WFA FUNDED GRANTS (2009 – 2017): Background Information

D08CA-002: Studying Immune System's Response to Allergens
Morris Animal Foundation Grant
Dr. Mark Rutherford and Sheila Torres
University of Minnesota
Co-sponsors: Anonymous; Westie Foundation of America; Pfizer Animal Health

Atopic dermatitis, which is skin inflammation caused by environmental allergens, affects many dogs and most will develop secondary skin infections that aggravate suffering and require antibiotic treatment. In addition to cost, repeated antibiotic use can lead to antibiotic resistance. The skin's immune system contains small antimicrobial peptides that defend the skin against infections. Humans with atopic dermatitis along with secondary bacterial infections are deficient in expression of certain antimicrobial peptide genes. This study will investigate whether allergic dogs also lack these peptides. The findings could help veterinarians predict disease risk and monitor therapies of dogs with atopic dermatitis and secondary infection.

Active Grant: 1312
Association mapping study of Legg-Calve-Perthes Disease in the West Highland White Terrier, Yorkshire Terrier, and Miniature Pinscher
Grant Duration:
01/01/2010 - 12/31/2011
Disease(s):
Orthopedic Disorders: Legg-Calve-Perthes Disease
Sponsor(s):
Orthopedic Foundation for Animals
Researcher(s):
Dr. Keith E. Murphy, PhD
Breed(s):
Miniature Pinscher, West Highland White Terrier, Yorkshire Terrier
Background: Legg-Calve-Perthes Disease (LCPD) is a debilitating developmental disease that affects small breeds of dog, particularly terrier breeds. The only outward indications of this condition are pain, lameness, and muscle atrophy of the hip joint. These signs are not exclusive to LCPD, and are often attributed to minor trauma during the early stages of disease. LCPD is primarily diagnosed by radiographic changes of the femoral head within the hip joint. Due to the developmental nature and the unknown etiology of the disease, LCPD is difficult to predict and prevent. No disease mapping strategies have been employed to date. Objective: This study is using the Affymetrix canine single nucleotide polymorphism (SNP) chip to identify regions that are linked to LCPD in the West Highland White Terrier, Yorkshire Terrier, and Miniature Pinscher breeds.

1240-A: Development of a Diagnostic Method for Canine Atopic Dermatitis;

Daniel A. Gingerich, DVM, Imulan Bio Therapeutics. LLC
Start Date: 5/1/2009 Grant Amount: $11,880

Abstract: This proposal is to develop simple blood tests to detect whether or not a particular dog is hyper-reactive to its own immune cells, which is characteristic of atopic dermatitis. Atopic dermatitis, an autoimmune disease in which dogs develop hypersensitivity to environmental or food allergens, is a common and frustrating canine skin condition. There are few effective therapies and many dogs require prolonged administration of steroids or other immunosuppressive drugs. The only specific cure is skin testing and desensitization treatments over prolonged periods of time, managed by skilled veterinarians. Palliative treatments, including newer immunosuppressive drugs such as cyclosporine are only partially effective. It is now known that dogs with atopic dermatitis have specific immunological imbalances compared to normal dogs. A new vaccine has been developed that may correct the underlying immunological imbalance, and is showing encouraging results in ongoing trials. Unfortunately, there is at present no convenient, cost-effective way of determining whether or not a particular dog has that immunological imbalance or whether the dog would likely respond to the new vaccine. Fortunately, research has shown that animals and humans with autoimmune disease have serum antibodies against their own T-cell receptors (TCR). This hyper-reactivity can be detected with simple blood tests. However, the tests must be specifically designed for each species (dog, human, etc). This project is to develop screening tests for dogs and to use these tests to determine response to treatment.

D05CA-049 Candidate Gene Analysis in Dogs Affected with Hereditary Cataracts

UPDATE: Hereditary canine cataracts are one of the most common disorders affecting various dog breeds; however, very little is known about cataracts. To date only mutations in one specific gene (the HSF4 gene) have been identified as associated with canine cataracts in some breeds. Yet numerous breeds, including Labrador and golden retrievers, Portuguese water dogs and huskies, analyzed by scientists at the Medical College of Wisconsin do not carry mutations in the HSF4 gene. In this Morris Animal Foundation–funded study the researchers evaluated 26 genes associated with hereditary cataracts in humans and mice to see if mutations in these genes may be responsible for hereditary cataracts in Labrador and golden retrievers, Portuguese water dogs and huskies. In spite of their enormous efforts, the researchers did not identify cataract associated mutations in these particular breeds. Still, these results suggest that certain breeds of dogs may harbor mutations in novel, not yet identified canine genes associated with cataracts.

