carry and transmit the pathogens that cause debilitating diseases such as canine ehrlichiosis and babesiosis. Prevention of these diseases is accomplished through tick control. BDT's can complete their entire life cycle indoors, making management difficult. Records of infestations are increasing and unpublished data indicates that a high level of pesticide resistance is present in domestic populations. Consequently once introduced, these ticks are particularly hard to eradicate and as one female tick may lay 5,000 eggs, the problem soon gets out-of-hand. Pesticide resistance leads to aggressive treatment regimes, which in turn, lead to increased exposure of humans and pets to chemical residues. Alternatives to pesticides are needed. Studies have shown that BDT's are attracted to dog odor, a blend of volatile chemicals used by ticks to find a blood meal. In this study, Dr. Weeks will identify the chemicals BDT's use to locate a dog. This will enable manipulation of tick behavior thereby facilitating management and reducing the need for extensive use of pesticides. Improved tick control without the need for increased environmental pesticide applications will improve the quality of life for dogs and their owners.

02284-A

One Health

Lyme Disease in Dogs: Prevalence, Clinical Illness, and Prognosis

Principal Investigators: Thomas Wittum, MS, PhD; Andréia Arruda, DVM, MSc, PhD; Ohio State University and Jason Stull, VMD, MPVM, PhD; Ohio State University and University of Prince Edward Island

Total Grant Amount: \$14,148

Grant Period: 7/1/2016 - 6/30/2019

Project Abstract: Lyme disease (or Borreliosis) is a bacterial disease of dogs and humans that is transmitted by tick bites. In people, Lyme is the most common tick-transmitted disease in the U.S., with over 25,000 cases in 2014. While most common in the northeastern coastal states and the upper Midwest, Lyme disease is moving into other regions of the U.S. and Canada. Dogs infected with Lyme disease rarely show signs of illness (typically lameness), but can be severe (e.g., kidney disease). Diagnosis, treatment and prevention of Lyme disease in dogs are complicated by limited research and conflicting professional guidance. Current practices may unnecessarily place dogs at risk for illness and negative outcomes. The investigators will follow a large group of dogs from different regions of the U.S. and Canada. During this period the investigators will determine how often healthy dogs test positive for Lyme disease (meaning they have been bitten by an infected tick) and identify how often they later develop a Lyme-related illness. The risks and benefits of management strategies for Lyme-positive dogs and obstacles to effective tick prevention will be determined to help clarify unmet pet owner education needs. These findings are likely to extend to better understanding of canine and human Lyme disease, and improve health outcomes. Collectively, this work will allow us to identify, define and improve upon best practices for prevention and control of Lyme disease in areas with different Lyme risks, ultimately improving the health of dogs and people.

02383

One Health

Identifying Cellular Mechanisms of Inflammation During Canine Tick-Borne Diseases

Principal Investigator: Christine Petersen, DVM, PhD; University of Iowa

Total Grant Amount: \$207,526

Grant Period: 9/1/2017 - 8/31/2019

Project Abstract: Tick-borne diseases are found in all 50 states of the United States and are the most common vector-borne disease diagnosed in people in the U.S. The predominant disease is Lyme disease, caused by *Borrelia burgdorferi* and related species (sensu lato). Other important canine tick-borne diseases include those caused by *Anaplasma platys*, *Anaplasma phagocytophilum* (*Anaplasmosis*, *Babesia canis*, *Babesia conradae* and *Babesia gibsonii* (*Babesiosis*, and *Ehrlichia canis*, *Ehrlichia chaffiensis* and *Ehrlichia ewingii* (*Ehrlichiosis*). Many of these diseases also affect people. Dogs can serve as sentinel species for human disease and there are many areas where the immune responses and disease outcomes are very similar in people and dogs, meaning that important lessons can be learned by sharing information between human and animal health (One Health). The researchers will further investigate the dog's immune system to determine which immune cells are responsible for the cure or creation of canine tick-borne disease. Through understanding which cells are responsible for causing disease, the goal is to then specifically target the molecules they produce using immunotherapy or immune modulation to improve treatment of tick-borne diseases in all dogs.

02386-A

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 - 1/31/2020

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.

02528

One Health

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 - 5/31/2020

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 USA 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.

02553

New

One Health

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.

CHF Clinician-Scientist Fellowship Program

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.

2019 AKC Canine Health Foundation Clinician-Scientist Fellows



Ana Costa, DVM, MS, Diplomate ACVIM; Washington State University

Mentors: Michael H. Court, BVSc, PhD, Diplomate ACVA; Katrina L. Mealey, DVM, PhD; and Nicolas Villarino, DVM, PhD, Diplomate ACVP

Dr. Costa received her DVM from Escola Universitária Vasco Da Gama in Portugal. Her project focuses on the *in vitro* impact of uremic toxins on drug binding to albumin. Since these conditions mimic canine chronic renal failure, results may lead to improved management and care of these compromised patients.

