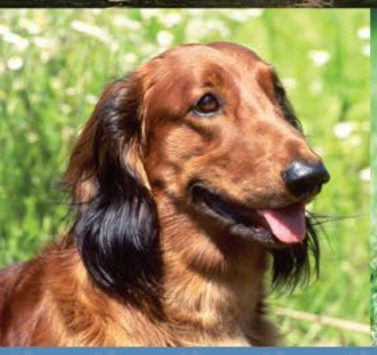


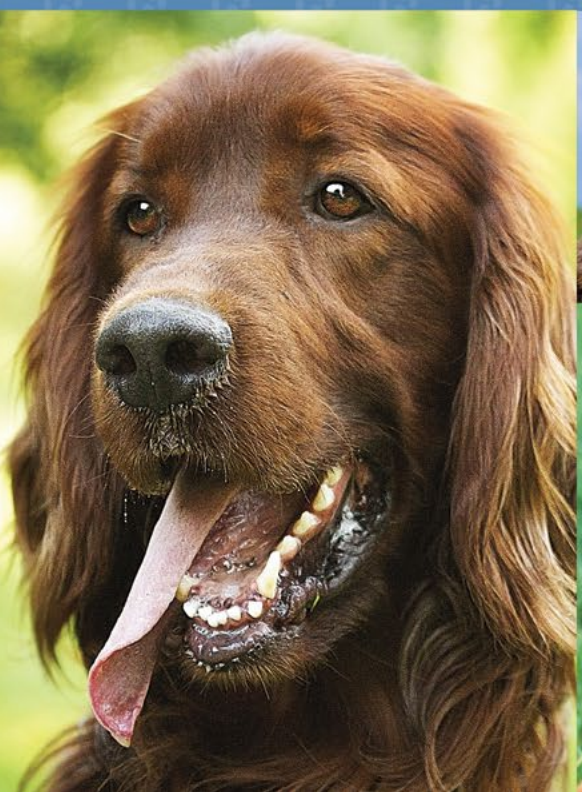




AMERICAN KENNEL CLUB

20 years

CANINE HEALTH FOUNDATION

2015 RESEARCH PORTFOLIO





INTRODUCTION

For 20 years, the AKC Canine Health Foundation, with your support, has helped all dogs live longer, healthier lives by funding cutting-edge canine health research. Together, we have made great strides in addressing the health needs of dogs across their entire lifetime by focusing on all aspects of their physical, mental, and social well-being.

On the following pages are descriptions of active grants awarded by the AKC Canine Health Foundation. Each grant is reviewed for scientific merit, potential impact in the field of study, and the significance the findings will have for our dogs. Additionally, we take into consideration the information gathered from dog owners, breeders, veterinarians, and dog clubs about the most pressing health concerns in dogs so that our research is doing the most good and having the greatest impact.

Science does not work in isolation, but builds from each new finding to bring about better treatments, more accurate diagnoses, and a better understanding of the mechanisms that cause disease. New grants are selected to either fill a gap or complement ongoing research in our canine health portfolio.

By classifying our grants by research program area, donors are able to support efforts important to them. Program areas also allow us to create depth in areas of importance and fund complementary studies that will build on the progress made from one research study to the next.

We invite you to support these research projects with a donation today. Together, we can help move canine health research forward, benefiting the dogs we love today, and the dogs we will love in the future.

To sponsor research, contact chfgrants@akcchf.org.

JOIN US!

*Join us for the **2015 National Parent Club Canine Health Conference** hosted by the AKC Canine Health Foundation and sponsored by Nestlé Purina. An integral component of CHF's mission is to educate our donors about the cutting edge research they are supporting. This biennial event gathers nearly 300 representatives from AKC Parent Clubs and other areas of the dog fancy who have specific interest in canine health, who are eager to learn about the research advances, and who actively support research both financially and through study participation. Throughout this grant portfolio you will see abstracts from our funded researchers who have agreed to speak at out conference. Dog clubs and fanciers have led the way in the fighting canine disease, and the results of your grant sponsorship will be on display at our 2015 conference, we hope to see you there!*

CONTENTS

Behavior Research Program Area

01995: Understanding the Flexibility and Limitations of How Dogs Acquire Knowledge and Understanding: Application to Service Dog Emotional Health and Selection

Principal Investigator: Dr. Evan L. MacLean, PhD **Institution:** Duke University

Total Grant Amount: $97,809.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Dogs are being used to help people with mental and physical disabilities in more ways than ever before. There is increasing evidence that trained dogs can dramatically improve the lives of people with a wide variety of disabilities, and the demand for these dogs climbs higher each year. The biggest challenge faced is increasing the supply of well-trained dogs to serve individuals who will benefit from their help, while at the same time ensuring the reciprocal emotional health of the dogs chosen for service. The research aims of Dr. MacLean and his colleagues are to increase the supply of these dogs by improving our ability to identify and train dogs with the greatest potential for success. The Duke Canine Cognition Center and Canine Companions for Independence will work together to identify cognitive traits that predict success during assistance dog training. They will pose the question: Do a dog's communicative abilities, memory, empathy for humans, or ability to independently solve problems predict success? For the first time, a series of cognitive games will be used to determine which dogs have the cognitive abilities that best predict their abilities to help humans. With this new tool they will be able to more rapidly identify and train the best dogs in order to increase the number of people assisted by our best friends. This research will ensure that we begin to take the steps to understand canine emotional health and well-being in the service dog selection process and beyond.

02085-A: Reducing Animal Shelter Surrender by Enhancing the Human-Animal Bond

Principal Investigator: Dr. Clive D.L. Wynne, PhD **Institution:** Arizona State University Foundation

Total Grant Amount: $12,960.00

Grant Period: 2/1/2014 – 1/31/2015

Project Abstract:

The AKC Canine Health Foundation has long admired the tireless work of breed club rescue groups that are committed to finding long-term, committed homes for their dogs. Despite their efforts the current statistics are overwhelming: 7 million dogs are relinquished to shelters every year in the US, and after adoption nearly 50% of adopted dogs are returned back to the shelter. These returns may be emotionally painful for the owner but they can be deadly for the dog. In order to reduce owner surrenders Dr. Clive Wynne aims to evaluate whether an owner-dog exercise program can decrease return rates of newly adopted dogs by improving the Human-Animal bond. Dr. Wynne hypothesizes that shared structured exercise between the new owner and the newly adopted dog will provide a buffer against return by promoting social bonding and attachment to the dog and improving the physical and mental health of both parties. In collaboration with the Arizona Animal Welfare League/SPCA, one hundred and eighty dog-owner pairs will be randomly assigned to one of two conditions upon adoption of the dog: an exercise program and a control condition. The exercise group participants will receive pedometers and be asked to log their physical activity with their dog. The exercise group participants will also participate in a weekly social event with their dogs in which they will be asked to bring their logged data, hear about the benefits of dog walking, get ideas on ways to exercise with their dogs, and receive advice in basic dog training. Return rates of the dogs in both groups will be collected from shelter statistics. Dr. Wynne predicts that owner-dog pairs that are assigned to the exercise program will have lower return rates and a higher attachment compared to the owner-dog pairs that are assigned to the control condition. Furthermore, he predicts that the return rates will correlate with the amount of physical activity as measured by the pedometers. The proposed study will be the first step in developing a more thorough understanding of the Human-Animal bond and its relation to the elimination of owner surrenders at animal shelters.

Blood Disease Research Program Area

01988: Identification of a Safe Storage Time for Canine Blood Used In the Treatment of Anemia

Principal Investigator: Dr. Mary Beth Callan, VMD **Institution:** University of Pennsylvania

Total Grant Amount: $113,499.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Red blood cells (RBCs) can be refrigerator stored for up to 35 – 42 days in humans and dogs. Given that blood is a precious and limited resource, both human and veterinary blood banks typically dispense the oldest RBC units first to reduce waste. However, accumulating evidence suggests that transfusion of RBCs stored >14 days is associated with increased rates of complications and death in human patients. Preliminary data from a study of more than 2000 dogs receiving RBC transfusions suggest that administration of older RBCs to dogs with certain types of anemia negatively

impact survival. Dr. Callan's goal is to conduct a randomized clinical trial in which dogs with anemia in need of RBC transfusions will receive either "fresh" RBCs (stored <7 days) or "old" RBCs (stored 21–28 days). If they document that administration of older RBCs is associated with increased inflammation and poorer outcome in dogs with anemia, the results of this study will have a significant impact on canine health and veterinary blood banks by changing current transfusion practices; that is, by providing fresh rather than older RBCs to anemic canine patients.

02052: Defining the Mechanism of Severe, Life-Threatening Bleeding Disorders in Dogs

Principal Investigator: Dr. Dana N. LeVine, DVM, PhD **Institution:** Iowa State University

Total Grant Amount: $51,297.00

Grant Period: 2/1/2014 – 1/31/2015

Project Abstract:

Immune thrombocytopenia (ITP) is a common bleeding disorder in dogs. It occurs when the immune system destroys the body's own platelets – blood cells that prevent hemorrhage. The resulting lack of platelets in some dogs causes mild bruising and in others causes severe, life-threatening hemorrhage. Veterinarians do not understand what triggers ITP and cannot predict its severity. Consequently, all ITP patients are treated with potent medications that suppress the entire immune system. Many dogs experience treatment side-effects including excessive thirst and urination, ulcers, weight gain, and recurrent infections. For some dogs, the side-effects, rather than ITP, prove fatal. Dr. LeVine will investigate the specific causes of ITP by measuring immune cells and proteins that are likely involved in platelet destruction. Further, her laboratory will identify protein-based biological markers that predict bleeding severity. Finally, they will define genes associated with the disease in breeds especially prone to ITP. Together, these efforts will benefit ITP patients through individualized therapy that matches treatment intensity with disease severity. Discovery of the immune and genetic causes of ITP will not only improve disease treatment, but ultimately help to prevent it.

02148-A: The Prevalence of a Novel Canine Blood Type and Its Mode of Inheritance in Doberman Pinschers and in Dalmatians

Principal Investigator: Dr. Marie-Claude Blais, DVM **Institution:** University of Montreal

Grant Amount: $12,376.80

Funding Provided by The Doberman Pinscher Club of America

Project Abstract:

Blood transfusions have become an integral part of advanced veterinary medicine. As in humans, several blood groups have been identified in dogs. A dog negative for a given blood group can produce antibodies following exposure to that specific blood group, which could lead to life-threatening hemolytic transfusion reactions with subsequent transfusions.

Recently Dr. Blais and colleagues identified a new canine blood type, named Dal, in an anemic Dalmatian patient. The Dal blood type can be associated with the production of anti-Dal antibodies, which may result in ineffective transfusions and hemolytic transfusion reactions. The frequency of the Dal blood type reported was 100% (55/55) in non-Dalmatian dogs and 81% in Dalmatians (5 out of 26 Dalmatians were Dal negative).

The high frequency of the Dal blood type creates particular challenges: 1) Dal-negative anemic dogs will most likely be sensitized via their first blood transfusion and produce anti-Dal antibodies, and 2) if further blood transfusions are required in those patients, compatible Dal-negative blood may be very difficult to find. This problematic scenario was seen in 2 recent cases of anemic Doberman pinschers, which led to preliminary blood testing in the breed. About a third of Doberman pinschers tested to date in Canada are Dal-negative.

The purpose of this study is to establish the prevalence of the Dal-negative blood type in Doberman pinschers and in Dalmatians and its mode of inheritance. The secondary objective is to identify Dal-negative healthy blood donors in order to offer readily available compatible blood to Dal-negative anemic patients.

Canine Athlete Initiative Research Program Area

01985: Defining Novel Drug Targets to Treat Chronic and Neuropathic Pain in the Dog

Principal Investigator: Dr. Ronald Sluyter, PhD **Institution:** University of Wollongong

Total Grant Amount: $69,128.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Through a previous grant from the AKC Canine Health Foundation, Dr. Ronald Sluyter discovered a novel canine protein named the P2X Receptor. This receptor is responsible for movement of positively charged ions into cells and has been implicated in a wide range of cellular function in humans. Due to its ubiquitous expression and broad-based function, the P2X receptor is thought to play a decisive role in multiple diseases including chronic neuropathic and inflammatory pain, dry eye, irritable bowel syndrome, interstitial cystitis, dysfunctional urinary bladder, and cancer. In this grant

Dr. Sluyter will focus on the role of the P2X receptor in pain in the dog. Chronic or long-lasting pain is a major health problem and welfare issue in dogs. Improved understanding of the mechanisms that define chronic pain will greatly aid in the development of new approaches and drugs to alleviate or treat chronic pain in dogs.

Regenerative medicine is a rapidly developing field with the potential to transform the treatment of canine disease. The ability to repair damaged tissue and treat diseases once believed to be incurable may soon be a reality. However, there are concerns that some techniques are being used prematurely. Due to the lower regulatory barriers in veterinary medicine, company-sponsored regenerative medicine products and techniques are currently used in general practice and specialty hospitals without the benefit of having been preceded by stringently controlled, independently funded clinical trials. As a result, techniques vary widely and the evidence that they work is anecdotal at best. The AKC Canine Health Foundation has made the evidence-based practice of regenerative medicine a major focus within our research portfolio. Through an ongoing commitment to fund research studies that will inform the veterinary community in the use of safe and effective regenerative medicine techniques, we intend to protect dog owners and support veterinarians with innovative technology that will consistently improve outcomes for dogs.

02078: Development of a Regenerative Medicine Technique to Treat Cartilage Disorders in Dogs

Principal Investigator: Dr. William Brian Saunders, DVM, PhD* **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $120,872.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Osteochondrosis is a common and debilitating disease affecting large, athletic dogs. Osteochondrosis is caused by abnormal endochondral ossification, the process by which growth plate cartilage adjacent to joint surfaces transitions from cartilage to bone. The result is excessively thickened cartilage that partially or completely separates from surrounding bone. Cartilage separation exposes the joint to underlying bone and creates a large loose body, termed a joint mouse, within the joint. Surgical or medical treatment results vary widely based on the affected joint, size of the osteochondrosis defect, and intended purpose for each dog. Treatment options for osteochondrosis have remained essentially unchanged for decades. Tissue engineering represents a promising treatment alternative for dogs suffering from OC. Dr. Saunders believes the key to successful tissue engineering involves generation of regenerative osteochondral plugs, or ROPs. ROPs are tri-layered cylindrical plugs composed of hydrogels seeded with adult mesenchymal stem cells (MSCs). Each ROP layer is composed of materials that closely mimic specific zones of the joint and adjacent bone. ROP layers are bioactive, directing encapsulated MSCs to differentiate into specific tissues to more efficiently restore normal joint anatomy. Dr. Saunders will optimize the materials used to generate ROP layers and will determine if MSCs from tissue lining the joint (synovium) or inner cavity of bones (bone marrow) more effectively reconstruct native cartilage, transitional tissue, or bone. This work represents an important advance in canine regenerative medicine and is highly applicable to dogs with osteochondrosis or other common joint ailments such as osteoarthritis.

02107: Landmark Clinical Trial to Establish the Evidence-Based Use of Regenerative Medicine to Treat Tendon Injury in Dogs

Principal Investigator: Dr. Jennifer G. Barrett, DVM, PhD* **Institution:** Virginia-Maryland Regional College of Veterinary Medicine

Total Grant Amount: $254,509.00

Grant Period: 7/1/2014 – 6/30/2016

Project Abstract:

In support of our effort to provide evidence-based regenerative medicine research, CHF has awarded this landmark study to evaluate the effectiveness of Platelet-Rich Plasma (PRP) and stem cells in the treatment of the most common sporting injury in dogs: supraspinatus tendonopathy (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. Dr. Jennifer Barrett, MS, PhD, DVM, DACVS, DACVSMR, and Dr. Sherman Canapp, DVM, MS, CCRT, DACVS, DACVSMR, propose to conduct the first randomized, placebo-controlled clinical trial evaluating the effectiveness of PRP, adipose-derived, cultured stem cells (ASC) and commonly used stromal vascular fraction (SVF) cells. This will be the first study 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 study will be conducted at the Veterinary Orthopedic and Sports Medicine (VOSM) Group in Annapolis Junction, MD in order to recruit real-world cases in a clinically relevant, state of the art canine sports medicine environment. Using the gold-standard 'Blinded, Placebo Controlled' clinical trial design, Drs. Barrett and Canapp will not only identify an effective treatment for supraspinatus tendon injury, but their research will have a profound impact on the treatment of a wide array of musculoskeletal conditions affecting dogs and humans.

Cardiology Research Program Area

01753: Identification of Genetic Factors That Alter the Severity of Cardiomyopathy

Principal Investigator: Dr. Kathryn M Meurs, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $73,343.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Arrhythmogenic right ventricular cardiomyopathy is a genetic-based heart disease in adult dogs that was recently found to be due to a deletion mutation in the striatin gene. Dogs with this genetic mutation can suffer from irregular heartbeat, loss of consciousness and sudden death. Dr. Meurs' lab has demonstrated that Boxer dogs with 2 copies of a genetic deletion (homozygous) are most likely to have the more severe form of the disease, however dogs with 1 copy of the mutation are more likely to have variable disease; some will become quite sick while others will remain free of clinical signs. The mechanism for the variability in clinical signs is unknown but is thought to be associated with the concurrent inheritance of other genetic factors. Dr. Meurs' research will determine if additional genetic factors exist, thus greatly improving our ability to use and interpret the genetic test for the striatin mutation.

01760: Use of Gene Therapy to Treat Dilated Cardiomyopathy

Principal Investigator: Dr. Margaret M. Sleeper, VMD **Institution:** University of Pennsylvania

Total Grant Amount: $146,774.00

Grant Period: 1/1/2013 – 6/30/2015

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.