Active Grant: 1336A Purdue University

Finding the Mutations that Increase Susceptibility to Transitional Cell Carcinoma in the Scottish Terrier, West Highland Terrier, and Shetland Sheepdog

Grant Duration:
01/01/2010 - 12/31/2011

Disease(s):
Oncology: Transitional Cell Carcinoma, Urinary Bladder Cancer

Sponsor(s):
National Beagle Club, Scottish Terrier Club of America, Westie Foundation of America, Inc.

Researcher(s):
Dr. Deborah Knapp, DVM

Breed(s):
Scottish Terrier, Shetland Sheepdog, West Highland White Terrier

Abstract:
Background: Cancer is a major cause of death in older dogs. The treatment of advanced cancer is often ineffective. There is interest in discovering the causes of cancer in order to learn how to prevent cancer, or at least to detect cancer earlier when treatment may be more effective. Genetic (heritable) factors are important in cancer development. Objective: The researchers wish to determine ways to identify dogs with genetic risk factors for cancer. These dogs could then: enter cancer prevention trials, undergo screening tests in order to detect the cancer earlier when it might be more treatable, and in the future to possibly receive "genetic" therapy. This team of researchers has recently identified "loci" (regions of the DNA) that are strongly associated with increased risk for urinary bladder cancer (transitional cell carcinoma, TCC) in Scottish Terriers, West Highland White Terriers and Shetland Sheepdogs. Now, they will identify which gene(s) are involved within these loci and the causative mutation(s) in the gene(s). This is the crucial next step in being able to identify dogs at risk for TCC. Methods being developed will also facilitate work in other cancers, and thus the potential to help dogs in many breeds.

National Human Genome Research Institute (Government)

Active Grant: 1336B

Finding the Mutations that Increase Susceptibility to Transitional Cell Carcinoma in the Scottish Terrier, West Highland Terrier, and Shetland Sheepdog

Grant Duration:
01/01/2010 - 12/31/2011

Disease(s):
Oncology: Transitional Cell Carcinoma, Urinary Bladder Cancer

Sponsor(s):
Not Listed

Researcher(s):
Dr. Elaine Ostrander, PhD

Breed(s):
Scottish Terrier, Shetland Sheepdog, West Highland White Terrier

Abstract:
Background: Cancer is a major cause of death in older dogs. The treatment of advanced cancer is often ineffective. There is interest in discovering the causes of cancer in order to learn how to prevent cancer, or at least to detect cancer earlier when treatment may be more effective. Genetic (heritable) factors are important in cancer development. Objective: The researchers wish to determine ways to identify dogs with genetic risk factors for cancer. These dogs could then: enter cancer prevention trials, undergo screening tests in order to detect the cancer earlier when it might be more treatable, and in the future to possibly receive "genetic" therapy. This team of researchers has recently identified "loci" (regions of the DNA) that are strongly associated with increased risk for urinary bladder cancer (transitional cell carcinoma, TCC) in Scottish Terriers, West Highland White Terriers and Shetland Sheepdogs. Now, they will identify which gene(s) are involved within these loci and the causative mutation(s) in the gene(s). This is the crucial next step in being able to identify dogs at risk for TCC. Methods being developed will also facilitate work in other cancers, and thus the potential to help dogs in many breeds.

Purdue University (University)

Active Grant: 1384-A

Improved Imaging to Monitor Therapy Response of Urinary Bladder Cancer Using 3D Volume Ultrasonography

Grant Duration:
02/01/2010 - 01/31/2011

Disease(s):
Oncology: Transitional Cell Carcinoma

Sponsor(s):
National Beagle Club, Scottish Terrier Club of America, Westie Foundation of America, Inc.