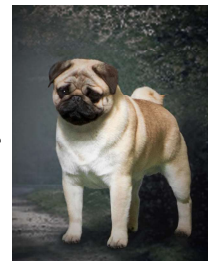


Shelby Gasson, DVM; Texas A&M University

Mentor: W. Brian Saunders, DVM, PhD, Diplomate ACVS

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.



GCHP Hill Country's
Let's Get Ready To Rumble



Mariah Gentry, DVM; University of Pennsylvania

Mentor: Margaret L. Casal, DVM, PhD, Diplomate ECAR

Dr. Gentry received her DVM from Cornell University. Her work focuses on the heritability of renal dysplasia in Cairn Terriers and she aims to develop a DNA-based marker test so the disorder can be diagnosed at an early age. The findings of this work would allow for more informed breeding decisions as well as recommended lifestyle changes to prolong the life of affected dogs.

This fellowship is generously sponsored by the Foundation of the Cairn Terrier Club of America.



Sarah Murphy; Clemson University

Mentor: Leigh Anne Clark, PhD

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).



Caroline Wood, DVM, PhD; University of Minnesota

Mentor: Jaime Modiano, VMD, PhD

Dr. Wood received her DVM and PhD from the University of Minnesota. Her research aims to define the unique DNA methylation patterns (epigenetic signatures) for specific dog lymphocyte subsets found in osteosarcoma (bone) tumors in dogs. Understanding these tumor-infiltrating lymphocytes will inform osteosarcoma immunobiology and prognosis for both dogs and humans affected by this cancer.

This fellowship is generously sponsored by the American German Shepherd Dog Charitable Foundation.

To support this program visit: akcchf.org/clinsci

AKC/AKCCHF/TF Theriogenology Residency Program

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.



2019 Theriogenology Resident



Jamie Douglas, DVM; (CHF Grant 2538-E)

Residency Coordinator: Robyn R. Wilborn, DVM, MS; Auburn University

Total Grant Amount: \$100,000

Grant Period: 7/1/2019 - 6/30/2022

Dr. Jamie Douglas received her DVM from Michigan State University College of Veterinary Medicine in 2014 and her master's degree in animal science (focus: 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.

2018 Theriogenology Residents



Alyssa Helms, DVM; (CHF Grant 2390-E)

Residency Coordinator: Julie T. Cecere, DVM, MS, DACT; Virginia-Maryland College of Veterinary Medicine

Total Grant Amount: \$99,036

Grant Period: 7/1/2018 - 6/30/2021

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.



Kate Withowski, DVM; (CHF Grant 02395-E)

Residency Coordinator: C. Scott Bailey, DVM, MS; North Carolina State University

Total Grant Amount: \$100,000

Grant Period: 7/1/2018 - 6/30/2021

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. During her undergraduate experience, Dr. Withowski also worked as a veterinary assistant. Most recently, she spent a year in field service and completed a theriogenology internship at the University of Georgia.

2016 Theriogenology Resident



Karen Von Dollen, DVM; North Carolina State University (CHF Grant 02281-E)

Residency Coordinator: C. Scott Bailey, DVM, MS; North Carolina State University

Total Grant Amount: \$100,000

Grant Period: 7/1/2016 - 6/30/2019

Dr. Karen Von Dollen attended Bryn Mawr College in Pennsylvania, where she majored in chemistry with minors in mathematics and biology and was a member of the varsity lacrosse team. She returned to California to earn her DVM degree from the University of California, Davis. Following graduation, she completed internships at Alamo Pintado Equine Medical Center in Los Olivos, California and Goulburn Valley Equine Hospital in Victoria, Australia.

To support this program visit: akcCHF.org/therio

Impact of CHF Funding: 2019 Scientific Publication Outcomes of Research

January 1, 2019 - May 22, 2019

- Agler, C. S., Friedenbergs, S., Olivry, T., Meurs, K. M., & Olby, N. J. (2019). **Genome-wide association analysis in West Highland White Terriers with atopic dermatitis.** *Veterinary Immunology and Immunopathology*, 209, 1–6. <https://doi.org/10.1016/j.vetimm.2019.01.004>
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- Chu, C. P., & Nabity, M. B. (2019). **Comparison of RNA isolation and library preparation methods for small RNA sequencing of canine biofluids.** *Veterinary Clinical Pathology*, 0(0). <https://doi.org/10.1111/vcp.12743>
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- Martel, D. P., Fox, P. R., Lamb, K. E., & Carmichael, D. T. (2019). **Comparison of closed root planing with versus without concurrent doxycycline hyclate or clindamycin hydrochloride gel application for the treatment of periodontal disease in dogs.** *Journal of the American Veterinary Medical Association*, 254(3), 373–379. <https://doi.org/10.2460/javma.254.3.373>
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