01898-A: Enhancing Diagnosis and Treatment of Cardiomyopathy Through Identification of Biological Markers of Disease

Principal Investigator: Dr. Suzanne M. Cunningham, DVM **Institution:** Tufts University

Total Grant Amount: $12,960.00

Grant Period: 2/1/2013 – 1/31/2015

Project Abstract:

Cardiomyopathy is a common heart disease associated with irregular heart rhythm (arrhythmia), cardiac dilation, or both. The recent discovery of a mutation in the striatin gene in dogs with cardiomyopathy allows us to identify carrier animals that are at increased risk for developing the disease. However, genetic tests are imperfect and genetic screening usually entails a combination of family history, genetic testing, Holter monitoring and echocardiographic findings. Dr. Cunningham hypothesizes that dogs with cardiomyopathy will have increased levels of a cardiac biomarker known as NT-proBNP and inflammatory markers when compared to healthy dogs, and that these changes will be more profound in dogs with cardiac dilation. The results of this study are anticipated to improve our understanding of cardiomyopathy in the dog, and to open exciting new avenues for screening and treatment of affected dogs.

01982: Personalized Medicine: The Intersection of Genotype and Drug Responsiveness in the Treatment of Canine Pulmonary Hypertension

Principal Investigator: Dr. Joshua A Stern, DVM, PhD* **Institution:** University of California, Davis

Total Grant Amount: $27,971.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Genetic background is thought to alter the way animals and humans respond to disease and drug therapy. The unique DNA signature of an individual is now recognized as a pivotal influence on disease outcome during treatment and has become the central concept propelling the study of pharmacogenomics and individualized medicine. Dr. Stern will apply this cutting-edge knowledge to pulmonary hypertension in dogs, a common disease with serious consequences including exercise intolerance, respiratory distress, and sudden death. Dr. Stern has identified a mutation in the gene phosphodiesterase 5A (PDE5A), the target of a drug called sildenafil, and believes this mutation may influence

responsiveness of dogs to the drug. Dr. Stern will evaluate the responsiveness of dogs to sildenafil through pre- and post- echocardiogram, identification of biological markers of disease, and quality of life questionnaires. Differences between treatment responses will be compared to genotype. He aims to establish a diagnostic test that allows clinicians to make treatment recommendations on a personalized basis and tailor the therapeutic approach to treatment of pulmonary hypertension.

01994: Early and Accurate Prediction of Mitral Valve Disease Development

Principal Investigator: Dr. Sydney N. Moise, DVM **Institution:** Cornell University

Total Grant Amount: $36,881.00

Grant Period: 1/1/2014 – 12/31/2014

Project Abstract:

In the dog, 75% of heart disease is caused by myxomatous mitral valve degeneration (MMVD). The cause of MMVD remains incompletely defined but likely involves the interplay of genetics, aging, and mechanical damage. A dog's mitral valve opens and closes approximately 120,000 times per day under a constant barrage of mechanical forces. With such stress, the struggle of the valvular tissue to stay 'normal' is constant. Dr. Moise hypothesizes that dogs that suffer from MMVD have an altered structure of the mitral valve apparatus, which in turn is linked to breed size and/or cartilage development. Using a computer algorithm to assess the motion of the mitral valve leaflets, Dr. Moise and colleagues will define the mechanical signatures of valvular strain. They believe that these signatures are identifiable at a young age in the breeds most commonly affected with MMVD. A quantitative understanding of mitral leaflet strain will both improve our ability to predict MMVD susceptibility and increase the power and resolution of gene mapping efforts, and if successful, will inform new targets and timelines for therapeutic intervention.

02046: Using a Novel Combination of Drugs to Treat Arrhythmia and Heart Failure in Dogs

Principal Investigator: Dr. Janice McIntosh Bright, DVM, BSN **Institution:** Colorado State University

Total Grant Amount: $33,060.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Atrial fibrillation is a common heart rhythm abnormality (arrhythmia) in dogs. This arrhythmia affects all dog breeds and frequently coexists with heart failure causing worsening of disease and high mortality. Atrial fibrillation may be managed by administering drugs to slow heart rate or by restoring normal rhythm (cardioversion). Dr. Bright will evaluate dogs with naturally occurring atrial fibrillation and heart failure for their responsiveness to two drugs -- amiodarone, an antiarrhythmic agent, and ranolazine, a drug used in humans with coronary heart disease. She will determine whether ranolazine given with amiodarone prolongs normal rhythm compared to amiodarone alone and whether ranolazine also improves heart function. Results will validate combined ranolazine/amiodarone administration as an improved new treatment for atrial fibrillation in dogs with heart failure, extending their quality of life.

02086: Defining the Genetic Basis of Myxomatous Mitral Valve Disease

Principal Investigator: Dr. Mark A. Oyama, DVM **Institution:** University of Pennsylvania

Total Grant Amount: $43,563.00

Memorandum of Understanding Grant with the Friends of Norfolk Terriers

Grant Period: 3/1/2014 – 2/28/2015

Project Abstract:

Myxomatous mitral valve disease (MMVD) is a slowly progressive condition in which the mitral valve thickens, resulting in an imperfect seal between the chambers of the heart. This allows blood to "leak" backward into the atrium as the ventricle contracts and leads to impaired cardiac function. Risk of disease increases with age and is most common in small to medium sized dogs. Dr. Mark Oyama, working in collaboration with Dr. Kate Meurs, will identify single nucleotide polymorphisms associated with myxomatous mitral valve disease (MMVD) in the Norfolk Terrier using genome-wide association studies (GWAS). These investigators believe that GWAS will help narrow down the number of possible disease genes, enabling them to identify risk factors that can be used in informed breeding programs and for veterinary cardiologists to better manage clinical cases. It is anticipated that identification of risk factors in the Norfolk Terrier will inform focused gene searches in additional breeds that are similarly at greater risk of developing MMVD.

02101: Whole Genome Sequencing for Great Dane Dilated Cardiomyopathy

Principal Investigator: Dr. Kathryn M Meurs, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $27,134.00

Memorandum of Understanding Grant with the Great Dane Club of America

Grant Period: 7/1/2014 – 6/30/2015

Project Abstract:

Dilated cardiomyopathy (DCM), a primary heart muscle disorder characterized by poor cardiac function, is thought to be inherited in the Great Dane. Therapy does not cure the disease or even successfully control the clinical signs. The inability to effectively treat the disease has led to increased interest in disease prevention by careful selection of unaffected dogs for breeding. However, since DCM is an adult onset disease many dogs are selected for breeding before they develop the disease, inadvertently passing it on to their offspring. A genetic test that could identify affected animals before they are used for breeding would greatly decrease the prevalence of DCM.

In this study, Dr. Meurs will utilize a whole genome sequencing approach for evaluation of this disease. She hopes that ultimately the identification of a genetic cause for DCM in the Great Dane can be used to reduce the prevalence of this disease. In addition, it is also very likely to provide information on DCM in other breeds of dogs by improving our overall understanding of the disease in the dog. The identification of a genetic marker linked to DCM will be the first step in the development of a genetic screening test that can be used in Great Danes of breeding age.

02147: Use of MicroRNA Profiles in the Serum of Dogs For Early diagnosis of Mitral Valve Disease and Dilated Cardiomyopathy

Principal Investigator: Dr. Gerhard Wess, PhD **Institution:** Ludwig-Maximilians-Universitaet Muenchen

Total Grant Amount: $24,850.00

Collaborative Project with Zoetis

Grant Period: 2/1/2015 – 1/31/2016

Project Abstract:

Mitral valve dysfunction is a common cardiac disease in dogs, especially in small breeds < 20 kg. Diagnosis is made using echocardiography. As for other cardiac diseases, reliable serum markers for a quick and easy diagnosis are in great demand. MicroRNAs are small molecules that are naturally produced by all cells and are known to regulate many cellular reactions. They can be detected in every body fluid, even in samples stored for years, since they are very stable. In human patients suffering from diabetes, heart attack or cancer, specific MicroRNAs have been found to be either elevated or reduced in the serum compared to healthy individuals. In a clinical setting, the use of these molecules as disease markers is still in its infancy. To prove their applicability as diagnostic or prognostic parameters, rigorous studies have to be conducted. For the health of companion animals, reliable diagnostic markers are just as essential as they are for humans. MicroRNA molecules are very similar between humans and mammals, making it possible to use the same tests and to compare results across species. MicroRNAs in the serum of both human and canine patients with mitral valve disease have not been studied. This project aims to find MicroRNAs in the serum of dogs that could be used as specific diagnostic markers for mitral valve disease. To corroborate the specificity, a group of dogs with a different heart disease, dilated cardiomyopathy, will also be included.

02160: Identification of Genetic Variants Associated with Myxomatous Mitral Valve Degeneration in the Whippet Dog Through Whole-Genome Sequencing

Principal Investigator: Dr. Joshua A Stern, DVM, PhD **Institution:** University of California, Davis

Total Grant Amount: $23,188.00

Project Abstract:

Myxomatous mitral valve degeneration (MVD) is one of the most common heart diseases in dogs. MVD leads to structural heart changes and congestive heart failure, making this disease one of high morbidity and mortality. The Whippet breed is overrepresented in cases of MVD and pedigree analysis suggests this to be an inherited condition in this breed. Longitudinal clinical investigations into Whippet dog MVD reveals that Whippets frequently suffer from this common disease and may be affected at a significantly younger age than the general dog population.

Dr. Stern's proposed study will complete the next phase of his ongoing genetic studies of MVD in Whippets and utilize prospective cardiac screenings already completed at the Whippet National Specialty and stored affected and unaffected DNA samples. Genome wide association studies performed by the investigators have already provided chromosomal regions of interest most likely to contain disease-associated variants within genes or micro-RNAs. DNA samples will be used to complete whole genome sequencing and identify variants of interest that segregate with disease.

Identification of genetic markers associated with MVD in Whippets would facilitate discovery of a causative mutation and ultimately enable genetic testing and reduction of disease prevalence in this breed. Additionally, identification of the molecular basis of MVD may help elucidate novel therapeutic or testing strategies in the treatment and management of this condition.

Funding for this research is provided through the efforts and generosity of the Whippet Health Foundation and the American Whippet Club.

02163: Is Hypothyroidism a Contributor to Progression of Arrhythmogenic Right Ventricular Cardiomyopathy?

Principal Investigator: Dr. Kathryn M Meurs, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $50,857.00

Memorandum of Understanding Grant with the American Boxer Charitable Foundation

Grant Period: 1/1/2015 – 12/31/2016

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. Dr. Meurs' research group identified a causative mutation in the cardiac Striatin gene that is highly associated with the development of Boxer ARVC. They 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 that individual dog which could include genetic or other more external factors including diet, exercise and hormonal levels.

Genetic factors could include common variants in the nucleotide sequence of other cardiac modifying genes that have been shown to influence the severity of cardiac diseases. In addition, endocrine issues like hypothyroidism complicate ARVC and may play a role in disease progression. Dr. Meurs hypothesizes that low thyroid levels and/or other genetic variants may lead to the development of the more severe form of Boxer ARVC. Understanding the role of these factors in the severity of disease will greatly improve the ability to manage the common and sometimes fatal heart disease of ARVC.

Funding for this 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 administration of funds and scientific progress reporting.

Dermatology & Allergic Disease Research Program Area

02111-A: Evaluating the Contribution of Fungal Infection to the Pathogenesis of Atopic Dermatitis: Putting Evidence Under the Use of Antifungal Medication

Principal Investigator: Dr. Jan S Suchodolski, DVM, PhD* **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $12,960.00

Grant Period: 6/1/2014 – 5/31/2015

Project Abstract:

Fungi are established agents of disease in dogs and are thought to exacerbate inflammatory and allergic diseases such as atopic dermatitis (environmental allergies). In order to fully understand the role of fungi in these diseases we must first have a comprehensive picture of the commensal fungi living on the skin of dogs and then begin to decipher how these communities change when disease is present. DNA sequencing technologies can provide a more accurate status of commensal fungi residing on canine skin than what has been previously shown with traditional culture based methods. Dr. Suchodolski proposes to use next-generation DNA sequencing to investigate the fungal microbiome, or mycobiome, of healthy canine skin. They will then compare the mycobiome of healthy canine skin to that of dogs with allergic skin disease. This will provide insight into the involvement of fungi in atopic dermatitis as well as reveal fungal genera that may serve as opportunistic pathogens and potential targets for therapeutics in this chronic skin disease that affects both the canine pets who suffer from severe pruritus (itch) and their owners who must provide long-term and costly care.

02116-A: Establishing Best Practices in the Treatment of Atopic Dermatitis to Prevent Antimicrobial Resistance

Principal Investigator: Dr. Shelley Rankin, PhD* **Institution:** University of Pennsylvania

Total Grant Amount: $12,312.00

Grant Period: 6/1/2014 – 1/31/2015

Project Abstract:

Atopic dermatitis (AD/Allergic skin disease) is a common condition affecting approximately 10% of the canine population, with strong breed predilections. Affected dogs often succumb to recurrent bacterial skin infections, namely by *Staphyloccus species*. As in human medicine, one of the major obstacles in treating these infections is combating antimicrobial resistance. Frequently, multidrug resistant (MDR) bacteria are encountered and limited treatment options are available. These resistant bacteria can also be transferred between pets and their owners. Though a common clinical threat, knowledge of how resistance is acquired by bacteria warrants further investigation. Are MDR bacteria present on the skin at the onset of infection or do they evolve with the selective pressure of treatment?

Current technologies provide sensitive means of detection of mechanisms of resistance, but this has yet to translate into tools for clinical practice. Genetic and genomic analysis of bacterial swabs acquired from dogs with AD and concurrent skin infections and from normal dogs will be compared to current laboratory culture techniques. Sampling dogs before, during, and after treatment will allow Dr. Rankin and her team to predict the effect of treatment on bacterial acquisition of antimicrobial resistance. This study will provide a framework for implementation of new technologies in clinical practice, and give insight into how antimicrobial resistance develops overtime.

Endocrinology Research Program Area

01602: Defining the Cause of Hyperadrenocorticism

Principal Investigator: Dr. Kurt Zimmerman, DVM, PhD **Institution:** Virginia-Maryland Regional College of Veterinary Medicine

Total Grant Amount: $66,226.00

Grant Period: 1/1/2012 – 3/19/15

Project Abstract:

Hyperadrenocorticism (HAC) is a chronic debilitating disorder in dogs and contributes to the development of negative health and behavior outcomes including diabetes mellitus, obesity, musculoskeletal weakness, immune system dysfunction, and inappropriate urination. Increased serum alkaline phosphatase (ALP) activity and increased noncortisol steroids are associated with HAC. Using Scottish Terriers (due to their predisposition to atypical HAC), Dr. Zimmerman will: 1) determine if the severity of the HAC increases over time; 2) determine if HAC is due to a functional problem of the brain or adrenal gland itself; and 3) determine if there is a problem with steroid production in the adrenal gland. It is hoped these efforts will help us understand breed predisposition to developing atypical HAC and how to best treat and screen for this disorder.

02011: Identification of Novel Drugs to Halt the Metastasis of Tumors That Cause Cushing's Syndrome

Principal Investigator: Dr. Sara Galac, DVM, PhD **Institution:** University of Utrecht

Total Grant Amount: $41,700.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Tumors of the adrenal gland that lead to Cushing's syndrome are characterized by excessive cortisol secretion which in turn causes these tumors to be aggressive and rapidly metastasize. Recently, a critical role of steroidogenic factor (SF-1) in adrenal tumor formation has been demonstrated. Elevated SF-1 levels trigger tumor formation in mice and are associated with poor prognosis in humans and dogs. Blocking SF-1 with medical compounds (SF-1 inverse agonists) may suppress both tumor growth and cortisol production, thus enhancing the ability of veterinary surgeons to successfully remove adrenocortical tumors and prevent metastasis. In this study, Dr. Galac will obtain adrenal cancer cells from dogs after adrenal surgery and culture these tumors with SF-1 inverse agonists. The effect of these SF-1 agonists on cortisol production and cell growth will be evaluated, and if drugs are found to suppress cortisol production, Dr. Galac predicts they can enter the drug pipeline for the treatment of canine adrenal cancer. Due to the similarities with adrenal cancer in humans, the results of this study could be applied to human medicine.

Despite a sufficient understanding of the mechanisms underlying acquired canine hypothyroidism, diagnosis of the disease is not straightforward and remains one of the greatest challenges in veterinary medicine. Age, breed and systemic illness all affect thyroid hormone concentrations, and clinical signs of hypothyroidism are often indistinguishable from other diseases. As such, consensus opinion is that hypothyroidism is commonly over-diagnosed in the dog. In an effort to support veterinarians in the evidence-based practice of medicine, the AKC Canine Health Foundation approved a grant to improve diagnosis of canine hypothyroidism for all breeds.

02138: Development of Accurate Diagnostic Tests for Canine Hypothyroidism

Principal Investigator: Dr. Jan A Mol, PhD **Institution:** University of Utrecht

Total Grant Amount: $48,195.00

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Primary hypothyroidism is one of the most common endocrine disorders in dogs. The insufficient secretion of thyroid hormones may result in severe physical and mental changes, such as lethargy, alopecia, obesity, decreased cardiac output, and decreased renal perfusion. The diagnosis of hypothyroidism is sometimes problematic. The circulating thyroxin (T_4) concentration is below the reference range in most dogs with primary hypothyroidism, but T_4 is not very specific as it can also be low in sick dogs with a normal thyroid function, i.e., dogs with non-thyroidal illness (NTI). However, a combination of a low T_4 concentration and a clearly elevated plasma thyroid stimulating hormone (TSH) concentration is definitive proof of hypothyroidism. Unfortunately, about 30% of dogs with primary hypothyroidism have a TSH concentration within the reference range and therefore cannot be distinguished from dogs with NTI. Consequently, either dogs with NTI are unnecessarily treated with thyroxin supplementation or dogs with primary hypothyroidism may lack proper treatment. Dr. Mol and colleagues propose to investigate 3 methods that may provide a more accurate diagnosis than the currently available tests for practitioners. They will test whether 1) a stimulation test with measurements of plasma growth hormone and TSH concentrations, 2) the plasma TRH or ghrelin concentration, or 3) a reporter assay for plasma thyroid hormone bioactivity, can be used to differentiate between dogs with primary hypothyroidism and dogs with NTI.