Researcher(s):
Dr. James F. Naughton, DVM

Breed(s):
All Dogs

Abstract:
Urinary bladder cancer (transitional cell carcinoma, TCC) strikes 20,000 to 30,000 pet dogs each year in the United States, and TCC prevalence is increasing. Breeds with the highest risk for developing this type of cancer include the Scottish Terrier, West Highland White Terrier, Shetland Sheepdog, Beagle and the Wire Hair Fox Terrier. Although substantial progress is being made in TCC treatment, most dogs eventually die from the cancer. The purpose of the proposed work is to determine a new method to measure TCC masses in the bladder, and therefore to be able to accurately determine the response to TCC therapy. There are three main reasons that this is so important. 1. In each individual dog, the change in tumor size is used to determine if the treatment the dog is currently receiving is being effective in that dog. If the cancer is regressing or remaining stable, the same treatment is continued. If the cancer is increasing in size, it is important to recognize this and switch to a different treatment. 2. There are several new therapies that may potentially work against TCC, and it is crucial to be able to measure the tumor size and thus the efficacy of these new therapies in dogs in clinical trials. 3. The currently available methods to measure TCC all have disadvantages or serious limitations. Computed tomography (CT, CAT scan) is the most accurate way to measure tumor volume, but this test is prohibitively expensive for most pet owners. CT also requires general anesthesia, and visualization of bladder masses requires urinary catheterization, both of which involve some risks. Two dimensional ultrasound (2D US) is currently most often used to measure TCC at our institution and other institutions. Tumor volume is estimated by evaluating US images that are made from two different angles, as the US probe is moved over the bladder multiple times. This technique may be inaccurate if the bladder is not distended to the same degree each time the

ultrasound exam is done on the dog, or if the US probe angle varies. To increase the accuracy, at our institution, the same person performs the US on each dog at each of the dog's visits. This is not a practical approach for many hospitals. Here we propose the evaluation of an exciting novel approach to measure TCC masses: three dimensional ultrasound (3D US). New, cutting edge technology allows 3D images to be produced from a single scan with a 3D US probe. In fact, once the US probe is placed in an optimal position over the bladder, the operator does not move the probe. Instead, an automated process captures the 3D volume with no operator movement. Thus the results are much less dependent on the same person doing each scan. In addition, the images are produced with the dog awake, and bladder catheterization is not expected to be required. In the study, 3D US will be tested in 10 dogs with comparison made to the gold standard, CT. The success of this study will allow an accurate, repeatable and cost-effective method for monitoring therapeutic success and allow for more timely and accurate adjustments in therapeutic regimens. Although the cost of 3D US equipment has been initially high, like most new technologies, the costs are rapidly dropping to an affordable investment in veterinary hospitals. In addition to imaging TCC, gaining experience with this technique is expected to allow its use to be expanded into assessing other types of cancer.

Proposal for WFA support of CMO research

May 4, 2010

The Westie Foundation was contacted by a researcher in Switzerland in February, 2010, about the possibility of collecting samples of affected CMO (craniomandibular osteopathy) dogs and their families. Dr. Cord Droegmeuller , Institute of Genetics at Berne, Switzerland is heading this research and currently they have made one run of samples on CMO by snip chip analysis to find a gene marker.

After much discussion back and forth by Dr. John Robertson and Dr. Droegmeuller, it was decided the best way to support the research was to collect, store and freeze samples at Virginia Tech with Dr. Robertson who would then catalog and ship the samples to Switzerland.

I have been working contacting select people that have shown an interest in CMO to see if this would be feasible and if people were willing to cooperate. With effort from many people, this looks entirely feasible.

I propose to the board of the WFA to approve funds up to $1000.00 to help procure shipping items, collect samples, and postage to help this study go forward. We may finally make headway in this nasty disease.

