AMERICAN KENNEL CLUB
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AKC Canine Health Foundation

2013 OAK Grants

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Cardiology Program Area

01753: Identification of Genetic Factors That Alter the Severity of Cardiomyopathy
Research Program Area: Cardiology
Principal Investigator: Dr. Kathryn M Meurs, DVM PhD, North Carolina State University
$51,516.00, 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
Research Program Area: Cardiology
Principal Investigator: Dr. Margaret M. Sleeper, VMD, University of Pennsylvania
$146,774.00, 1/1/2013 - 12/31/2014

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.

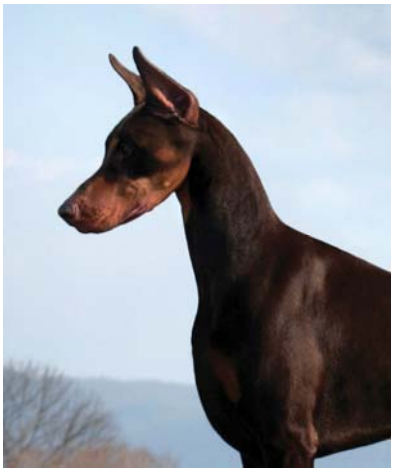

Photo courtesy of Miguel Betancourt

Musculoskeletal Program Area

01782: Defining the Elements of Successful Cranial Cruciate Ligament Repair
Principal Investigator: Dr. Gina Bertocci, PhD, University of Louisville
$75,816.00, 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.


Photo courtesy of Miguel Betancourt

Neurology Program Area

01731: A Novel Approach to Understanding How Meningoencephalomyelitis Develops In Dogs
Principal Investigator: Dr. Nick Jeffery, BVSc, Iowa State University
$31,104.00, 1/1/2013 - 12/31/2014

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.

Oncology Program Area

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

Principal Investigator: Dr. Matthew Breen, PhD, North Carolina State University
$131,265.00, 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.

Photo courtesy of Miguel Betancourt

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

Principal Investigator: Dr. Robert K Wayne, PhD, University of California, Los Angeles
$29,923.00, 1/1/2013 - 12/31/2013

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, University of Georgia
$119,065.00, 1/1/2013 - 12/31/2015

Project Abstract:
Drs. Platt (University of Georgia College of Veterinary Medicine) and 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 will be to detect a significant effect of the novel treatment on the progression free survival of the patients and the MRI volume of the tumors.

01759: Disrupting the Differentiation of Cancer Stem Cells to Prevent the Spread of Hemangiosarcoma
Research Program Area: Oncology/Hemangiosarcoma
Principal Investigator: Dr. Jaime F Modiano, VMD PhD, University of Minnesota
$247,979.00, 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.


Photo courtesy of Miguel Betancourt

01787: Clinical Advancement of a Cancer Vaccine in Dogs
Dr. Nicola J Mason, BVetMed, PhD, University of Pennsylvania
$96,660.00, 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.

01806: A Novel Virus-Based Anti-Tumor Treatment for Canine Osteosarcoma
Principal Investigator: Dr. Bruce F Smith, VMD PhD, Auburn University
$118,848.00, 1/1/2013 - 12/31/2014

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.

Renal Disease Program Area

01766: Identification and Validation of the Genes That Define Abnormal Development of the Kidney in Dogs
Principal Investigator: Dr. Kerstin Lindblad-Toh, PhD, Broad Institute
$25,000.00, 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, 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, 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, North Carolina State University
$116,184.24, 1/1/2013 - 12/31/2014

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.

Immunology and Infectious Disease Program Area

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

Principal Investigator: Dr. Aravind Ramakrishnan, MD, Fred Hutchinson Cancer Research Center

$178,200.00, 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. Ramakrishnan 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.

Photo courtesy of Miguel Betancourt

01780: Defining the Mechanism by Which Ticks Locate Dogs In Order To Better Prevent Disease Transmission

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

$104,867.31, 1/1/2013 - 12/31/2014

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

General Canine Health Program Area

01827: Defining the Specific Species of Bacteria That Contribute To Canine Periodontal Disease
Principal Investigator: Dr. Marcello Pasquale Riggio, PhD, University of Glasgow
$31,000.00, 1/1/2013 - 12/31/2013

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.


Photo courtesy of Miguel Betancourt

All Program Areas

01849: Filling the Gaps in the Canine Genome
Principal Investigator: Dr. Shaying Zhao, PhD, University of Georgia
$108,000.00, 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.

Recently emerged next-generation sequencing (NGS) technologies provide an unprecedented opportunity to correct these errors and to supply the missing information in the current dog gene annotation in a time- and cost-effective fashion. We propose herein to use state of the art NGS 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.