The seizure-related syndromes collectively known as epilepsy represent one of the most common neurological disorders in dogs, and as such are a significant concern to the AKC Canine Health Foundation and our donors. In response to donor concern, CHF launched a major, two phase research effort to better classify disease, understand the underlying mechanisms that predispose dogs to epilepsy, and finally, to introduce new drugs into the canine epilepsy treatment pipeline. Because these grants represent a major, long term investment for our donors we required the formation of collaborative pre-clinical/clinical research groups who will work together to define the molecular basis of epilepsy and develop disease modification or prevention strategies. Our goal is to accelerate the discovery phase and thus the translation of research from laboratory bench to patient so that we can rapidly improve patient outcomes.

Epilepsy Research Program Area

01896-A: A Pilot Study: Establishing the Role of Melatonin in the Occurrence of Seizures in Dogs

Principal Investigator: Dr. Stephanie Ann Thomovsky **Institution:** Washington State University

Total Grant Amount: $3,000.24

Grant Period: 7/1/2013 – 12/31/2014

Project Abstract:

Epilepsy or recurrent seizures is reported to be the most common neurologic condition in dogs. Of dogs affected with seizures, 20-30% are considered to be resistant to the commonly used canine anticonvulsant drugs. Alternative canine epilepsy treatments are desperately needed. Recent advances in animal models suggest the hormone melatonin may have significant anti-seizure effects. Human case reports indicate that melatonin levels increase during and immediately following seizure activity but are significantly lower than normal between seizures. The central hypothesis of Dr. Thomovsky's study is that serum and cerebrospinal fluid (CSF) levels of melatonin will be lower in dogs with seizures than in normal dogs. If data are in the affirmative these investigator will design future studies that examine the use of melatonin supplementation as a means of abrogating seizures in dogs.

02131: Neurostimulation: A Groundbreaking New Treatment for Canine Epilepsy

Principal Investigator: Dr. Sam Nicholas Long, PhD **Institution:** The University of Melbourne

Total Grant Amount: $116,000.00

Grant Period: 10/1/2014 – 9/30/2016

Project Abstract:

Epilepsy is a debilitating condition that affects a large number of dogs, resulting in premature death and distress for their owners. For many dogs the underlying cause is unknown. In people, advances in some types of imaging have identified subtle abnormalities, including abnormal development and shrinkage of particular regions in the brain of some people with epilepsy that can be surgically removed to improve the control of seizures. This project will apply the same advanced techniques to the brains of dogs with epilepsy to determine whether those same abnormalities exist in dogs. In those dogs in which no abnormalities can be found, this project will investigate a new form of treatment, known as neurostimulation which has been shown to reduce the frequency of seizures dramatically in human clinical trials. This involves surgically implanting a new, highly sophisticated device called the Brain Radio that can provide controlled electrical stimulation to parts of the brain while simultaneously recording the brain's activity. This device is one of the very first that could potentially provide successful therapy only when needed to treat imminent seizures and if it proves successful in dogs it will enter clinical trials in people with epilepsy.

02133: Canine Epilepsy: Genetic Variants, Biomarkers, and New Therapies

Principal Investigator: Dr. Ned E. Patterson, DVM PhD* **Institution:** University of Minnesota

Total Grant Amount: $104,781.00

Grant Period: 10/1/2014 – 9/30/2015

Project Abstract:

Epilepsy is a significant seizure disorder affecting all dog breeds. It is the most common chronic nervous system disorder in dogs, with a prevalence of 0.5% – 5.7%, resulting in approximately 2 million affected dogs in the USA. Dr. Patterson has assembled a trans-disciplinary team to attempt to improve the fate of dogs that have epilepsy with a special emphasis on dogs with drug-resistant epilepsy. Dog with drug-resistant epilepsy have frequent seizures even when on 2 or more anti-epileptic drugs. The team includes Veterinarians, Canine Geneticists, Pharmacologists, Human Neurologists, Basic Scientists and Biomedical Engineers from the University of Minnesota College of Veterinary Medicine, College of Pharmacy, Institute for Engineering in Medicine, and Departments of Neurology and Surgery, and Mayo Clinic in Rochester, MN. Under the guidance of Dr. Ned Patterson, the collaborative group proposes to evaluate traditional DNA genetic markers, blood biomarkers called microRNAs (miRNAs), and potential new drugs for the emergency treatment of seizures in dogs.

In phase 1 of Dr. Patterson's study he and his team will 1. Identify genetic markers associated with epilepsy in Australian shepherds and Vizslas, and identify markers associated with epileptic dogs that are unresponsive to anti-epileptic drug therapy in order to develop genetic screening tests in phase 2; 2. Document microRNA levels in the blood of dogs with epilepsy in order to develop potential blood markers that vary between epileptic and non-epileptic dogs, and dogs with drug-resistant epilepsy; and 3. Perform initial testing of two new potential drugs for the emergency treatment of canine epilepsy.

Gastrointestinal Disease Research Program Area

01609: Use of Probiotic to Reduce the Symptoms of Inflammatory Bowel Disease

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

Total Grant Amount: $97,416.00

Grant Period: 1/1/2012 – 12/31/2014

Project Abstract:

Idiopathic inflammatory bowel disease (IBD) is a common cause of chronic gastrointestinal disease in dogs. Accumulating evidence in human IBD and animal models suggests that imbalances in composition of the intestinal microbiota contribute to the pathogenesis of chronic intestinal inflammation. Recent studies have also shown that dogs with IBD have distinctly different duodenal microbial communities compared to healthy dogs. Current treatments for IBD include the administration of nonspecific anti-inflammatory drugs which may confer serious side effects and do not address the underlying basis for disease, namely, altered microbial composition. Use of probiotics (viable, non-pathogenic bacteria that exert health benefits beyond basic nutrition) offers an attractive, physiologic, and non-toxic alternative to shift the balance to protective species and treat IBD. The aim of the proposed study is to investigate the clinical, microbiologic, and anti-inflammatory effects of probiotic VSL#3 in the treatment of canine IBD. These studies will provide highly relevant insight into the anti-inflammatory effects of probiotics for treatment of human and canine IBD.

01930-A: Development of Minimally Invasive Laparoscopic Surgery as a Definitive Diagnostic Tool for Gastrointestinal Obstruction

Principal Investigator: Dr. J. Brad Case, DVM, MS **Institution:** University of Florida

Total Grant Amount: $12,960.00

Grant Period: 7/1/2013 – 12/31/2014

Project Abstract:

Gastrointestinal (GI) foreign bodies are very common in dogs, particularly in sporting breeds that are prone to chewing. Foreign bodies cause blockage of the GI tract and can result in life-threatening complications, namely septic peritonitis (abdominal infection), which carries a mortality rate of 40-60%. Diagnosis of GI obstruction is often difficult. Radiography (x-rays) and ultrasound are commonly performed in dogs with GI disease but an obstruction can be obscured by the presence of gas-filled bowel. Frequently, exploratory surgery becomes the only means to accurately diagnose an obstruction, and complications of GI surgery include pain, infection, septic peritonitis, death, and prolonged hospitalization. Dr. Case proposes to establish the accuracy of laparoscopic-assisted gastrointestinal exploration in dogs suspected of having a gastric and/or intestinal disease/obstruction. Laparoscopy is a technique that uses small (5-10 mm) cameras and instruments to perform surgery through small incisions, and has the potential to reduce GI surgery complications. A growing body of evidence demonstrates laparoscopy in dogs reduces pain, infection rates, and complications when compared to traditional surgery. Results from this study will help to improve diagnostic accuracy and minimize morbidity and pain in dogs undergoing surgery for GI obstruction.

01935-B: Abnormalities in the Stomach's Ability to Contract Predisposes Large-Breed Dogs to Bloat

Principal Investigator: Dr. Laura L. Nelson, DVM* **Institution:** Michigan State University

Total Grant Amount: $233,774.00

Grant Period: 1/1/2014 – 12/31/2015

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. The goals of Dr. Nelson's study are to determine the relationship of abnormal stomach contraction with GDV and to define the biochemical and genetic alterations that may be associated with these stomach abnormalities. In the long term, they hope to develop a test to identify dogs at high risk for GDV that would allow selective breeding to eliminate the condition and to determine which dogs will benefit most from prophylactic gastropexy or other preventive therapies.

01937-B: Evaluating the Complex Genetic Basis of Bloat

Principal Investigator: Dr. Claire Rebecca Sharp, BVMS* **Institution:** Tufts University

Total Grant Amount: $251,097.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Gastric dilatation and volvulus (GDV), or bloat, is a common condition in large and giant breed dogs with an unacceptably high morbidity and mortality rate. Due to the importance of GDV in many dog breeds, several previous studies have investigated potential risk factors for the development of GDV. It is known that there is no single cause for GDV, rather its occurrence is multifactorial, with both genetic and environmental factors contributing. Dr. Sharp proposes to further investigate how these risk factors cause GDV through the application of genomic and molecular methods. She will do this by analyzing samples from purebred dogs with GDV and comparing them to dogs of similar age and breed that have not developed GDV. She will perform a genome wide association study (GWAS) to identify differences in the genetic makeup of dogs with GDV, and see which genes are turned on and off in GDV (epigenomics). She will also determine if dogs with GDV have different types or amounts of proteins, hormones and other molecules in their blood and tissues (transcriptomics, proteomics and metabolomics). She and collaborators hypothesize that only when we put all of this information together (genomic, epigenomic, transcriptomic, proteomic and metabolomic) will we truly understand what causes GDV. The ultimate aim of understanding what causes GDV is to allow us to best intervene to prevent the disease from occurring.

02002: Defining the Genetic Basis of Inflammatory Bowel Disease

Principal Investigator: Dr. Karin Allenspach, DVM, PhD **Institution:** Royal Veterinary College, University of London

Total Grant Amount: $119,268.00

Grant Period: 10/1/2014 – 9/30/2016

Project Abstract:

Inflammatory Bowel Disease (IBD) is a group of disorders in which the intestinal tract has become invaded with the dog's own white blood cells leading to inflammation. Over time, this inflammation causes the intestine to become less efficient at absorbing nutrients from digested food and weight loss, and vomiting or diarrhea often result. IBD can be controlled, but not cured. The cause of IBD is poorly understood, but it appears that genetics, diet, intestinal bacteria, and abnormalities of the dog's immune system all play a role. Dr. Allenspach has recently identified genetic markers known as SNPs (single nucleotide polymorphisms) which she believes contribute to disease susceptibility. Beyond genetics, this research group has mechanistic data showing one of the putative mutations contributes to the inflammation seen in the intestine of dogs with IBD. In order to find all underlying genetic factors that could contribute to disease, they propose to perform a genome-wide association study. This study will lead to the development of new diagnostic and therapeutic avenues for canine IBD as has already been the case in people with IBD.

02050: Defining the Genetic Susceptibility to Granulomatous Colitis, a Severe Form of Inflammatory Bowel Disease

Principal Investigator: Dr. Kenneth W. Simpson, BVMS, PhD* **Institution:** Cornell University

Total Grant Amount: $187,730.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Granulomatous colitis is a severe inflammatory bowel disease (IBD), usually diagnosed in young dogs. Affected dogs present with hemorrhagic diarrhea, often progressing to weight loss and debilitation. Recent studies have identified invasive *Escherichia coli (E. coli)* bacteria within macrophages in the inflamed large intestine, and eradication of E.coli induces dramatic clinical and histologic improvement. Unfortunately, the emergence of antimicrobial resistance has greatly reduced our ability to treat this disease, and persistently affected dogs are frequently euthanized. The type of *E.coli* isolated from dogs with granulomatous colitis is very similar to adherent and invasive *E. coli* (AIEC) associated with IBD in people. This type of *E.coli* are considered opportunistic pathogens that can exploit genetic defects in bacterial killing in an IBD susceptible individual. Dr. Simpson suspects this is due to a heritable abnormality that confers susceptibility to invasion and persistence of *E.coli*. In preliminary studies his research group has identified a region of the canine genome that is associated with *granulomatous colitis* affected dogs. This region contains candidate genes associated with IBD in people and mouse models, and has been specifically linked to sensing and killing of *E.coli*. The purpose of this study is to identify the gene(s), causal variant(s) and cellular pathways involved in the development of granulomatous colitis. This would enable the development of screening tests to eradicate this disease, and advance understanding of the development of IBD in dogs and people.

General Canine Health & Obesity Research Program Area

01827: Defining the Specific Species of Bacteria that Contribute to Canine Periodontal Disease

Principal Investigator: Dr. Marcello Pasquale Riggio, PhD **Institution:** University of Glasgow

Total Grant Amount: $31,000.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Extensive studies have led to the consensus opinion that specific bacteria cause periodontal disease in humans. In contrast, we know very little about the underlying cause of gum disease in dogs, despite its high prevalence and associated pain. To overcome this gap in knowledge, Dr. Riggio will use cutting edge laboratory technology (known as 'high-throughput deep sequencing') to provide an in-depth understanding of the types of oral bacteria in dogs with periodontal disease vs. dogs without disease. This method detects the DNA of live bacteria and allows bacteria to be identified and quantitated without the need to grow them from clinical samples. This study will give us the most up to date knowledge on gum disease in dogs and will help in the development of vaccines and improved treatment methods for canine periodontal disease.

01943-A: In Support of Our Working Dogs: Medical Surveillance of Dogs Deployed to the World Trade Center and the Pentagon 2013-2014

Principal Investigator: Dr. Cynthia M. Otto, DVM, PhD **Institution:** University of Pennsylvania

Total Grant Amount: $12,960.00

Grant Period: 6/1/2013 – 5/31/2015

Project Abstract:

In its twelfth year, the 9/11 Medical Surveillance Study continues to follow the surviving dogs. Of the initial group consisting of 95 deployed and 55 non-deployed search and rescue dogs, 9 deployed dogs and 12 control dogs remain. As these dogs age Dr. Otto will be placing emphasis on health issues occurring in later years of life. Dr. Otto's goal is to obtain a complete picture of causes of death and incidences of cancer so that the long-term impact of September 11th will become visible. This vital information will provide the most inclusive understanding of the impact of the deployment on long-term canine health and will be critical to the future tactics employed in Search and Rescue missions.

02103-A: Development of an Effective Canine Periodontal Disease Vaccine

Principal Investigator: Dr. Paola Massari, PhD **Institution:** Boston Medical Center

Total Grant Amount: $12,960.00

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Eighty percent of dogs will experience some form of periodontal disease in their lifetime. Halitosis (bad breath) is a minor side effect of disease, but in its more severe form disease can cause gum inflammation, oral bone and tooth loss, all of which are painful and debilitating. Current treatment options include manual removal of plaque and tartar; however, this only delays disease progression and often must be supplemented with antibiotics, anti-inflammatory and pain medications. Periodontitis is caused by infection with oral pathogens including *Fusobacterium* nucleatum and *Porphyromonas* gulae. The most effective targeted interventions against periodontal pathogens will be through effective immunization, directing a dog's own immune system to combat the bacteria responsible for disease. At the current time research efforts on vaccine strategies against canine periodontitis are still scarce compared to human disease. Dr. Massari proposes a novel vaccine containing purified *Fusobacterium* nucleatum and *Porphyromonas* gulae bacterial proteins. She believes that dogs immunized with these bacterial proteins and an effective adjuvant (immune enhancer) will generate antibodies against the pathogens. Further, her research group believes that the ideal adjuvant must enhance vaccine efficacy by driving an antibody-mediated response that will not cause cell-mediated inflammation, thereby preventing the exacerbation of oral tissue disruption and pain. Rigorous testing of efficacy and safety of this vaccine in a laboratory setting is required prior to immunization of animals. Therefore, Dr. Massari will conduct proof-of-principle studies with candidate antigens and adjuvants in cell culture, as well as conduct a laboratory mouse model study to determine if their candidate vaccine has the potential to prevent oral infection. This study will guide future studies for vaccine trials designed to prevent periodontal disease in dogs.

02161-A: Supporting the Evidence-Based Use of Antibiotic Gels After Extensive Dental Plaque Removal in Dogs

Principal Investigator: Dr. Django Martel, DVM **Institution:** The Animal Medical Center

Total Grant Amount: $12,156.00

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Canine periodontal disease (gum disease) is the most common cause of tooth loss and is a source of chronic bacterial infection, contributing to adverse health conditions including kidney failure and endocarditis. Treatment options are limited and their benefits remain uncertain due to a lack of evidence-based research. The cause of canine periodontal disease is accumulation of plaque under the gum line that leads to inflammation and progressive erosion of normal periodontal structures, including the gums, tooth root and supporting facial bones. The first step in the evolution of gum disease is development of a periodontal "pocket;" a gap between the gum line and tooth margin that traps food and bacteria and promotes continued destruction of these supporting structures. In healthy gums the depth of the periodontal space measures less than 2 millimeters. With periodontal disease this space becomes larger, and consensus opinion is that deep pockets promote rapid progression of gum disease. Detection of mild pockets (measuring 3-5 mm) indicates that dental disease is present and progressing. A treatment technique called root planning (deep plaque removal) can slow the deepening of periodontal pockets, and veterinarians often consider use of local antibiotic gel therapy placed into the pockets after root planning under the assumption that they retard plaque regrowth and potentially reduce pocket depth. However, this benefit has not been clearly demonstrated in the dog through studies funded independent of corporate-sponsored studies. Dr. Martel and colleagues will establish whether the use of antibiotic gel therapy (doxycycline hyclate gel or clindamycin hydrochloride hydrogel) reduces periodontal disease and provide veterinarians with the evidence needed for effective periodontal disease management.