Kay McGuire, DVM
VP of Health, WFA

01415: *Development of Anti-IgE Peptide for Treatment of Canine Allergy*

Primary Investigator: Dr. Bruce Hammerberg, DVM PhD
Institution: North Carolina State University

Total Grant Amount: $84,861.00

Project Abstract:

Treatment of chronic allergic diseases in dogs, often seen as recurring dermatitis, frequently results in less than optimal outcomes. When the disease can be linked to exposure to specific allergens, such house dust mites, desensitization injections can be effective in some individuals when carried out over an extended time; however, most cases are not resolved by desensitization and require a combination of allergen avoidance and anti-inflammatory drugs. The prolonged use of these drugs, such as corticosteroids, can result in severe side effects. These same challenges exist for human allergy suffers, but recently there has been a major breakthrough in the development of a new, safe and effective therapy using a monoclonal antibody that specifically binds and neutralizes human IgE that is responsible for activating inflammation-producing cells. This new product is called Xolair® and it has been used safely by millions of allergy patients for more than 5 years. Our laboratory has developed a monoclonal antibody that specifically binds canine IgE in the same manner as the monoclonal antibody used to develop Xolair®. There are two obstacles remaining in providing the canine equivalent to Xolair® for treatment of allergies in dogs and they are the Ojectives of this proposal: 1. Modifying the monoclonal antibody to reduce the dog's natural response to clear this protein; and, 2. Developing cost effective production of the modified antibody. Our Approach is to: 1. Generate a single chain recombinant peptide from the IgE-binding region of our canine IgE-specific monoclonal antibody that is small in size and of limited antigenic potential; and 2. Develop a transgenic plant (eg. tobacco) containing the gene for this recombinant peptide using well established techniques that will allow production of the therapeutic peptide in kilogram quantities. The expected outcome will be to provide a new, safe and highly effective treatment option for canine allergic diseases that is affordable to use for maintenance therapy.

01421: *Genomic Resources for the Control of Canine Pyoderma*

Primary Investigator: Dr. Stephen A. Kania, PhD
Institution: University of Tennessee
Total Grant Amount: $42,466.00
Project Abstract:

Staphylococcal bacteria are responsible for most canine skin infections as well as other important diseases. Until recently antibiotic therapy was very effective for the treatment of these conditions. However, antibiotic resistance is increasing rapidly and we envision running out of useful antibiotic options. Alternatives to antibiotics may include vaccines or bacterial factors naturally produced by staphylococci that inhibit competing strains. The key to developing these strategies is discovering the genes responsible for antibiotic resistance, bacterial growth inhibitors, and targets for vaccines. The first step in our project is the collection of staphylococci causing skin infections from dogs in designated regions throughout the United States. Unique strains of antibiotic resistant bacteria will be identified and their genes of interest characterized for use in the development of the next generation of therapies for the treatment of canine infections.

01663-A: Placebo-controlled trial of T-cell receptor (TCR) peptide treatment in dogs with non-responsive atopic dermatitis

Grant Status: Open
Grant Amount: $12,960
Dr. Daniel A. Gingerich, DVM, Imulan Bio Therapeutics, LLC
May 1, 2011 - April 30, 2012
Disease(s): Atopic Dermatitis

Abstract
The purpose of this proposal is to provide funding to complete an ongoing clinical trial on the efficacy and safety of T-Cell receptor (TCR) peptide treatment of dogs with atopic dermatitis.

Atopic dermatitis is a frustrating, chronically relapsing allergic skin disease in dogs. Treatment options are limited; many dogs require prolonged administration of steroids or other immunosuppressive drugs. The only specific cure is skin testing and desensitization treatments by skilled veterinarians over prolonged periods of time. Palliative treatments and newer immunosuppressive drugs such as cyclosporine are effective under carefully managed conditions.

It is now known that the underlying cause of atopic dermatitis in dogs is impaired immune responsiveness, specifically T-cell imbalance. In laboratory mice, TCR peptide treatment consistently rebalances T-cells and restores normal immunity. In dogs with atopic dermatitis, previous CHFsponsored studies showed that TCR peptide treatment resulted in long lasting (60-90 days) improvement in itchiness and other signs of the disease, consistent with restoration of normal immune responsiveness. Furthermore, dogs with atopic dermatitis were found to have 16 fold higher anti-TCR antibody activity compared to normal dogs, suggesting new diagnostic tests.

Based on results of these pilot trials, a larger randomized controlled trial has been initiated in dogs with atopic dermatitis treated with TCR peptides or placebo. Interim trial results are promising and show the mean clinical scores improved significantly in the TCR peptide group but not in placebo controls.

Treatment of Idiopathic Pulmonary Fibrosis with adult bone marrow stem cells (July 2011)

Dr. Richard Vulliet, PhD, DVM
Professor
Laboratory of Veterinary Cytotherapeutics
U C Davis Vet School
Davis, CA 95616

The Westie Foundation has approved $6000 towards the pilot study on stem cell treatment of IPF in Westies on a case by case basis for the 2011 budget.

01591: ***Discovery of Genetic Susceptibility Loci in Atopic Dermatitis using a Genome-Wide Association Study in West Highland White Terriers***
Principal Investigator: Dr. Natasha J Olby, VetMB PhD
Institution: North Carolina State University
Total Grant Amount: $107,133.00
Grant Period: 1/1/2012 - 12/31/2012
Project Abstract:
Atopic dermatitis (AD) is a common, chronic, allergic skin condition that causes severe itching. Indeed, it has been estimated that approximately 8% of all dogs that present to their veterinarian do so because of clinical signs due to AD. Affected dogs scratch and rub their skin, causing damage to the skin and frequently causing bacterial or yeast infections. Treatment focuses on appropriate antibiotic therapy of infections, and controlling the allergic response, but AD cannot be cured and so owners and their pets face a lifelong struggle to control the signs. There is evidence that AD is a hereditary problem, and it is extremely common in the West Highland White Terrier (WHWT) in which it was estimated to affect 15% of all dogs. In preliminary work we have collected DNA on over 200 dogs, including affected and normal WHWT in addition to affected dogs of other breeds. We propose to use this DNA to perform a genome wide association study of AD in WHWT to identify chromosomal regions associated with the disease. The long-term goal is to develop genetic tests that can be used by breeders to decrease the prevalence of this condition.

01577: ***Fine Mapping of Loci for Transitional Cell Carcinoma in the Scottish Terrier, West Highland White Terrier, and Shetland Sheepdog***
Principal Investigator: Dr. Elaine Ostrander, PhD
Institution: National Human Genome Research Institute
Total Grant Amount: $45,000.00
Grant Period: 1/1/2012 - 12/31/2013
Project Abstract:
Cancer is a major cause of death in older dogs and treatment is often ineffective. We wish to identify the causes of cancer in order to learn how to more effectively predict, prevent, and treat the disease.

Genetic (heritable) factors are important in development of Transitional cell carcinoma (TCC) of the bladder. The Scottish and West Highland White terriers and the Shetland sheepdog are at high risk for TCC, and a subset of dogs of each breed are born with errors in critical genes that predispose them to the disease. We wish to develop ways to identify dogs with genetic risk factors for TCC. Dogs at risk could then either enter cancer prevention trials, undergo screening tests to detect cancer at its earliest state, and in the future, possibly receive â€oegeneticâ€_ therapy. In the first years of this grant, we found two regions of the genome where error-prone genes lie. We were able to determine how the gene errors were unique for each of the three breeds. We narrowed the first region to a few hundred bases in an interval that has only two genes. We are requesting continued funding to allow us to find the mutation as well as fine map the remaining critical gene. Methods developed in this effort will translate to other cancers and thus have the potential to help dogs of many breeds.

01609: ***Probiotic VSL# 3 Reduces Enteritis in Dogs with 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 - 12/31/2013
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. We hypothesis that VSL#3 used as an adjunct to standard therapy (i.e., elimination diet and prednisone) will induce a beneficial alteration of enteric bacteria leading to induction and maintenance of remission in dogs with IBD. A randomized, controlled clinical trial of 8 weeks duration will assess the efficacy of standard therapy + probiotic versus standard therapy alone. There is a need for additional data to be generated to provide proof of efficacy in probiotic therapy before these agents can be applied to widespread clinical use. These studies will also provide highly relevant insight into the anti-inflammatory effects of probiotics for treatment of human and canine IBD.

01620: ***Clinical and Laboratory Efficacy and Safety Studies of T-Cell Receptor (TCR) Peptides in Canine Atopic Dermatitis***

Principal Investigator: Dr. Daniel A. Gingerich, DVM
Institution: Imulan Bio Therapeutics, LLC
Total Grant Amount: $77,039.00
Grant Period: 1/1/2012 - 12/31/2013
Project Abstract:

The purpose of this proposal is to provide funding to confirm the efficacy and safety of T-cell receptor (TCR) peptide treatment in dogs with non-responsive atopic dermatitis.