Hepatic Disease Research Program Area

01986: Profiling the Metabolic and Lipid Imbalances that are Causative of Gallbladder Disease in Dogs

Principal Investigator: Dr. Jody L. Gookin, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $135,354.00

Grant Period: 1/1/2014 – 12/31/2015

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, Dr. Gookin hypothesizes these dogs have a unique disturbance in cholesterol or lipid metabolism. If the cause of this disturbance can be identified we will be able to understand why GBM form, develop tests for early diagnosis and design diets or drugs to prevent GBM formation.

Immunology & Infectious Disease Research Program Area

01699-A: Preventing Inaccurate Diagnosis of Brucellosis

Principal Investigator: Dr. Christina M Larson, DVM **Institution:** University of Minnesota

Total Grant Amount: $10,567.00

Grant Period: 3/1/2012 – 8/30/2015

Project Abstract:

Brucellosis testing is often made difficult due to the fact that the most commonly-used Brucellosis test, the Rapid Slide Agglutination Test (RSAT) also gives false positive results when the dog has recently experienced a bacterial infection due to Bordetella bronchiseptica, which is one of the common causes of kennel cough. Vaccinating the dog by injection of Bordetella (kennel cough) vaccine is likely to cause false positive results on the RSAT. This study will evaluate whether false positive RSAT results are obtained after vaccinating the dog via nasal spray with a commercially-available Bordetella (kennel cough) vaccine.

01771: Defining the Unique Genetic Markers in Dogs That Define Immune Function, Disease Resistance and Tissue Transplantation

Principal Investigator: Dr. Beverly Torok-Storb, PhD **Institution:** Fred Hutchinson Cancer Research Center

Total Grant Amount: $178,200.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

The Major Histocompatibility Complex (MHC) genes encode proteins that are critical for a wide range of biological functions, from immune protection against infectious disease to the predisposition of an individual to develop diabetes and auto immune diseases. The MHC genes in the dog are incompletely characterized, thereby severely limiting our ability to full define the cause of many canine diseases. Dr. Torok-Storb has developed improved methods for identifying the different forms of canine MHC genes in a large number of dogs of diverse breeds. In this study he will characterize the patterns of MHC genetic variation in over 1200 dogs from at least 50 breeds using a high throughput sequencing strategy. The distribution and frequency of different forms of each of these genes and their specific clustering among different breeds will greatly enhance our knowledge of the genetic diversity among breeds. The methodology and data gained from this study will enhance the power of association studies between MHC types and canine diseases. Such a database will also enable tissue transplantation from unrelated but matched donors as a treatment for advanced malignancies (stem cell transplants) and other diseases (tissue transplantation). Fully defining the canine MHC will have broad impact across canine health, including oncology, immunology and infectious disease.

01780: Defining the Mechanism by Which Ticks Locate Dogs in Order to Better Prevent Disease Transmission

Principal Investigator: Dr. Emma Natalie Ivy Weeks, PhD **Institution:** University of Florida

Total Grant Amount: $104,867.31

Grant Period: 3/1/2013 – 8/28/2015

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.

01857-A: Decreasing the Mortality Rate of Shock Through Enhanced Monitoring of Tissue Oxygen Levels

Principal Investigator: Dr. Kelly Tart, DVM **Institution:** University of Minnesota

Total Grant Amount: $12,960.00

Grant Period: 7/1/2012 – 6/30/2015

Project Abstract:

Without medical intervention, dogs that develop shock from hemorrhage (e.g., trauma, hemangiosarcoma, gastrointestinal ulcers, etc.), severe dehydration or severe infection are at risk for organ failure and death. The ability to identify shock in veterinary patients is hampered by the diagnostic tests that are available to veterinarians. Standard monitoring (including blood pressure, heart rate, respiratory rate and pulse oximetry) provides insight into an animal's health status but is not specific for shock and has limited ability to guide patient treatment. More invasive methods for identifying and treating critical patients that are used in human medicine are often not financially feasible in the veterinary setting and require advanced training for placement and monitoring. A search for a more sensitive, non-invasive, readily available, and easy to use monitoring tool, is needed to better evaluate veterinary patients, guide therapy more appropriately and improve overall survival. The InSpectra Tissue Spectrometer which monitors tissue oxygenation is an emerging technology that may more effectively help veterinary clinicians identify patients with underlying shock and aid in directing therapy to resuscitate such patients. The objective of this study is to evaluate the use of the InSpectra Tissue Spectrometer as part of a goal directed therapy protocol. The pilot data obtained will be used to design further studies in dogs in an effort to improve outcome in dogs presenting to the emergency room in shock.

02102-A: Stopping Tick Infestation to Prevent Human and Canine Disease

Principal Investigator: Dr. Emma Natalie Ivy Weeks, PhD **Institution:** University of Florida

Total Grant Amount: $12,960.00

Grant Period: 4/1/2014 – 3/31/2015

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 transmit pathogens that cause canine Ehrlichiosis and Babesiosis as well as other diseases. Consensus opinion is that prevention of these diseases is best accomplished through tick population control. Because the BDT can lay 5000 eggs at one time and complete its entire lifecycle inside our homes, the current challenge facing dog owners is managing tick populations in the face of growing pesticide resistance. Alternatives to traditional pesticide applications are desperately needed.

Dr. Weeks will address this concern by taking advantage of the BDT Achilles' Heel: their predilection for hiding in cracks and crevices. She will evaluate direct application of products to hiding spots to determine if enhanced tick control can be achieved while simultaneously reducing broad environmental exposure to pesticides. Using a novel contact assay, Dr. Weeks will evaluate the effectiveness of a variety of desiccants, botanicals and conventional pesticides. The most effective products will then be tested in a crack-and-crevice assay to simulate a real-world application. The end goal is identification of a tick product that can control ticks in the environment while simultaneously enhancing safety for both dogs and their people.

02128-A: Redefining the Recommendations for Prevention of Infectious Disease at Dog Shows and Other Areas Where Dogs Meet and Compete

Principal Investigator: Dr. Jason Stull, VMD, PhD* **Institution:** Ohio State University

Total Grant Amount: $11,942.00

Collaborative Project with the Orthopedic Foundation for Animals

Grant Period: 7/1/2014 – 2/29/2016

Project Abstract:

The AKC Canine Health Foundation and the Orthopedic Foundation for Animals have a long standing commitment to supporting research that aims to prevent, treat, and cure canine disease. As the sport of dogs increases in popularity, we realized that one major gap in our current body of knowledge is how to reduce the risk of infectious disease spread at the intersection of the dog and the environment. Put another way, now that more and more large groups of dogs congregate at dog shows, agility events, field trials, animal shelters and dog parks, where are the risks and how should we manage them? To that end, Dr. Jason Stull and colleagues at the Ohio State University and Ontario Veterinary College will conduct a retrospective analysis of the veterinary infectious disease literature in order to provide updated recommendations for mitigation of risk of contraction of infectious disease at events where dogs congregate. Lead by Dr. Stull, this influential collaborative group of veterinary epidemiologists, infectious disease experts, immunologists, and internal medicine specialists will evaluate peer reviewed studies defining the incidence, clinical presentations, and outcomes of diseases; mechanism of infection, replication, spread and/or pathogenesis of diseases, computer modeling of disease transmission, characterization of susceptible cohorts for particular pathogens, and emerging concerns for novel pathogens to assess risk and develop management strategies. They will also include major stakeholders within the dog community in the process, guaranteeing that recommendations made at the outcome of this study will be practical and possible to accomplish in the 'real world'. The end result will be a peer-reviewed publication defining an up-to-date risk assessment and management recommendations, and most importantly, a white paper that can be used by dog owners and organizers of canine events and facilities. Finally, the researchers hope to create an open-access website that will be an interactive, living document, helping all those involved with dogs reduce the risk and spread of infectious disease where dogs meet and compete.

Research Team:

Jason W. Stull, VMD, MPVM, PhD, DACVPM (Public Health, Epidemiology), Principal Investigator

Armando Hoet, DVM, PhD, DACVPM (Public Health, Epidemiology)

Jeanette O'Quin, DVM, MPH (Public Health, Epidemiology)

Mary Jo Burkhard, DVM, PhD, DACVP (Immunology/Infectious Disease, Clinical Pathology)

Michelle Evason, DVM, DACVIM (Internal Medicine)

J. Scott Weese, DVM, DVSc, DACVIM (Infectious Disease, Internal Medicine)

Musculoskeletal Conditions & Disease Research Program Area

01584: Creation of a Conformation Score to Evaluate Susceptibility to Cranial Cruciate Ligament Disease

Principal Investigator: Dr. Dominique J. Griffon, DVM, PhD **Institution:** Western University of Health Sciences

Total Grant Amount: $34,000.00

Grant Period: 1/1/2012 – 12/31/2015

Project Abstract:

A torn ligament in the knee, known as cranial cruciate ligament deficiency (CCLD), is the leading cause of lameness affecting the knees of large breed dogs. The focus of Dr. Griffon's research is to establish a way to identify individual dogs that are susceptible to this problem and, ultimately, prevent CCLD. This research group previously developed a "CCLD conformation score" to differentiate limbs of Labradors with or without CCLD based on their characteristics. They later found that sound Labradors with a high "CCLD conformation score" displayed stride and body mechanics that could predispose them to CCLD. They now intend to evaluate the ability of this score to predict CCLD and explore the genetic origin of the disease in a large pet population.

01762: Use of Plasma-Derived Growth Factors to Heal Cruciate Rupture

Principal Investigator: Dr. Peter Muir, BVSc, PhD **Institution:** University of Wisconsin, Madison

Total Grant Amount: $160,246.00

Grant Period: 1/1/2013 – 6/30/2015

Project Abstract:

Cruciate rupture (CR) is a common degenerative condition of the canine knee (stifle). This economically important condition causes 20% of lameness in dogs and is disabling. Each knee contains two cruciate ligaments (cranial and caudal) that are located within the joint and stabilize the knee. Degeneration, fraying and progressive fiber rupture commonly affects both ligaments, but particularly the cranial or anterior cruciate ligament (ACL). Current surgical treatments stabilize the knee but do not directly treat the damaged or ruptured ligament. The main goal of Dr. Muir's research is to develop a safe and effective therapy that will prevent progressive tearing of ligament fibers, enable ligament healing, and block arthritis progression in affected dogs. To accomplish this goal, his research group will study a new regenerative medicine treatment using growth factors derived from a type of white blood cell, the platelet, concentrated from the patient's own blood. They will determine whether this treatment can promote cruciate healing and reduce progressive ligament rupture in dogs with early CR and clinically stable knees. Overall, this work promises improved outcomes for all dogs affected by CR disease.

01782: Defining the Elements of Successful Cranial Cruciate Ligament Repair

Principal Investigator: Dr. Gina E Bertocci, PhD **Institution:** University of Louisville

Total Grant Amount: $75,816.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Cranial cruciate ligament (CrCL) deficiency affects the canine stifle and is one of the most common orthopedic problems in dogs, having an economic impact of more than $1 billion in the US and a prevalence of 2.55% across all breeds of dogs. Some breeds have exceedingly high rates of CrCL deficiency, with Newfoundlands (8.9%), Rottweilers (8.3%), and Labrador Retrievers (5.8%) having the greatest prevalence of disease. Surgical intervention is the treatment of choice to stabilize the CrCL-deficient stifle, but no single surgical procedure has been shown to conclusively provide long-term joint stability and prevent the development of osteoarthritis. Dr. Bertocci proposes to investigate commonly employed surgical procedures (tibial plateau leveling osteotomy, tibial tuberosity advancement and extra-capsular stabilization) using her previously developed canine pelvic limb 3D computer model to gain an improved understanding of stifle biomechanics following CrCL-deficient stifle stabilization. She and her research team will investigate parameters specific to each surgical procedure using their novel computer model to further our understanding of stifle stabilization. Furthermore, they will investigate anatomical characteristics (e.g. tibial plateau angle) to gain an improved understanding of their role in the efficacy of surgical intervention. The outcome of this study will be a biomechanical, evidence-based assessment of the currently used stifle stabilization surgical procedures.

01828: Mapping of Genetic Risk Factors for Canine Hip Dysplasia

Principal Investigator: Dr. Antti Iivanainen, DVM, PhD **Institution:** University of Helsinki and the Folkhälsan Institute of Genetics

Total Grant Amount: $79,488.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Canine hip dysplasia is a common developmental disorder of the hip joint that severely affects a dog's quality of life. As the disease has several genetic risk elements and is influenced by environmental factors like diet and exercise, it is of paramount importance that genetic association studies are conducted using adequately-sized cohorts of genotyped diseased and healthy animals. Dr. Iivanainen will sample a large population of dogs (>300-400 dogs) so that contributing genetic loci can reliably be discovered. This research group expects that with such a strongly powered

study all major genetic risk factors can be uncovered with a high statistical significance. Investigators expect that identified loci will be discovered across breeds. The identification of genetic risk elements will allow the development of genetic tests that can be used in breeding programs to control the disease incidence, as well as further studies regarding the possible role of diet and exercise in hip dysplasia development.

02109: Studying Hypertrophic Osteodystrophy (HOD) In Irish Setter Dogs

Principal Investigator: Dr. Danika L Bannasch, DVM, PhD **Institution:** University of California, Davis

Total Grant Amount: $65,340.00

Memorandum of Understanding Grant with the Irish Setter Club of America Foundation

Grant Period: 8/1/2014 – 7/31/2015

Project Abstract:

Hypertrophic Osteodystrophy (HOD) is a canine developmental disease that affects dogs between eight weeks and eight months of age. Sick dogs exhibit swelling and pain in their legs with reluctance to stand or walk. In addition to bone pain, there are variable general signs including fever, lethargy, depression, and loss of appetite.

The prognosis for severe cases is poor due to relapsing episodes and the low quality of life for the affected puppies which often results in euthanasia. HOD has a strong familial component and is reported among closely related individuals in the Irish Setter breed as well as other large breeds such as the Weimaraner, Great Dane, German Shepherd Dog, German Shorthaired Pointer, Labrador Retriever, Great Pyrenees, and Boxer. Although the exact cause of HOD is unknown, frequent occurrences within an inbred population of dogs suggests an inherited component plays a role in HOD.

A similar disease in children is called Chronic Recurrent Multifocal Osteomyelitis (CRMO). Affected children suffer from recurrent episodes of unexplained debilitating bone pain between the ages of five and 18 years that prevents them from experiencing a normal childhood.

The aims of this study are to better describe the immune component, and to identify the genetic basis of HOD in Irish Setter dogs. This will allow breeders to reduce the number of HOD affected puppies and perhaps save puppies and owners from the devastating outcome of euthanasia. Results from this study have the potential to assist other breeds with HOD, and children with CRMO.

02120: Investigating Hypertrophic Osteodystrophy in Weimaraner Dogs

Principal Investigator: Dr. Danika L Bannasch, DVM, PhD **Institution:** University of California, Davis

Total Grant Amount: $26,460.00

Memorandum of Understanding Grant with the Weimaraner Club of America

Grant Period: 8/1/2014 – 7/31/2015

Project Abstract:

Hypertrophic Osteodystrophy (HOD) is a developmental autoinflammatory disease affecting young, rapidly growing dogs. Affected dogs exhibit clinical signs of fever, anorexia, lethargy and lameness. A similar disease called chronic recurrent multifocal osteomyelitis (CRMO) is seen in children.

The cause for HOD remains unknown, but since specific breeds are predisposed, an inherited etiology is probable. The Weimaraner breed is susceptible to HOD, and closely related dogs such as full-siblings can be affected. Additional predisposed breeds are the Irish Setter, Great Dane, German Shepherd Dog, German Shorthaired Pointer, Labrador Retriever, Great Pyrenees, and Boxer. Currently, dog breeders do not have genetic resources available to select against HOD in their lines.

Dr. Bannasch and her team hypothesize that exonic non-synonymous mutations associated with HOD in dogs can be identified by comparing whole-genome sequence reads from HOD cases and controls. She will investigate exonic non-synonymous variants homozygous in Weimaraners with HOD, and will study the immune basis of HOD in the breed by testing serum levels for immune markers.

Evaluating candidate causative mutations will enable Dr. Bannasch and her team to recognize etiological pathways, and together with investigating the immune component of HOD, will advance understanding of the disease pathogenesis. This could also lead to the development of a DNA test to allow Weimaraner breeders to minimize the number of HOD cases. Understanding the etiology of HOD could also lead to the development of specific means of prevention, and treatment regimens. Advances in prevention and/or treatment of HOD will benefit susceptible dogs, and may aid human patients with autoinflammatory syndromes, such as CRMO.

02142-A: Development of Magnetic Resonance Imaging as a Non-Invasive Tool to Accurately Evaluate Elbow Dysplasia

Principal Investigator: Dr. Samuel Patrick Franklin, DVM, PhD **Institution:** University of Georgia Research Foundation, Inc

Total Grant Amount: $12,398.40

Grant Period: 8/1/2014 - 8/31/2015

Project Abstract:

Canine elbow dysplasia (CED) is a common problem with numerous different forms of varying nature and severity. Currently, radiographs (X-rays), computed tomography (CT; CAT scan), and arthroscopic surgery are used to make a diagnosis of elbow dysplasia and to characterize the degree of joint damage that a dog has suffered as a result of having CED. Unfortunately, neither radiographs nor CT provides evaluation of the cartilage in the joint. Rather, surgery has to be performed, either standard or arthroscopic, to visualize the cartilage before a thorough appreciation of the joint abnormalities can be obtained. As a result, definitive treatment plans cannot be established until after surgical assessment of the joint is performed. This stands in contrast to human medicine in which magnetic resonance imaging (MRI) can be used to assess cartilage non-invasively in order to make diagnoses and direct treatments prior to surgery. Theoretically MRI could similarly be used in veterinary medicine to more thoroughly evaluate cartilage health in the canine elbow, thus enabling determination of a treatment plan before surgery is performed. Likewise, MRI might be used to assess the response to different treatments and progression of disease. Working in collaboration with human radiologists, Dr. Franklin will perform MRI in dogs with elbow dysplasia using novel quantitative MRI protocols to determine whether MRI can be used for complete characterization of the nature and severity of joint damage in dogs with elbow dysplasia. Ultimately, accurate disease phenotyping will facilitate the treatment of patients, the development of novel therapeutics, and the prevention of disease through informed breeding programs.