Atopic dermatitis is a frustrating, chronically relapsing allergic skin disease in dogs. Treatment options are limited; many dogs require prolonged administration of steroids or other drugs. The only specific cure is skin testing and desensitization treatments over prolonged periods of time, managed by skilled veterinarians. Palliative treatments and newer immunosuppressive drugs such as cyclosporine are effective under carefully managed conditions.

It is now known that the underlying cause of atopic dermatitis in dogs is impaired immune responsiveness, specifically T-cell imbalance. In laboratory mice, TCR peptide treatment consistently rebalances T-cells and restores normal immunity. In dogs with atopic dermatitis, previous AKC sponsored studies showed that TCR peptide treatment resulted in long lasting (60-90 days) improvement in itchiness and other signs of atopy, consistent with restoration of normal immune responsiveness. Furthermore, dogs with atopic dermatitis were found to have 16 fold higher anti-TCR antibody activity compared to normal dogs, suggesting new diagnostic tests.

The objective of research described in this proposal is to complete clinical trials to verify the efficacy and safety of TCR peptide treatment in dogs with atopic dermatitis. Laboratory tests will also be conducted on serum samples from these dogs to confirm the immunological effects of TCR peptide treatment and to develop new diagnostic tests for the disease.

01312
1/1/2010 - 12/31/2011
$78,688.00
Musculoskeletal\Legg-Calve-Perthes Disease
Clemson University
Dr. Keith E. Murphy, PhD

Association mapping study of Legg-Calve-Perthes Disease in the West Highland White Terrier, Yorkshire Terrier, and Cairn Terriers

Background: Legg-Calve-Perthes Disease (LCPD) is a debilitating developmental disease that affects small breeds of dog, particularly terrier breeds. The only outward indications of this condition are pain, lameness, and muscle atrophy of the hip joint. These signs are not exclusive to LCPD, and are often attributed to minor trauma during the early stages of disease. LCPD is primarily diagnosed by radiographic changes of the femoral head within the hip joint. Due to the developmental nature and the unknown

etiology of the disease, LCPD is difficult to predict and prevent. No disease mapping strategies have been employed to date.
Objective: This study is using the Affymetrix canine single nucleotide polymorphism (SNP) chip to identify regions that are linked to LCPD in the West Highland White Terrier, Yorkshire Terrier, and Cairn Terrier breeds.

01415
1/1/2011 - 12/31/2012
$84,861.00
Dermatology\AtopicDermatitis
North Carolina State University
Dr. Bruce Hammerberg, DVM, PhD
Development of Anti-IgE Peptide for Treatment of Canine Allergy
Treatment of chronic allergic diseases in dogs, often seen as recurring dermatitis, frequently results in less than optimal outcomes. When the disease can be linked to exposure to specific allergens, such house dust mites, desensitization injections can be effective in some individuals when carried out over an extended time; however, most cases are not resolved by desensitization and require a combination of allergen avoidance and anti-inflammatory drugs. The prolonged use of these drugs, such as corticosteroids, can result in severe side effects. These same challenges exist for human allergy suffers, but recently there has been a major breakthrough in the development of a new, safe and effective therapy using a monoclonal antibody that specifically binds and neutralizes human IgE that is responsible for activating inflammation-producing cells. This new product is called Xolair® and it has been used safely by millions of allergy patients for more than 5 years. Our laboratory has developed a monoclonal antibody that specifically binds canine IgE in the same manner as the monoclonal antibody used to develop Xolair®. There are two obstacles remaining in providing the canine equivalent to Xolair® for treatment of allergies in dogs and they are the Objectives of this proposal: 1. Modifying the monoclonal antibody to reduce the dog's natural response to clear this protein; and, 2. Developing cost effective production of the modified antibody. Our Approach is to: 1. Generate a single chain recombinant peptide from the IgE-binding region of our canine IgE-specific monoclonal antibody that is small in size and of limited antigenic potential; and 2. Develop a transgenic plant (eg. tobacco) containing the gene for this recombinant peptide using well established techniques that will allow production of the therapeutic peptide in kilogram quantities. The expected outcome will be to provide a new, safe and highly effective treatment option for canine allergic diseases that is affordable to use for maintenance therapy.

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

Grant Status: Open
Grant Amount: $12,312
Dr. Shelley Rankin, PhD, University of Pennsylvania
June 1, 2014 - January 31, 2015
Breed(s): -All Dogs
Disease(s): Atopic Dermatitis
Research Program Area: Dermatology and Allergic Disease

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 Staphylococcus 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.

Publication(s): None at this time.

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

Grant Status: Open
Grant Amount: $12,960
Dr. Jan S Suchodolski, DVM, PhD, Texas A&M AgriLife Research
June 1, 2014 - May 31, 2015
Breed(s): -All Dogs
Disease(s): Atopic DermatitisResearch Program Area: Dermatology and Allergic Disease

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.

CHF Grant 2105-A

The genetics of Keratoconjunctivitis sicca (KCS) in the West Highland White Terrier

April, 2015

The following research study is being conducted by the Ophthalmology Service at the University of California, Davis - Veterinary Medical Teaching Hospital. Dr. Sara M. Thomasy DVM, PhD, DACVO is the principle researcher.

Many canine breeds suffer from discomfort due to dry eye and are often are seen by veterinarians for keratoconjunctivitis sicca (KCS). However, little is known about the causes of this disease and the current non-specific treatment methods are sometimes ineffective. It has been noted that several canine breeds including West Highland White Terriers are overrepresented with KCS which suggests that the disease may have a heritable basis. This study aims to fully characterize KCS in West Highland White Terriers with various tear film assessments and non-invasive imaging techniques and determine any genome-wide associations for KCS.

We are currently looking for West Highland White Terriers *with and without* KCS to participate in this study. The participants would receive a detailed ophthalmic examination performed by the UC Davis VMTH Ophthalmology Service at no charge, including digital slit lamp examination, an indirect ophthalmic examination, and tests to assess the tear film. Blood will also be drawn from these patients for use in the genotyping component of this study. Some participants will be selected for non-invasive imaging as well.

Animals that meet the following criteria may be eligible: West Highland White Terriers with KCS (dry eye) of any age and West Highland White Terriers with normal eyes that are greater than 7 years of age.

http://www.vetmed.ucdavis.edu/clinicaltrials/current_trials/by_service/ophthalmology.cfm

02237-A: Capturing Tumor Cells in Canine Blood

Grant Amount: $10,239
Dr. Tracy Stokol, PhD, Cornell University
January 1, 2016 - December 31, 2016
Sponsor(s): American Boxer Charitable Foundation

Abstract

Just like their human owners, many dogs suffer from cancer, which is often malignant, spreading through the body via blood. Once tumors have spread, they usually result in a poor outcome, including death. The tumor cells in circulation (CTCs) can be counted in the blood of people with cancer using immunocapture devices. The number of CTCs in blood can tell the clinician how aggressive the tumor is, its potential to spread, and how long a patient might survive. There is currently no such way of detecting CTCs in our canine companions. Development of an assay for counting CTCs in canine blood would be of tremendous benefit to our canine patients because, from a simple blood test, we could detect hidden tumors and gather information on tumor severity and the likelihood of spread or metastasis. The investigators will test a novel immunocapture microdevice - the GEDI - for counting tumor cells in canine blood. This device can capture CTCs from blood in human patients with various cancers. This study will test its potential to do the same for dogs. In this pilot study, blood samples from healthy dogs will be manipulated to test the ability to count how many added tumor cells are captured by the GEDI device. If the GEDI does capture the tumor cells, the next step will be to determine if the device can capture CTCs from the blood of dogs that are known to have cancer, paving a path to early detection of cancer in dogs.