Neurology Research Program Area

01455: Identification of Genes That Confer Risk for Inflammation of the Brain

Principal Investigator: Dr. Simon R. Platt, BVMS **Institution:** University of Georgia

Total Grant Amount: $75,000.00

Grant Period: 1/1/2011 - 12/31/2014

Project Abstract:

Necrotizing meningoencephalitis (NME) is an inflammatory disorder of the brain and its surrounding membranes that most commonly affects small dogs. Breeds affected include the Pug, Maltese, Chihuahua, Shih Tzu, Lhasa Apso, Boston Terrier, Papillion, Pekingese, Pomeranian, Yorkshire Terrier and West Highland White Terrier. Affected dogs can develop seizures, depression, difficulty walking, circling and blindness. The cause of NME is unknown. Dogs with NME typically develop neurological signs very quickly and often die due to a lack of ideal treatment regimens. There is no way to definitively test for NME before death. Multiple laboratories have shown NME to be inherited within families of Pug dogs, supporting a role for genetic factors in the development of this disease. The goal of this study is to characterize previously identified DNA regions of interest in order to identify specific genetic mutations that are responsible for this disorder in Pugs, Maltese and Chihuahuas. The identification of genes associated with NME will improve our understanding of the disease process, allow for the development of DNA tests and potentially more directed treatment strategies. Genetic testing ultimately should allow for a dramatic reduction in the incidence of NME through non-disruptive alteration of breeding programs.

01731: A Novel Approach to Understanding How Meningoencephalomyelitis Develops In Dogs

Principal Investigator: Dr. Nick D Jeffery, BVSc, PhD **Institution:** Iowa State University

Total Grant Amount: $31,104.00

Grant Period: 1/1/2013 - 6/30/2015

Project Abstract:

'Meningoencephalomyelitis of unknown etiology', otherwise known as 'MUE', is the clinical term for combined inflammation of the brain and spinal cord. MUE affects a wide variety of dogs, particularly small breeds such as the Miniature Poodle, Maltese, Dachshund, West Highland White Terrier, Chihuahua, Yorkshire Terrier and Pug Dog. The onset of MUE is acute and can cause paralysis, seizures, disorientation, loss of balance, blindness, and in some cases can be rapidly fatal. A recent experimental breakthrough has implicated bacteria in the digestive system as triggers for a similar disease in laboratory mice and rats. Dr. Jeffery's novel research will determine whether imbalances in the number or type of digestive system bacteria might also be a cause for MUE in dogs. This research has the potential to open a new approach to treatment of affected dogs and may also produce information useful for treating neurologic disease in humans.

02139-A: Development of a Neuromusculoskeletal Computer Simulation Gait Model to Characterize Functional Recovery in Dogs with Intervertebral Disk Herniation

Principal Investigator: Dr. Gina E Bertocci, PhD **Institution:** University of Louisville

Total Grant Amount: $12,740.00

Grant Period: 9/1/2014 – 8/31/2015

Project Abstract:

Intervertebral disk herniation (IVDH) leads to spinal cord injury (SCI) in dogs. The most commonly affected breed is the Dachshund, of which 19% develop IVDH. IVDH compresses the spinal cord and can lead to paralysis, incontinence, reduced quality of life, permanent neurological deficits and secondary conditions. Dogs that receive decompressive surgery (standard of care) and rehabilitation immediately following IVDH may regain the ability to walk. Certain aspects of recovery, such as muscle activation patterns, are not clearly understood and play a pivotal role in whether dogs regain full function of their limbs. Scientists know that neurologic disruption following IVDH alters muscle recruitment strategies leading to compensatory changes in muscle function post-injury. An improved understanding of muscle activation during walking following IVDH-associated SCI is paramount to developing strategies to enable full recovery. The goal of Dr. Bertocci's study is to characterize individual muscle activation patterns during walking. Her research group is responsible for development of landmark computer simulation techniques that have transformed our understanding of Cranial Cruciate Ligament Disease. She will now apply this successful methodology to IVDD and assess muscle function in: 1) a healthy Dachshund, 2) a Dachshund with moderate IVDH-associated SCI following surgical decompression at multiple time points during recovery. Proof-of-principle computer models will be developed based on medical imaging, and hind-limb motion, ground reaction forces, and body weight support provided during walking. They will characterize differences in hind-limb motion and muscle activation patterns during walking between the healthy dog and dog with SCI, as well as differences in the dog with SCI throughout recovery. Their outcomes will enhance understanding of functional recovery following surgical treatment of IVDH, which will provide a foundation for improved clinical decision making regarding treatment options and investigating future therapeutic interventions.

Funding for this research is provided through the efforts and generosity of the Dachshund Club of America.

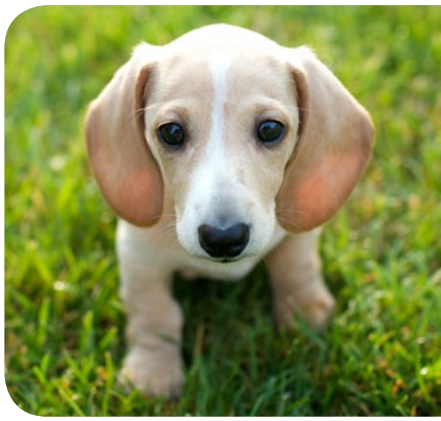
02141-A: Describing the Kinetic and Kinematic Recovery of Dachshunds with Spinal Cord Injury

Principal Investigator: Dr. Gwendolyn J. Levine, DVM **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $12,935.00

Grant Period: 9/1/2014 – 8/31/2015

Project Abstract:



Intervertebral disk herniation (IVDH) is common in dogs and results in injury by compressing and bruising the spinal cord. The most frequently affected breed is the Dachshund, with as many as 19% of Dachshunds developing IVDH. Effects of IVDH include paralysis, paresis, incontinence, reduced quality of life, and permanent neurological disabilities; these facets of injury place a tremendous burden on caregivers. Traditionally, qualitative scoring systems have been used to determine injury severity, recovery, and identify if therapies are effective. More recently, computerized gait assessment (kinematics) has been applied to dogs with IVDH. These studies have examined dogs at single time points and suggest that kinematics is more sensitive than traditional scoring in detecting changes in gait. The goal of Dr. Levine's research is to characterize gait recovery in Dachshunds with IVDH using kinematics. She will utilize dogs with moderate and severe injury to capture the spectrum of dysfunction and recovery that occurs following injury. All dogs will receive spinal decompression surgery (standard) and be assessed at 5 time points: pre-surgery and 7, 14, 30 and 90 days post-surgery. Information will be compared to the gait of healthy Dachshunds. This work is novel based on the quantitative, kinematic and longitudinal characterization of locomotion in healthy and spinal cord injured Dachshunds. The major outcomes will be: 1) an enhanced understanding of natural recovery post-IVDH; 2) improved clinical decision making with respect to treatment options; 3) identification of effective assessment parameters; and 4) creation of a baseline for future clinical trials assessing therapies.

Funding for this research is provided through the efforts and generosity of the Dachshund Club of America.

02143-A: Development of a Novel Treatment for Intervertebral Disc Disease

Principal Investigator: Dr. Gordon S. Mitchell **Institution:** University of Wisconsin, Madison

Total Grant Amount: $11,903.00

Grant Period: 8/1/2014 – 1/31/2016

Project Abstract:

The spinal cord transmits information from the brain to muscles that initiate movements, such as breathing and walking. Spinal cord injury disrupts these neural pathways, causing partial or even complete loss of walking ability. In dogs, spinal injury commonly occurs as a consequence of vertebral disc herniation. While some recovery of walking ability occurs through uninjured spinal pathways, the extent of spontaneous recovery is slow and frustratingly limited in most cases. Neural plasticity (i.e. changes in neural pathways and synapses) in the spinal cord increases the strength of these uninjured neural pathways and increases the strength of muscular contractions and walking ability. One recently established method of inducing spinal plasticity involves breathing intermittent periods of slightly lowered oxygen levels to create a non-life threatening state of hypoxia. Dr. Mitchell's research group recently discovered that this technique increases walking ability in rats and humans with chronic, incomplete spinal injuries, and has an even greater effect when paired with traditional rehabilitation strategies such as walking practice. In a similar way, they believe administration of very modest protocols of intermittent hypoxia will

improve walking endurance and speed in dogs with spinal injuries due to intervertebral disc disease. Dr. Mitchell and colleagues intend to investigate the impact of intermittent hypoxia, with and without paired locomotor training as a completely new canine rehabilitation strategy. Intermittent hypoxia has proven to be a very safe and effective means of restoring motor function in other species, and they predict that the same will be true in dogs with chronic injuries – a population with no prognosis for further recovery using any currently available technique.

Funding for this research is provided through the efforts and generosity of the Dachshund Club of America.

In 2014, there were approximately 1.6 million human patients diagnosed with cancer and approximately 6 million dogs diagnosed with cancer in the U.S. Translation of research from the laboratory bench to the patient is our ultimate goal, and we include both canine and human patients in this objective. Human researchers are beginning to understand that the model system they study has a tremendous influence on the relevance of the research to real patients, and unfortunately the average rate of successful translation from rodent models to human clinical cancer trials is less than 8%. Comparative oncology that utilizes dogs with naturally occurring cancers to study cancer biology has the potential to have tremendous impact on improving the success rate of early cancer research studies. Naturally occurring tumors in dogs and cats have more clinical and biological similarities to human cancers than any other animal cancer model for several reasons: 1) the tumors in both species are similar at the molecular level 2) tumors in both species develop recurrent and drug-resistant disease and 3) tumors in both species metastasize to tissues beyond where they started. Finally, extensive dog genome sequencing has enabled better understanding of the genetics of cancer and allows comparisons in canines and humans. Supporting canine cancer research also supports the quest for a cure for human cancer.

02157: Genomics of Deafness in the Dalmatian

Principal Investigator: Dr. Claire M Wade, PhD **Institution:** University of Sydney

Total Grant Amount: $120,960.00

Memorandum of Understanding Grant with the Dalmatian Club of America Foundation

Grant Period: 1/1/2015 – 12/31/2016

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, Dr. Wade 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 this 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 administration of funds and scientific progress reporting.

02162: Defining the Genetic Foundations of Chiari-Like Malformation and Syringomyelia as a Tool to Better Treat Neuropathic Pain in the Dog

Principal Investigator: Dr. Natasha J Olby, VetMB, PhD **Institution:** North Carolina State University

Total Grant Amount: $37,530.00

Memorandum of Understanding grant with the American Cavalier King Charles Spaniel Club Charitable Trust

Grant Period: 1/1/2015 – 12/31/2015

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 to investigate sensory thresholds in affected and normal CKCS to improve our 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 this 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 administration of funds and scientific progress reporting.

02165: Identification of Biomarkers and Therapeutic Targets for Canine Degenerative Myelopathy: The Search for a Cure

Principal Investigator: Dr. Joan R. Coates, DVM **Institution:** University of Missouri, Columbia

Grant Amount: $154,077.00

Memorandum of Understanding grant with the American Boxer Charitable Foundation

Grant Period: 1/1/2015 – 12/31/2016

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 is proposing to develop 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. They 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 is underway in a cohort of DM-affected dogs [Boxers and Pembroke Welsh Corgis (PWC)] (funded by NIH/NINDS). They 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 this 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 administration of funds and scientific progress reporting.

Oncology Research Program Area

01426: Personalized Medicine for the Treatment of Canine Mast Cell Tumors

Principal Investigator: Dr. Douglas H Thamm, VMD* **Institution:** Colorado State University

Total Grant Amount: $89,976.79

Grant Period: 1/1/2011 – 6/30/2015

Project Abstract:

While surgery remains the mainstay of treatment for canine mast cell tumors (MCT), surgery alone is not curative in some cases, and not possible in other cases. Medical therapy remains an important component of MCT therapy. New drugs that impair signaling through growth factor receptors know to "feed" the tumor are showing considerable promise for the treatment of canine MCT, and MCT with mutations in these growth factor receptors may make tumors more sensitive to certain drugs. Dr. Thamm's research group recently developed a rapid test, which can be performed on fine-needle aspirates, to determine whether MCT possess mutations in growth factor receptors. In this study they will determine if testing for the presence of a growth factor receptor mutation is a useful decision-making tool for the selection of the best possible medical therapy for dogs with MCT. This study will be the first step toward personalized medicine in the treatment of canine mast cell tumors.

01557: Narrowing the Search for the Genetic Basis of Histiocytic Malignancies

Principal Investigator: Dr. Matthew Breen, PhD* **Institution:** North Carolina State University

Total Grant Amount: $125,000.00

Grant Period: 7/1/2012 – 12/31/2014

Project Abstract:

In a previous study (CHF-760) Dr. Breen demonstrated that canine histiocytic malignancies (HMs) present with a high degree of DNA copy number alterations. His research group identified several aberrant regions of the genome that are highly recurrent between cases, suggesting that such regions are associated causally with the malignant process. Understanding the biology of genes within such regions is key to developing ways to halt the cancer and prolong life in patients whom otherwise have a poor prognosis. They now have an approach to identify DNA copy number changes that allows them to zoom in on regions of the genome with ~75-fold greater resolution than was possible even just one year ago. Using this technology they will refine the genome regions of interest and identify additional, smaller aberrations. Within these regions they will identify a series of candidate genes for functional analysis. They have developed an assay for use with archival

canine tumor samples that allows them to rapidly determine the level of activity of multiple genes with higher sensitivity than was possible previously. Once they have identified the key genes of interest, they will use this assay to screen HM cases for the extent of gene deregulation, as well as identify DNA copy number changes that are shared with human HMs. Combining these approaches, they will narrow down the search for genes playing a key role in HMs and thus move a step closer to developing targeted therapies for canine patients diagnosed with this devastating cancer.

01633: Novel Therapy for Melanoma, Lymphoma, Meningioma and Nephroblastoma

Principal Investigator: Dr. Heather M. Wilson, DVM **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $80,000.00

Grant Period: 1/1/2012 – 12/31/2014

Project Abstract:

Spontaneous melanoma strikes an estimated 50,000 dogs each year. Even with aggressive treatment, the median survival time is < 1 year. Dr. Wilson's research group has identified a new class of drugs, S100B inhibitors, which prevent the growth of canine/human melanoma cells as well as in vivo murine tumors. Two of these inhibitors, pentamidine and chlorpromazine, are currently used in veterinary medicine to treat other diseases. Thus, it is a legitimate, and some would say from a patient, owner, and veterinarian's perspective, a compellingly urgent question as to whether these agents have clinical value in treating canine melanoma. The proposed study is a collaborative effort between basic scientists and clinicians, the goal of which is to determine if combined pentamidine/chlorpromazine therapy is safe for canine melanoma patients. There is a high probability that this research will culminate in the identification of a new disease modifying therapy that will alleviate suffering and improve survival for dogs, as well as other companion animals, suffering from melanoma. Finally, this therapy may also be useful in treating other veterinary cancers that exhibit increased S100B activity, including lymphomas, meningiomas, and nephroblastomas.

01669-A: Determining the Role of Bacterial Infection in Complications After Chemotherapy

Principal Investigator: Dr. Jonathan F Bach, DVM **Institution:** University of Wisconsin, Madison

Total Grant Amount: $6,115.39

Grant Period: 5/1/2011 – 4/30/2015

Project Abstract:

Since cancer cells lack the normal response to 'stop replicating' signals, the approach to treatment of this cellular proliferation is use of chemotherapeutic agents that target rapidly dividing cells. However, the use of chemotherapy also targets the patient's own normal rapidly dividing cells (e.g., bone marrow and gastrointestinal tract). Therefore, patients receiving chemotherapy are often immune-suppressed (low white cell count) and have a weakened natural barrier (gastrointestinal tract cell death). As a result, chemotherapy patients are highly susceptible to life-threatening infections from overgrowth of opportunistic bacteria already present in their body, or to other community- or hospital-acquired infections. Collection of samples such as blood or urine for culture and sensitivity are standard protocol for human chemotherapy patients suspected of having an infection. In veterinary medicine, data are lacking of the basic incidence of bacterial infection in such patients, and what types of bacteria are most common in immune-suppressed cancer patients receiving chemotherapy is undocumented. Therefore it is difficult to ascertain which antibiotics will be the most useful. The primary purpose of this observational study is to determine the frequency and type of bacteria in the blood and urine of dogs receiving chemotherapy, and to determine whether there is a difference in either the incidence or types of organisms found in cancer patients with low white blood cell counts with or without fever. Dr. Bach hypothesizes that chemotherapy patients with fever and low white blood cell counts will more frequently have bacteria isolated from urine or blood samples compared to those without fever.

01689-A: Increasing the Effectiveness of Radiation Therapy in Treatment of Mast Cell Tumors

Principal Investigator: Dr. Keijiro Shiomitsu, DVM **Institution:** Louisiana State University

Total Grant Amount: $12,921.54

Grant Period: 4/1/2012 – 3/31/2015

Project Abstract:

Canine mast cell tumors are the most common cutaneous malignant tumors in dogs. Histologic grades, I, II, and III, provide very useful information because they are indicative of a patient's prognosis. Treatment options depend on negative prognostic factors, but in general surgery and radiation therapy are very effective. Chemotherapy could be applied if the patient has either systemic disease or a grade III mast cell tumor. The most commonly used chemotherapy drugs for mast cell tumors are CCNU and vinblastine. A new therapeutic agent, Palladia, targets a receptor on mast cell tumors called c-kit (CD117). Dr. Shiomitsu will investigate if Palladia can enhance the radiosensitivity of canine mast cell tumor cells in vitro and determine the mechanism of radiosensitization when it occurs. Radiosensitization by Palladia may be able to improve local tumor control, and hopefully prolong survival time for radiation oncology patients.

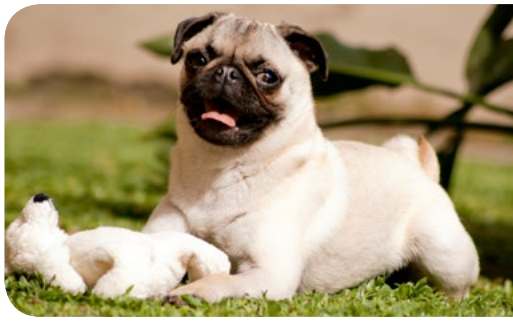
01822: Beyond the Genome: The Intersection of Genes and the Environment in Canine Cancer

Principal Investigator: Dr. Robert K Wayne, PhD **Institution:** University of California, Los Angeles

Total Grant Amount: $29,923.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:



Not all genes are active at all times. DNA methylation (the addition of methyl groups to DNA) is one of several mechanisms that cells use to control gene expression. Abnormal patterns of DNA methylation have been observed in human cancer. However, methylation remains an unexplored dimension of canine disease. This seed grant to Dr. Wayne will allow him to establish the techniques and methodologies necessary to define the pattern of normal variation in methylomes (the genome-wide collection of methylated sites) from an array-based analysis of a variety of domestic dog breeds. Differences in methylation found between breed lineages will be complemented by the study of gene expression to understand how methylation regulates levels of expression. Upon completion of this study, Dr. Wayne's laboratory will have proof-of-principle for evaluation of the canine methylome. Ultimately, he intends to establish a public web-based resource to serve as a repository for the dog methylomes. The collection of methylomes they generate will contribute to the growing resources that are available for investigation of disease etiology as well as advancing therapeutic approaches. These data will provide a new resource for understanding how gene regulation through methylation affects phenotype, disease and overall canine health.

01826: A Novel Treatment for Brain Tumors Using a One Medicine Approach

Principal Investigator: Dr. Simon R. Platt, BVMS **Institution:** University of Georgia

Total Grant Amount: $119,065.00

Grant Period: 1/1/2013 – 12/31/2015

Project Abstract:

Drs. Simon Platt (University of Georgia College of Veterinary Medicine) and Costas Hadjipanayis (Emory University School of Medicine) will take a One Medicine approach to treating canine glioma brain tumors. Brain tumors in humans and animals are often devastating and fatal diseases. Many are not accessible to surgical removal which is the main treatment option. Likewise, chemotherapy has traditionally been ineffective because systemic delivery is prevented by the blood-brain barrier. In an effort to deliver chemotherapy drugs directly into brain tumors, a procedure called convection-enhanced delivery (CED) has been developed. This procedure utilizes small catheters, placed directly into tumors which allow direct drug delivery, limiting systemic drug concentrations, and therefore minimizing side effects. In this study dogs will undergo CED treatment with the monoclonal antibody cetuximab conjugated to magnetic iron-oxide nanoparticles (IONPs). Cetuximab is a monoclonal antibody specific to the epidermal growth factor receptor (EGFR) which is over-expressed in the majority of canine gliomas. Cetuximab is FDA-approved for use in several cancers in humans. When combined with IONPs, cetuximab can be visualized utilizing MRI. The dogs will be monitored clinically and with MRI over the next twelve months. The aim is a significant decrease in MRI volume of the tumors and ultimately, tumor-free survival of patients.

01843: Further Investigation of the Genes Controlling Canine Leukemia to Properly Diagnose and Control the Disease

Principal Investigator: Dr. Matthew Breen, PhD* **Institution:** North Carolina State University

Total Grant Amount: $131,265.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Leukemia represents a range of cancers, most often classified according to the type of blood cell affected and the clinical progression. Leukemia may be chronic, progressing slowly for many years with minimal symptoms, or acute, with sudden onset and rapid progression of symptoms, often resulting in euthanasia. The true incidence of leukemia in dogs is unknown, but consensus opinion is that many cases remain undiagnosed. In previous studies Dr. Breen found that canine leukemia presents with characteristic chromosomal and genetic changes shared with those known in human leukemia. In humans these chromosomal and genetic aberrations have been linked to disease progression and response to therapeutics, and in turn, this information drives clinical management of the patient. In this multicenter study, Dr. Breen's group will use high-resolution genome-wide chromosomal evaluation to screen a large cohort of canine leukemia patients for the presence of recurrent chromosomal and genetic changes. This study will enhance our understanding of the pathogenesis of canine leukemia by identifying regions of the canine genome, and thus individual genes that may be critical for the control of these cancers. Additionally, this study will provide data that will impact our knowledge of the corresponding human disease.

01849: Filling the Gaps in the Canine Genome

Principal Investigator: Dr. Shaying Zhao, PhD **Institution:** University of Georgia Research Foundation, Inc.

Total Grant Amount: $108,000.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

The sequencing of the genome of man's best friend in 2005 has provided an invaluable resource to the canine research community, and has reinforced the position of the dog as an important model organism to study human physiology and disease. Unlike the human and the rodent models (the mouse and the rat), very few dog genes had been sequenced prior to its whole genome sequencing. Consequently, the dog genome has been annotated for its gene content primarily based on mapping the gene-related sequences from the human, the mouse, the rat, and other non-dog species to the dog genome. While providing the research community with an unprecedentedly large set of dog genes, the definition of DNA sequences as coding sequences (i.e. gene annotation) has substantial errors and is missing in dog-specific information in many aspects. This significantly hinders research in many fields such as disease gene discovery and cancer-causative gene mutation identification, where functional information about a gene is required to make progress. Dr. Zhao will use state of the art next-generation sequencing strategies to identify genes/transcripts expressed in major dog tissues and cell types. The valuable data, along with more refined sequence alignment between the dog and other species, will be used to build the most accurate and complete annotation of the dog genome for its gene annotation. The project will significantly facilitate research in areas of canine health most significant to the AKC Canine Health Foundation constituency and lead to important RNA-based (transcriptomic) and protein-based (proteomic) research in the future.

01872-A: Using Ultrasound as a Cost Effective and Non-Invasive Technique for Early Diagnosis of Solid Tumors

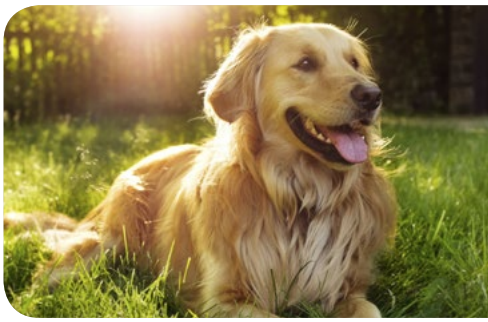
Principal Investigator: Dr. Nathalie Rademacher, Med Vet **Institution:** Louisiana State University

Total Grant Amount: $6,028.56

Grant Period: 9/1/2012 – 2/28/2015

Project Abstract:

Estimation of tissue elasticity by feel is the oldest tool in medicine used for disease diagnosis. Palpation of a mass relies on the fact that tumors often are harder and stiffer than the surrounding tissue. While practical, palpation is often not reliable because of its poor sensitivity and inaccessibility of lesions. Ultrasound elastography is the transformation of the palpation into imaging and has been shown to be useful in the differentiation of benign versus malignant breast masses, lymph nodes and thyroid nodules, as well as in the differentiation of other medical conditions such as liver cirrhosis and prostatic cancer in people. This technique has reduced the number of biopsies of benign breast masses. Dr. Rademacher will establish normal elastography values for canine lymph nodes in the caudal abdomen, neck and hind leg. An additional aim of this study is to determine the usefulness of ultrasound elastography in the differentiation of normal and metastatic lymph nodes in dogs with tumors.



01889-G: Innovations in Prevention, Diagnosis, and Treatment of Cancer – Goldens Lead the Way

Principal Investigator: Dr. Jaime F Modiano, VMD PhD* **Institution:** University of Minnesota

Total Grant Amount: $360,933.00

Grant Period: 1/1/2014 – 12/31/2016

Project Abstract:

Lymphoma and hemangiosarcoma are major health problems in Golden Retrievers, causing both suffering and premature death. Through ongoing collaboration, Drs. Jaime Modiano, Matthew Breen, and Kerstin Lindblad-Toh have identified several regions of the genome that contain genetic heritable risk factors for lymphoma and hemangiosarcoma in Golden Retrievers. They have tumor-specific mutations that occur recurrently in both cancers, some of which are linked to duration of remission when treated with standard of care. Their results indicate that a few heritable genetic risk factors account for as much as 50% of the risk for these cancers. These findings offer the potential to develop tests and strategies for DNA tests that can predict risk for individual dogs, as well as to manage risk across the population as a whole. Indeed, both the inherited risk factors and tumor mutations point to pathways that have been implicated in the pathogenesis of lymphoma and hemangiosarcoma, and thus should inform the development of targeted therapies. In the current study, Drs. Modiano, Breen, and Lindblad-Toh will find the precise mutations for the heritable genetic risk factors and to validate markers (mutations) used to determine risk at the heritable loci in a larger independent population of Golden Retrievers from the United States and from Europe in order to develop robust risk prediction tools and an accompanying DNA test. Further, they will identify and characterize tumor mutations and study their relationship to the heritable risk factors, tumor pathogenetic mechanisms, and disease outcome.

02071: Development of a Therapeutic Brain Tumor Vaccine

Principal Investigator: Dr. Grace Elizabeth Pluhar, DVM, PhD **Institution:** University of Minnesota

Total Grant Amount: $130,572.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Meningiomas are the most common primary brain tumor in dogs that affects more than 10,000 dogs in the U.S. annually. These tumors occur most frequently in older dogs and in certain breeds –– Golden Retrievers, Labrador Retrievers, Boxers, German Shepherd Dogs and Collies –– causing uncontrolled generalized grand mal seizures in most cases. Although the biological behavior of these tumors is generally considered benign, most meningiomas recur less than one year after either surgery or radiation therapy. Furthermore, radiation therapy is expensive, involves many, repeated episodes of general anesthesia, and cause severe adverse effects. Longer survival times can be achieved through special techniques, but most dogs treated undergo more standard surgical removal and/or radiation therapy. Clearly, there is an urgent need for novel therapies to prevent tumor recurrence and increase survival time after surgery. Dr. Pluhar has developed immunotherapy protocols for dogs with gliomas, and recently assessed this strategy in a pilot study treating meningiomas with tumor lysate vaccines. Her data from six dogs showed this approach was safe, feasible and effective. Dr. Pluhar now proposes a larger clinical trial treating 30 dogs with meningioma by surgery alone or surgery followed by vaccines. They expect to see a specific immune response to the vaccines that prevents tumor recurrence. The data from the proposed study will provide further proof of safety and efficacy of vaccine-based therapy to support: 1) more widespread use in dogs and 2) initiation of a Phase I trial for high grade and recurrent meningioma in humans.

02091-A: Differentiating Between Localized and Disseminated Histiocytic Sarcoma in Bernese Mountain Dogs

Principal Investigator: Dr. Elaine A Ostrander, PhD **Institution:** National Human Genome Research Institute

Total Grant Amount: $10,300.00

Memorandum of Understanding Grant with the Berner Lovers

Grant Period: 8/1/2014 – 7/31/2015

Project Abstract:

Canine histiocytic sarcoma (HS) is a disease arising chiefly from cells called histiocytes, which play an important role in the immune system. While HS is relatively uncommon among most dog breeds, it is present at high frequency in Bernese mountain dogs (BMD) and Flat-coated retrievers (FCR), with more moderate incidence reported in Labrador retrievers and Rottweilers. For BMDs, HS accounts for over 25% of deaths and the average survival time is just 49 days from diagnosis. Commonly, this cancer is divided into two subtypes: localized, a tumor rising in a single organ or limb and often metastasizing to other organs, and disseminated, multiple tumors arising at the same time (often referred to as malignant histiocytosis). Survival time is nearly 5x greater for dogs diagnosed with localized HS compared to disseminated HS. However, no clinical guidelines exist to differentiate between these two subtypes and diagnosing subtypes remains largely clinically subjective. Dr. Ostrander and her team will seek to develop clinical indicators of the differences between localized and disseminated HS. She will do this by comparing gene expression in tumors and complement this approach by investigating a marker that is crucial for tumor cell immortalization and cancer progression. Together, these experiments will provide them with the first insight into the differences that exist between these two types of HS tumors. Such information will be crucial to aid in the diagnosis and treatment options available to clinicians, providing a powerful step forward in treating this devastating cancer.

02093-A: Sequencing Histiocytic Sarcoma (HS) loci identified by Genetic Association studies in the Bernese Mountain Dog (BMD)

Principal Investigator: Dr. Catherine Andre, PhD **Institution:** CNRS – University of Rennes

Total Grant Amount: $10,300.00

Memorandum of Understanding Grant with the Berner Lovers

Grant Period: 8/1/2014 – 7/31/2015

Project Abstract:

Histiocytic sarcoma (HS) occurs at a high incidence in few breeds, specifically in Bernese Mountain Dogs (BMD), Rottweilers and Retrievers. Dr. Andre and her team have previously identified main genomic regions associated with HS in the BMD breed. The validations of these regions on over 1000 French BMDs allowed them to develop a first genetic "pre-test" to estimate the risk of developing and transmitting HS in BMDs. This pre-test, now available for breeders, is a first tool to progressively reduce the frequency of this cancer in BMDs.

While major regions involved in HS are known, involved genes and mutations are still unknown. Breed structure is expected to be powerful to study the genetics of complex traits such as cancers and to reduce large regions of association. The analysis of affected Rottweilers allowed Dr. Andre and her team to reduce the main region of CFA11 to 200 Kb and to confirm the involvement of a second region on CFA11. Using this multiple breed-strategy, they analyzed affected Rottweilers and Retrievers, and selected 3 main loci involved in HS predisposition. Sequencing these loci is now mandatory to determine the genetic alterations leading to the susceptibility for HS in BMDs. These experiments will lead them to improve the present genetic testing (Pre-test), improve diagnosis and test and use more adequate treatments for HS in BMDs.

Funding for this research is provided through the efforts and generosity of the Berner Lovers donor advised fund. The AKC Canine Health Foundation supports the funding of this effort and will oversee administration of funds and scientific progress reporting.

Oncology – Hemangiosarcoma Research Program Area

01759: Disrupting the Differentiation of Cancer Stem Cells to Prevent the Spread of Hemangiosarcoma

Principal Investigator: Dr. Jaime F Modiano, VMD PhD* **Institution:** University of Minnesota

Total Grant Amount: $233,914.00

Grant Period: 1/1/2013 – 12/31/2015

Project Abstract:

Hemangiosarcoma is a rapidly fatal disease. The lifetime risk is alarmingly high for some breeds like Golden Retrievers (~20% will die of this disease) and Portuguese Water Dogs (~15% will die of this disease). The risk of hemangiosarcoma is not limited to just these breeds but is considered a research priority for 40 different breed Parent Clubs. Despite considerable efforts to find effective treatments, the outcome for dogs with hemangiosarcoma has changed very little over the past 30 years. Recent evidence suggests hemangiosarcoma conforms to the "cancer stem cell" model, where a defined subset of cells is responsible for initiating and maintaining the tumor. These cells are resistant to conventional therapies and are very adaptable, being able to survive in a variety of tissues in the body. For this project, Dr. Modiano proposes to reduce the malignant potential of hemangiosarcoma stem cells by forcing them to terminally differentiate into cells which can no longer self-renew. He further proposes that by disrupting their ability to self-renew he will enhance the sensitivity of these cells to conventional and targeted therapies and improve the outcomes of dogs with this disease.

Oncology – Lymphoma Research Program Area

01418: Harnessing a Dog's Own Immune System to Kill Lymphoma Tumor Cells

Principal Investigator: Dr. Heather M. Wilson, DVM **Institution:** Texas A&M Research Foundation

Total Grant Amount: $150,000.00

Grant Period: 1/1/2011 – 12/31/2014

Project Abstract:

Lymphoma is the most common malignancy of dogs representing up to 25% of diagnosed cancers. Dogs often develop an aggressive form of lymphoma that is rarely curable, with most unfortunately succumbing to disease within 12 months of diagnosis despite best-available chemotherapies. Dr. Wilson will develop a new treatment to re-train the dog's own immune system to attack the most common type of canine lymphoma, B-cell lymphoma. In order to accomplish this they will obtain a small number of circulating white blood cells, called T cells, from the blood of affected dogs and insert a gene that will cause the T cell to express a receptor which recognizes the tumor "fingerprint". After docking with the lymphoma, the T cell will be triggered to mount an immune response against the tumor cells with the specific fingerprint. This therapy could be used alone or in combination with chemotherapy. Their preliminary data demonstrate that it is possible to genetically modify T cells. Further, they have been able to successfully harvest and grow T cells in the laboratory and return them safely to the dog. These infused cells can be found in the blood and tumor weeks after infusion, showing that it is possible for these cells to survive in the dog. If successful this study will be the first to develop an "in-dog" T-cell therapy targeting a tumor that has historically thought to be untreatable.

01585: Evaluating a Safer, Less Toxic Radiation Therapy in the Treatment of Lymphoma

Principal Investigator: Dr. Michael A. Deveau, DVM, MS **Institution:** Texas A&M Research Foundation

Total Grant Amount: $93,140.00

Grant Period: 1/1/2012 – 6/30/2015

Project Abstract:

Lymphoma is one of the most common neoplasms in canine companion animals accounting for upwards of 25% of all canine cancer. Chemotherapy results in high remissions rates but poor overall survival even with aggressive therapy. Lymphoma is extremely radiosensitive; however, incorporating full and half-body radiation therapy results in harmful toxicity to health tissue. In human medicine, full and half-body radiation has been abandoned for advanced Involved-Field Radiotherapy (IFRT) techniques utilizing advanced radiotherapy systems designed to kill diseased tissue while sparing normal tissues. As the technology becomes available in veterinary medicine, this treatment capability will also become available; however, there are no studies in the veterinary literature specifically interrogating this strategy. While demonstrable benefit is the ultimate clinical endpoint, it is critical to ensure safe implementation of IFRT for use in canine patients. To test feasibility and safety, Dr. Deveau will conduct a phase I study in which patients with advanced stage lymphoma will be treated with IFRT. Patients will be subjected to rigorous evaluation at each treatment and at one month intervals for dose limiting toxicities and/or adverse events, with the goal being to determine whether IFRT is a viable option for treatment of lymphoma in dogs.

01787: Clinical Advancement of a Cancer Vaccine in Dogs

Principal Investigator: Dr. Nicola J Mason, BVetMed, PhD **Institution:** University of Pennsylvania

Total Grant Amount: $96,660.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Canine lymphoma is the most common blood-based cancer in dogs with an estimated annual incidence of 30/100,000. Chemotherapy induces remission in 75-85% of patients; however, the majority of patients relapse with drug-resistant lymphoma within 8-10 months of diagnosis and most dogs die of their disease shortly thereafter. Cell-based vaccine strategies that stimulate anti-tumor immunity have shown promise in the treatment of many different cancer types including non-Hodgkin's lymphoma (NHL) in humans. In a previous study Dr. Mason developed a cell-based vaccine to induce anti-tumor immunity in dogs with NHL. Initial studies were hopeful as this early vaccine significantly prolonged second remission duration and overall survival, but ultimately the vaccine did not prevent relapse. These early findings suggest that while the lymphoma vaccine stimulated anti-tumor immunity it will require immunological boosting to achieve prolonged cancer-free survival. In the current study, Dr. Mason will optimize her cell-based vaccine approach to induce functional, long lasting tumor-specific immune responses that will prevent relapse and prolong survival in dogs with NHL.

01918-G: Discovery of Biomarkers to Detect Lymphoma Risk, Classify For Treatment, and Predict Outcome in Golden Retrievers

Principal Investigator: Dr. Jeffery N. Bryan, DVM* **Institution:** University of Missouri, Columbia

Total Grant Amount: $404,813.00

Grant Period: 7/1/2013 – 6/30/2016

Project Abstract:

Lymphoma strikes 1 in 8 Golden Retrievers, approximately one-third of the cases being B-cell. While T-cell classifications currently inform therapy choices for dogs, B-cell classifications have been investigated little in Golden Retrievers. Dr. Jeffrey Bryan, in collaboration with Drs. Anne Avery and Heather Wilson will focus their efforts on an area of emerging importance in cancer: epigenetics. Epigenetics is defined as stable and heritable patterns of gene expression that do not entail any alterations to the original DNA sequence. Epigenetic DNA methylation changes clearly underlie development of lymphoma in humans, but have been evaluated minimally in dogs. Dr. Bryan and collaborators propose to improve diagnostic, classification, and prognostic ability using flow cytometry paired with biopsy to characterize the B-cell lymphomas of Golden Retrievers. They will identify DNA methylation changes in lymphoma cells not present in normal cells to develop biomarkers of each class of lymphoma and identify new therapy targets for affected Goldens. More significantly, because DNA methylation changes occur so early in the process of cancer formation, they hypothesize that they could serve as biomarkers of risk, allowing medicine or diet to prevent lymphoma in Goldens before it develops. Finally, they propose to identify tumor initiating cells (TIC) in lymphoma biopsies to characterize stem-like cells by surface markers and DNA methylation changes. Identifying these cells will aid therapeutic strategy development. Each project advances a current frontier of research. By performing them in parallel, the markers from each can be combined, correlated, and translated into biomarkers of risk, diagnosis, and prognosis to advance the prevention and management of lymphoma in Golden Retrievers.

Oncology – Osteosarcoma Research Program Area

01660: Identifying the Genes That Confer Risk for Osteosarcoma

Principal Investigator: Dr. Carlos E. Alvarez, PhD **Institution:** The Research Institute at Nationwide Children's Hospital

Total Grant Amount: $120,000.00

Grant Period: 1/1/2012 – 12/31/2014

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.

01806: A Novel Virus-Based Anti-Tumor Treatment for Canine Osteosarcoma

Principal Investigator: Dr. Bruce F Smith, VMD PhD* **Institution:** Auburn University

Total Grant Amount: $118,848.00

Grant Period: 3/1/2013 – 2/28/2015

Project Abstract:

Osteosarcoma is an aggressive canine bone cancer, accounting for around 6% of all canine cancers. Even with the standard-of-care therapy of amputation and chemotherapy, the prognosis is poor, with most dogs dying due to tumor spread (metastasis) within one year, and less than 20% surviving to 2 years following diagnosis. Therefore, improved strategies to treat metastatic disease are needed. Using a novel approach, Dr. Smith has engineered a virus to multiply in and kill tumor cells while sparing normal cells. Preliminary studies have demonstrated that this virus-based anti-tumor treatment is safe when administered to canine osteosarcoma patients and is potentially efficacious in treating osteosarcoma. While this virus was hypothesized to kill osteosarcoma cells through its replication, Dr. Smith's research team hypothesizes that the viral vector may also stimulate an anti-tumor immune response in addition to the expected anti-viral response. In this study, the efficacy and mechanism of action of the virus-based anti-tumor treatment will be evaluated.

01949-A: Targeting the Cell's Activation Machinery to Halt Tumor Metastasis in Canine Osteosarcoma

Principal Investigator: Dr. Shay Bracha, DVM, MS **Institution:** Oregon State University

Total Grant Amount: $12,960.00

Grant Period: 4/1/2014 – 3/31/2015

Project Abstract:

Osteosarcoma is a type of bone cancer that kills approximately 8,000 dogs per year in the United States. It occurs mostly in large breed dogs; particularly Saint Bernards, Great Danes, Irish Setters, Doberman Pinschers, Rottweilers, Mastiffs, Golden Retrievers and Greyhounds. Tumors usually arise in the bone of a leg and rapidly spread to vital organs such as the lung. Present therapies are ineffective and there is no cure. Dr. Bracha believes that understanding how osteosarcoma tumors spread and grow will lead to more effective treatments for disease.

Based on our existing knowledge that cancer cells acquire mechanisms of regulatory avoidance that permit their spread and endless growth, Dr. Bracha will focus his research efforts on one main growth-stimulating molecule known as NF-kappaB. Dr. Bracha hypothesizes that if this molecule or its receptor becomes dysregulated they could initiate a perpetual growth signal giving rise to the characteristic, unchecked growth we observe in metastatic cancer. To address this hypothesis, Dr. Bracha will determine: 1) if the signaling molecule is released by the cancer cells, potentially driving tumor growth, and 2) if the receptor is abnormally activated. These data will lead to a better understanding of the cellular activation pathway in osteosarcoma and identify new targets to treat this devastating disease.

Ophthalmology Research Program Area

02057: Identification of the Genetic Cause of Corneal Ulcers

Principal Investigator: Dr. Kathryn M Meurs, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $27,201.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Spontaneous chronic corneal epithelial defects (SCCEDs) describe an eye disorder characterized by chronic corneal ulcers that fail to undergo normal healing. The predilection of certain breeds suggests that SCCEDs is inherited. 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. Although SCCEDs can be effectively treated, some dogs develop additional episodes of corneal ulcers during their lifetime. 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. Dr. Meurs will use a genome wide association approach to identify an association of a genetic region to SCCEDs. They will then more closely evaluate the chromosomal region of interest to determine the gene and ultimately the causative genetic mutation. They believe that the identification of a genetic cause for SCCEDs can be used to reduce the prevalence of this disease in multiple affected breeds.

02061: Emergence of Pigmentary Uveitis as a Potential Cause of Cataracts and Glaucoma

Principal Investigator: Dr. Wendy M. Townsend, DVM, MS **Institution:** Purdue University

Total Grant Amount: $74,070.00

Grant Period: 1/1/2014 – 12/31/2015

Project Abstract:

Pigmentary uveitis affects 10% of senior Golden Retrievers and frequently results in blindness due to cataracts and/or glaucoma. The pain of glaucoma often leads to removal of the eye. Currently there is no way to prevent or effectively treat pigmentary uveitis. Evidence strongly suggests pigmentary uveitisis is an inherited disease: it is observed exclusively in the Golden Retriever breed, and family members (parents/offspring, full- and half-siblings) can be affected. Complicating the phenotype is the fact that most dogs are 8 years or older before developing clinical signs of pigmentary uveitis. Therefore, affected dogs may be used extensively in a breeding program before being diagnosed. This has frustrated conscientious breeders in their efforts to decrease the prevalence of pigmentary uveitis. Dr. Townsend and her team hypothesize that a genome-wide association study (GWAS) will identify a chromosomal region associated with Golden Retriever pigmentary uveitis, and that high-throughput DNA sequencing will allow identification of the causative mutation. Previous CHF funding helped establish a bank of Golden Retriever DNA for use in the present proposal. Identification of the gene responsible for pigmentary uveitiswould permit development of a genetic test whereby affected individuals can be identified at a young age, allowing breeders to make informed breeding decisions. In addition, knowing the molecular basis underlying pigmentary uveitismay allow researchers to develop more effective treatments for dogs already affected by or genetically destined to develop pigmentary uveitis; this could possibly prevent the blindness, cataracts, and glaucoma caused by pigmentary uveitis.

02145-A: Prevention of Glaucoma and Goniodysgenesis Through Genetic Profiling of Disease

Principal Investigator: Dr. Cathryn S Mellersh, PhD **Institution:** Animal Health Trust

Total Grant Amount: $12,960.00

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Primary glaucoma is a painful and blinding disease associated with high pressure inside the eye. Glaucoma affects over 40 breeds of dogs worldwide, at least 1500 dogs in the UK each year and in the USA as many as 15,000 dogs per year could be affected. Treatment is usually unsuccessful and most affected dogs ultimately require removal of their eyes on welfare grounds. The most common form of canine glaucoma is primary angle closure glaucoma (PACG) which is known to be significantly associated with goniodysgenesis, an abnormality affecting the drainage angle of the eye. PACG and goniodysgenesis are prevalent in several breeds, and goniodysgenesis has been demonstrated to be highly heritable. Not all dogs with goniodysgenesis develop glaucoma, indicating that more than one mutation is probably involved. This complex inheritance and the progressive nature of goniodysgenesis mean that breeding strategies based on eye examinations alone probably won't be sufficient to eliminate the disease. Goniodysgenesis and PACG affect Welsh Springer Spaniels (WSS) in both Europe and the USA and are of considerable concern to breeders on both continents.

Dr. Mellersh and colleagues have collected DNA from WSSs with goniodysgenesis, PACG and with healthy eyes and now aim to compare the DNA from these three cohorts of dogs to identify region(s) of the DNA that harbor mutations responsible for goniodysgenesis and PACG. This is an essential first step towards their ultimate aim which to identify causal genetic mutations and develop DNA tests for multiple breeds that will enable disease prevalence to be effectively reduced.

02146-A: Development of a Novel Drug Delivery System to Prevent Vision Loss in Canine Cataract Patients

Principal Investigator: Dr. Heather Chandler, PhD **Institution:** Ohio State University

Total Grant Amount: $12,960.00

Grant Period: 9/1/2014 – 8/31/2015

Project Abstract:

Cataracts are the most common cause of treatable blindness in dogs. Surgery is the only way to restore normal vision and although every effort is made to remove as much lens material as possible during cataract surgery, it is inevitable that some lens cells are left behind within the eye. These lens cells will move and multiply, resulting in the most common complication to cataract surgery, posterior capsule opacification (PCO). PCO interferes with light transmission and results in secondary vision loss in 80-100% of canine cataract patients. Unfortunately, there is no consistently effective treatment for PCO. Studies performed in laboratory animals have found that use of a commonly prescribed drug, Cyclosporine, can decrease PCO formation. Dr. Chandler believes that Cyclosporine may provide a safe, cost-effective and reliable option to prevent PCO. Using a laboratory animal model system, Dr. Chandler will evaluate the effectiveness of a novel gel-based drug delivery polymer to release Cyclosporine at the correct dose and time needed to prevent PCO. Post-cataract surgery, eyes will be treated with the delivery device releasing Cyclosporine while other eyes will be treated with the delivery device and no Cyclosporine. Dr. Chandler expects that her novel drug delivery gel will be able to release Cyclosporine for at least one week at the correct dose to prevent PCO. If successful, future studies will focus on incorporating Cyclosporine drug delivery in canine clinical trials, potentially providing ophthalmologists a new method of restoring and maintaining excellent vision in dogs that have been blinded by cataracts.

02164: Determining the Genetic Contribution to Boxer Corneal Ulcers

Principal Investigator: Dr. Kathryn M Meurs, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $68,053.00

Memorandum of Understanding Grant with the American Boxer Charitable Foundation

Grant Period: 1/1/2015 – 12/31/2015

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 awarded by the AKC-CHF 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 this 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 administration of funds and scientific progress reporting.

Renal Disease Research Program Area

01658: Early Detection of Chronic Kidney Disease to Prevent Kidney Damage

Principal Investigator: Dr. Mary B Nabity, DVM, PhD **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $80,000.00

Grant Period: 1/1/2012 – 12/31/2014

Project Abstract:

Chronic Kidney Disease (CKD) is a significant source of illness and death in dogs, affecting up to 15% of elderly individuals. Dysfunction of the kidney filtration system is most often the cause of CKD. Early treatment generally prolongs the lives of dogs with CKD, but timely detection can be difficult and the outcome for each patient is unpredictable due to our lack of ability to rapidly diagnose disease. The purpose of this study is to evaluate promising indicators of kidney injury that might improve detection and/or assessment of progression or prognosis in dogs with CKD. Dr. Nabity will use urine samples from dogs with various kidney diseases to measure: 1) urinary proteins indicating tubular and glomerular damage, and 2) gene expression profiles indicating loss of kidney cells. Results will be correlated with conventional measures of kidney function, kidney biopsy findings, and information regarding disease outcome to determine the utility of the novel tests to non-invasively detect and accurately assess kidney damage in dogs.

01766: Identification and Validation of the Genes That Define Abnormal Development of the Kidney in Dogs

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

Total Grant Amount: $25,000.00

Grant Period: 1/1/2013 – 12/31/2014

Project Abstract:

Abnormal development of the kidneys, known as Renal Dysplasia, occurs in many breeds of dogs as well as humans. An increased prevalence in certain breeds such as Boxers, Miniature Schnauzers, Bedlington Terriers, Lhasa Apsos, Shetland Sheepdogs, and Soft Coated Wheaten Terriers suggests a genetic influence. Identification of the genetic cause in dogs is essential as there is no treatment and affected dogs progress to renal failure and death at a young age. Despite prior candidate gene studies, the genetic cause of canine renal dysplasia in various breeds remains unclear. It is unknown if the same gene is affected in all breeds with renal dysplasia or if different genetic variants exist in each breed. In this study Dr. Lindblad-Toh will conduct genetic and functional studies to identify the causative mutation in Boxers. Her research group will also collect additional samples from Miniature Schnauzers, Bedlington Terriers, Lhasa Apsos, Shetland Sheepdogs, and Soft Coated Wheaten Terriers. Genome-wide association studies in Boxers and other breeds will help dissect the genetics of canine renal dysplasia, improve our understanding of renal development in dogs and humans, and determine whether breed specific genetic tests will be required for prevention.

01844: Treatment of Urinary Incontinence with Multipotent Muscle Cells: A Regenerative Medicine Approach to a Common Canine Health Problem

Principal Investigator: Dr. Shelly Vaden, DVM, PhD **Institution:** North Carolina State University

Total Grant Amount: $116,184.24

Grant Period: 1/1/2013 – 12/31/2015

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: Dr. Mary B Nabity, DVM, PhD **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $108,243.00

Grant Period: 1/1/2014 – 12/31/2015

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.

02110-A: Investigating the Effects of an Infusion of Fenoldopam on Kidney Function to Improve Outcomes of Acute Kidney Injury Patients

Principal Investigator: Dr. Jonathan D Foster, VMD **Institution:** University of Pennsylvania

Total Grant Amount: $11,493.36

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Acute kidney injury (AKI) is a devastating disease in canine patients. AKI represents a spectrum of disease characterized by a rapid loss of kidney function, resulting in impaired kidney filtration of metabolic waste products. Regardless of the inciting injury, the resulting kidney dysfunction causes increased serum kidney values and often decreased urine production. The resulting retention of metabolic waste products causes the clinical illness of AKI. Decreased urine production (oliguria) or complete cessation of urine production (anuria) may indicate a more severe kidney injury and are associated with increased mortality. Patients with decreased urine production are more difficult to manage when hospitalized and have higher morbidity than patients with normal urine output. Therapeutic intervention with diuretics has historically been performed in an attempt to induce urine production and thus facilitate the filtration and excretion of metabolic wastes. Unfortunately these therapies are often ineffective and are not without risk of unwanted side effects. Fenoldopam (a selective dopamine DA-1 receptor agonist that induces renal vasodilation) has recently been shown to increase urine production in people with minimal side effects. Little is known regarding the effect of the drug on kidney filtration and whether there is potential for its use in dogs. The purpose of this study is to determine the effect of fenoldopam on kidney filtration by measuring glomerular filtration rate during fenoldopam administration. If fenoldopam increases filtration rate it may in turn facilitate removal of metabolic waste products, potentially leading to improved outcome in patients with AKI and decreased urine production.

02152: Translation of MicroRNA into an Early Diagnostic Test for Chronic Kidney Disease

Principal Investigator: Dr. Mary B Nabity, DVM, PhD **Institution:** Texas A&M AgriLife Research

Total Grant Amount: $26,988.00

Collaborative Project with Zoetis

Grant Period: 1/1/2015 – 6/30/2016

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, we lack an understanding of the mechanisms driving these diseases, limiting our 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.

Reproductive Conditions & Disease Research Program Area

01840: Health Implications of Early Spay/Neuter on Canine Health

Principal Investigator: Dr. Benjamin L Hart, DVM, PhD **Institution:** University of California, Davis

Total Grant Amount: $146,589.00

Grant Period: 2/1/2014 – 1/31/2016

Project Abstract:

Most dogs in the United States are spayed or neutered, and the default recommendation has been to perform these elective surgeries prior to physical maturity. However, recent data suggest that early spay and neuter may adversely impact the health and well-being of dogs. In preliminary studies funded by CHF, Dr. Ben Hart of the UC Davis College of Veterinary Medicine found that early spay or neuter, prior to 12 months of age, was related to a significant increase in risk in five diseases of concern: hip dysplasia; cranial cruciate ligament tear; lymphosarcoma; hemangiosarcoma; and mast cell tumor.

CHF has now awarded the second phase of Dr. Hart's research in which he will expand his work to consider breed differences in vulnerability to joint disorders and risks of various cancers after early or late spay/neuter. Breeds considered will include: Labrador Retrievers, German Shepherd Dogs, and Dachshunds. Rottweilers, Chihuahuas, Standard Poodles, and Miniature Poodles will be included if resources and patient data are available. The expectation is that by inclusion of multiple breeds in phase II Dr. Hart will be able to develop a generalized understanding of the impact of early spay and neuter on disease risk in dogs. This in turn will enable veterinarians and breeders to make data-driven recommendations regarding timing of spay/neuter procedures to reduce the risk of development of multiple devastating diseases.

02118-A: Targeting the Mechanism of Bacterial Adherence During Pyometra to Develop an Effective, Non-Invasive Treatment for Disease

Principal Investigator: Dr. Cordula Bartel, PhD **Institution:** University of Veterinary Medicine of Vienna

Total Grant Amount: $10,368.00

Grant Period: 7/1/2014 – 11/30/2015

Project Abstract:

Pyometra is the most common uterine disease in intact bitches leading to potentially life-threatening complications due to the systemic inflammation that occurs as a result of infection. We know that *E. coli* bacteria are the most abundant infectious agents associated with pyometra in bitches, but how and why these bacteria are able to colonize the endometrium and cause disease is unclear. In a previous study Dr. Bartel's research group characterized a unique epithelial cell type known as "foam cells" on the canine endometrial surface. Foam cells occur most often during diestrus (also called metestrus), the cyclic stage most commonly associated with the occurrence of pyometra. Foam cell formation appears to be part of the normal physiological process of preparation of an embryo for implantation. From other species we know that the foamy appearance of the epithelial cells is caused by lipid droplet accumulation and that the uptake of lipids from the blood is accomplished via special lipid receptors on these cells known as SR-B1. Interestingly, SR-B1 is a strong binding partner for bacteria and Dr. Bartel's lab hypothesizes that this receptor is a major contributor to the development of pyometra. They also believe selective blocking of this receptor will lead to a reduction of clinical signs of inflammation and decreased convalesce-time and tissue damage during pyometra. The first step to testing this hypothesis is to detect SR-B1 in the canine endometrial epithelial cells and to elucidate its role in lipid accumulation in endometrial epithelial cells during pyometra development. In this pilot project these researchers will evaluate SR-B1 mRNA and protein in the canine endometrium with the goal of ultimately establishing a new, non-invasive pyometra treatment that impairs bacterial adhesion to the endometrial wall.

02123-A: Identifying the Gene Responsible for Inherited Infertility and Sterility in 28 Breeds

Principal Investigator: Dr. Vicki Meyers-Wallen **Institution:** Cornell University

Total Grant Amount: $12,960.00

Grant Period: 7/1/2014 – 6/30/2015

Project Abstract:

In a previous study, Dr. Meyers-Wallen demonstrated that canine XX Disorder of Sexual Development (DSD) is a sex-limited autosomal recessive trait. Affected dogs develop testes or ovotestes and are masculinized in proportion to the amount of testis. Those having bilateral testes are sterile. Dogs with ovotestes range from sterile to fertile, with most developing female genitalia. Fertile affected dogs transmit the mutation to all their offspring. Carrier sires are fertile, and by founder effect, have increased mutation frequency in some breeds. Elimination of this mutation would reduce inherited female sterility and infertility in 28 breeds.

To this end, Dr. Meyers-Wallen hypothesizes that the XX DSD mutation is ancient, and therefore identical in most breeds. This predicts an identical XX DSD mutation in most, if not all breeds. In previous genomic studies, her research group identified a chromosomal region containing more than 16 fold enrichment for DNA sequence variants associated with XX DSD in the study pedigree. Using a custom designed array of 80 priority SNPs located in that region, they will now genotype affected dogs of 22 breeds and controls to identify variants that are identical in affected dogs. At the study conclusion, researchers are hopeful they will have an identical mutation candidate and be poised to develop a single DNA test for affected and carrier dogs in all breeds having this mutation.

02124-A: Determining the Characteristics of Sperm That Accurately Predict Fertility of Stud Dogs

Principal Investigator: Dr. Stuart Meyers, DVM, PhD **Institution:** University of California, Davis

Total Grant Amount: $12,960.00

Grant Period: 7/1/2014 – 6/30/2015

Project Abstract:

With the growing use of artificial insemination and frozen semen in dog breeding, the level of predictability and odds of fertile matings for any breed of dogs is currently unknown. The objective of Dr. Meyer's study is to determine the relationship of sperm characteristics to pregnancy outcome in a large population of a single breed of valuable service dogs (Labrador Retrievers) in which semen characteristics and known fertility has been tracked for a number of years. Researchers will collect semen samples from 35 Labrador Retriever stud dogs and determine a wide array of semen quality measures. Semen collections will be obtained twice weekly from each of two different males (4 dogs per week) at Guide Dogs for the Blind in San Rafael, CA. Semen will be evaluated at UC Davis using computer-assisted semen analysis, flow cytometry and brightfield and fluorescence microscopy. Each ejaculate will be cryopreserved according to standard methods at Guide Dogs for the Blind. Cryopreserved semen

will be thawed and evaluated for sperm post-thaw viability, motility, lipid peroxidation, acrosomal integrity, sperm chromatin structure assay, mitochondrial DNA, and reactive oxygen species generation (DHE fluorescence). They will evaluate semen parameters and male fertility using a multiple logistic regression model and Bayesian statistics to evaluate the relationship of sperm factors and male age to pregnancy. Successful completion of this project will result in predictability for semen fertility for frozen and fresh sperm from valuable stud dogs.

02136-A: Development of a Low Cost, Non-Invasive Test to Determine Whether Females Have Been Spayed

Principal Investigator: Dr. Margaret V. Root Kustritz, DVM, PhD **Institution:** University of Minnesota

Total Grant Amount: $6,031.80

Grant Period: 11/1/2014 – 10/31/2015

Project Abstract:

Dogs rescued from shelters often come without medical records or detailed medical histories, and while it is fairly straightforward for rescue groups to get dogs vaccinated and tested for heartworms, it is much harder for breed club groups to determine whether a female has been spayed. A non-invasive, low cost test to evaluate the presence or absence of ovaries could significantly reduce the need for costly, invasive procedures that become a barrier to breed club rescue efforts.

Data suggest concentrations of Insulin-like growth factor 1 (IGF-1), a component of the biochemical pathway controlling secretion and actions of insulin, is implicated in multiple aspects of growth and development including development and function of the ovaries. Dr. Root hypothesizes that IGF-1 in blood may be significantly lower in spayed than in unspayed female dogs, and that measurement of IGF-1 could be used to differentiate spayed from unspayed dogs. Through evaluation of IGF-1 concentrations in serum of 40 spayed and 40 intact dogs Dr. Root will determine whether IGF-1 can be developed into a diagnostic test for ovariectomy.

* 2015 National Parent Club Canine Health Conference Speaker

Clinician-Scientist Fellowship Program

The AKC Canine Health Foundation is pleased to announce the 2015 class of Clinician-Scientist Fellows. Six promising post-docs, residents and students were selected by their colleges of veterinary medicine and will receive support from the AKC Canine Health Foundation (CHF) for their training and research efforts.

Established in 2013, the AKC Canine Health Foundation Clinician-Scientist Fellowship Program seeks to encourage and support the next generation of canine health researchers in order to sustain future advancements in canine and human health.

Learn more about adopting a researcher: www.akcchf.org/fellows

Steven Friedenberg, DVM, MS, MBA
North Carolina State University

Dr. Steven Friedenberg is a PhD student in the laboratory of Dr. Kate Meurs at North Carolina State University College of Veterinary Medicine. The focus of his research is understanding the genetic causes of autoimmune diseases in dogs. Autoimmune diseases occur when the body attacks a part of itself – like joints, blood cells, or the pancreas – causing common diseases like rheumatoid arthritis or type I diabetes. Most of the time, we don't know why this happens, but the causes are likely a mix of both genes and the environment. Because dogs share a common environment with humans and have the same types of naturally occurring autoimmune diseases, they offer an excellent opportunity to learn about these debilitating diseases.The two diseases Dr. Friedenberg is currently studying are Addison's disease and immune-mediated hemolytic anemia (IMHA). Addison's disease is an endocrine disorder where the body attacks its own adrenal glands. The adrenal glands make important hormones that help humans and dogs cope with stress and control electrolyte balance. Similarly, IMHA is a blood disorder where the body attacks its own red blood cells – cells that are critical for carrying oxygen throughout the body. This disease is very common in breeds such as Cocker Spaniels and English Springer Spaniels, but is also seen in Labrador Retrievers, Shih Tzus, and other breeds. Current therapies for IMHA involve suppressing the immune system, which can cause additional complications. Dr. Friedenberg will take advantage of major advances in DNA sequencing to uncover the gene mutations that cause Addison's disease and IMHA. By finding the mutations, he believes we can work to decrease the incidence of the disease.

Hyun Ji Noh, MS, PhD
Broad Institute of MIT and Harvard

Dr. Noh obtained her Master's degree in pharmacology in 2008 and her PhD in computational biology from Oxford University in 2012. She is currently a postdoctoral fellow in the laboratory of Kerstin Lindblad-Toh at the Broad Institute, focusing on study comparative genetics. She is devoted to studying psychiatric disorders such as obsessive-compulsive disorder (OCD) in the dog. Dr. Noh has already published her first paper on canine OCD and has been speaking on the value and promise of canine genetics at international meetings worldwide. Dr. Noh's project is to understand the genetic risk factors that makes certain breeds, such as Doberman Pinschers, susceptible to obsessive-compulsive disorder. Canine OCD patients, like humans, show time-consuming repetitive behaviors that only partially respond to drug therapy. Using DNA from Doberman Pinschers with and without OCD, she identified 119 candidate genes responsible for OCD. The best gene candidates are all involved in nerve synapsis formation and function, and the mutations are usually in regulatory sequences near the genes, and not in the protein-coding sequence itself. She is now continuing to examine these same mutations in dog and human populations and using dog cell lines to understand exactly which mutations cause the disease, and how they disrupt normal brain function. Canine OCD is a severe and heartbreaking mental disease, and Dr. Noh's goal is to find appropriate drug targets to lead to new treatments in dogs, and hopefully also in humans.

Alana Redfern-Allen, DVM
Iowa State University

Dr. Redfern-Allen is currently working on a combined Internal Medicine Residency and MSc. program at Iowa State University. She has a strong interest in clinical research, particularly One health-focused research activities that aim to improve the health of humans and animals alike. Working under the guidance of Dr. Al Jergens, Dr. Redfern-Allen's research focus will be Diabetes mellitus, a common endocrine disease of dogs and humans. In humans it has been shown that imbalances in gastrointestinal bacteria are associated with Diabetes mellitus, and can contribute to high blood sugar concentrations by antagonizing the effects of insulin. The short-term aims of her study are to compare the fecal microbiota in healthy dogs with those in diabetic patients to see if significant differences in microbial composition between dog groups exist. Additionally, Dr. Redfern-Allen will evaluate the potential efficacy of probiotics in modulating gut microbial populations to a more favorable composition that improves the effectiveness of administered insulin.

Christine Sibigtroth, DVM
University of Missouri

Dr. Sibigtroth is working on a combined Neurology/Neurosurgery Residency and PhD in the Interdisciplinary Neuroscience Program with Dr. Joan Coates as her major advisor. She has a sincere enthusiasm for research and has a passion for study of canine degenerative myelopathy (DM) and neuroscience. Canine DM is an adult onset progressive neurodegenerative disease in dogs that shares many characteristics with inherited amyotrophic lateral sclerosis (ALS) in humans. ALS triggers a deterioration of the nerves that connect the brain to the muscles, leading to stiffness, slowing of movement, loss of muscle tissue and weakness. Dogs with DM initially develop incoordination and progressive weakness of their rear legs resulting in paralysis within one year from onset of signs.

The immune system, specifically microglia, the primary immune cells of the central nervous system (CNS), has been implicated in ALS disease progression. Dr. Sibigtroth's hypothesis is that the normal communication between motor neurons and microglia is similarly disrupted in canine DM, inducing a behavioral change in microglia cells. Microglia may transition from a neuroprotective to neurotoxic behavior, leading to progressive motor neuron damage and dysfunction. Owners of dogs with DM tend to have their pets euthanized at different stages of disease severity and examination of the donated tissues from these dogs will provide an effective way to study the various stages of DM progression. Her work will provide valuable insight into the role of microglia within canine DM disease progression and could identify key areas for the development of microglia-specific therapeutic targets that could slow or halt further disease progression.

Amelia Sinkin, VMD
University of Georgia

Dr. Sinkin is a cardiology resident working under Dr. Amanda Coleman, DVM, DACVIM (Cardiology). The focus of her research is myxomatous mitral valve disease (MMVD), a condition that affects an estimated 2 – 4.9 million dogs in the United States and leads to the development of congestive heart failure in approximately 15% of affected animals. The pathogenic role of renin-angiotensin-aldosterone system (RAAS) stimulation in the development and maintenance of MMVD is well accepted. Consequently, pharmacologic RAAS blockade, most frequently attempted through the use of angiotensin-converting enzyme inhibitors (ACEi), is considered standard-of-care for the treatment of patients with congestive heart failure and administration of these drugs is associated with improvement in both clinical signs and survival time in patients. While the clinical benefit of ACE inhibition is clear, an unexpected and undesirable phenomenon known as aldosterone "breakthrough" (ABT) can occur in some dogs impeding effective treatment. Addition of an aldosterone receptor blocker to standard congestive heart failure therapy may improve patient outcomes; however the evidence-based use of this drug in dogs has yet to be fully defined. The major objective of Dr. Sinkin's study will be to compare the incidence of ABT in client-owned dogs with advanced MMVD treated with an ACEi (enalapril) or an angiotensin receptor blocker (telmisartan). She hypothesizes that treatment with telmisartan will be associated with a significantly lower incidence of ABT than will treatment with enalapril. The results of this study will provide veterinarians with objective information to guide the way in which they approach RAAS blockade in clinical patients.

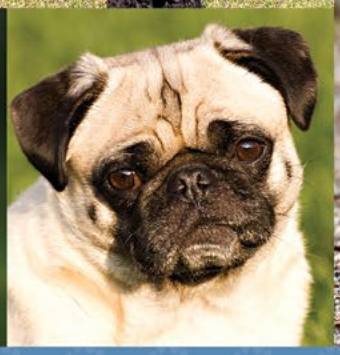
Ms. Emily Brown, DVM / PhD Candidate
UC. Davis

The Nova Scotia Duck Tolling Retriever Club of America, with matching funds from the U.C. Davis Center for Companion Animal Health is funding Emily Brown, a combined DVM/PHD student in the laboratory of Dr. Danika Bannasch, to conduct research investigating the genetic etiology of Addison's disease in the Nova Scotia Duck Tolling Retriever (NSDTR). Addison's disease is an endocrine disorder resulting from lack of hormone production by the adrenal gland and can occur in a dog of any breed at any age. Although relatively uncommon in the general dog population, certain breeds including the Nova Scotia Duck Tolling Retriever have been found to have a genetic predisposition. Previous research on Addison's disease in the NSDTR has shown a wide distribution of age at Addison's disease onset, suggesting 2 main categories of Addison's disease in the breed: a juvenile-onset form occurring in dogs under 12 months of age and an adult-onset form occurring on average at 4.6 years of age. An associated locus has been identified for the juvenile-onset form of the disease using genome-wide association analysis; however, no locus has been identified as associated with the adult-onset form of the disease in the breed. Over the course of her PhD, Ms. Brown hopes to elucidate the genetic cause of adult-onset Addison's disease in the breed, providing both tools for clinicians in diagnosis and for breeders in producing healthier dogs.

Ms. Brown is a previous recipient of a veterinary student travel grant from the Orthopedic Foundation for Animals and attended the 2013 AKC Canine Health Foundation National Parent Club Canine Health Conference in St. Louis, Missouri. Through attending this meeting, she was able to interact with breeders and other veterinary scientists united in the goal of improving purebred canine health. Attendance at this meeting motivated Brown to focus her PhD on genetic health issues affecting purebred dogs. Upon completion of her DVM/PhD degrees, Brown plans to pursue a residency in theriogenology and eventually an academic position at a veterinary school. She hopes that through her combined knowledge of veterinary medicine and genetics that she will be able to assist breeders in improving canine health, as well as be an active participant in the translation of basic science research to veterinary medicine.







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