Grant #2176A
Intralymphatic Immunotherapy for the Treatment of Canine Atopic Dermatitis

Canine Health Foundation
Dr. Andrea Lam, DVM
Tufts University

Description: Atopic dermatitis (AD) is a genetically predisposed inflammatory skin condition affecting approximately 10% of dogs globally and is probably the most prevalent skin disease in all canines. Affected dogs manifest with itchy skin and ears and secondary infections. Clinical features are associated with IgE antibodies produced against indoor/outdoor environmental allergens. Breeds such as Boxers, Terriers,

Retrievers, and Bulldogs are predisposed. Current treatment options include antihistamines, corticosteroids, cyclosporine, oclacitinib, and allergen-specific immunotherapy (ASIT), as well as adjunctive topical and antimicrobial therapy. Antihistamines are effective in about 25% of dogs. Corticosteroids are extremely efficacious; however, side effects are common, thus long-term use is strongly discouraged. Cyclosporine is effective in many dogs with few serious adverse effects, but cost can be a limitation in large breed dogs. Oclacitinib has been shown to have good efficacy, but long-term side effects have not been studied. ASIT appears as the only treatment that is able to induce a clinical cure. However, the percentage of atopic dogs that respond to this treatment is only 60-70% and in many, the response is only partial. It has been proposed that efficacy of subcutaneous ASIT is limited by the ability of the skin to stimulate the immune system. This study will test an alternative route of administration using ASIT for this important skin condition. The investigator will test if direct administration of allergens into a peripheral lymph node may be more effective in stimulating an immunologic reaction, and thereby increasing the response rate, and potentially the cure rate, for canine atopic dermatitis

Grant #2182A

Is Defective Secretion of Antimicrobial Peptides Associated with Reduced Microbicidal Effects in Atopic Keratinocytes?

Canine Health Foundation

Dr. Domineco Santoro, DVM

University of Florida

Description: Antimicrobial peptides (AMPs) are small proteins produced by many organisms. They have multiple functions, the most important of which is the defense against pathogens. The antimicrobial activity of such proteins has been demonstrated against multiple microorganisms. Recently, a lack of secretion of AMPs, after exposure to bacteria in human skin cells harvested from allergic patients, has been hypothesized as a possible cause of recurrent infections in allergic skin conditions. Allergies are common in dogs and frequently associated with recurrent, antibiotic-resistant skin infections. Thus, the identification of ways to boost ability to fight bacteria is important. The investigation of possible changes between healthy and atopic skin cells is fundamental in order to be able to intervene, and make such secretion more effective without the use of synthetic antimicrobials. Thus, the goal of this study is to determine if, like in people, lower AMP secretion is present in skin cells harvested from allergic dogs after stimulation with common cutaneous pathogenic bacteria. The hypotheses to test are 1)whether a lower amount of AMPs are secreted by allergic skin cells compared with healthy ones, and consequently, bacteria are not effectively killed; and 2)if a higher amount of AMPs is retained within the allergic cells. This study has the potential to open the way for a revolutionary approach to treating skin infections that occur secondary to allergies in dogs by increasing the secretion of natural antimicrobial defenses, and thus reducing the use of synthetic and expensive antimicrobials with potential side effects.

Grant # 2002
Defining the Genetic Basis of Inflammatory Bowel Disease

Canine Health Foundation
Dr. Karin Allenspach, DVM, PhD
Royal Veterinary College, University of London

Description: 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.

Pulmonary Fibrosis
Searching for a Plasma Marker for PF in Westies
Dr. Victor Thannickal
University of Alabama

RATIONALE:

Interstitial lung diseases (ILDs) are associated with oxidative stress. Plasma biomarkers that are directly linked to oxidative stress responses in this disease have not been identified. Stable oxidation products of tyrosine residues in proteins may reflect the oxidative microenvironment in the lung or a systemic inflammatory state.

OBJECTIVES:

To determine if levels of protein tyrosine oxidation are elevated in plasma of patients with ILD in comparison with an age- and sex-matched healthy control cohort.

METHODS:

Three tyrosine oxidation products, 3-chlorotyrosine, 3-nitrotyrosine, and o,o'-dityrosine, were quantified by tandem mass-spectrometry (MS/MS) in cellular models, a mouse model of injury-induced fibrosis, and in plasma of healthy controls and ILD patients (n = 42 in each group).

MEASUREMENTS AND MAIN RESULTS:

Plasma levels of 3-chlorotyrosine, 3-nitrotyrosine and o,o'-dityrosine were markedly elevated in ILD patients compared with control subjects with ROC curves separating these groups of 0.872, 0.893 and 0.997, respectively. In a murine model of lung fibrosis, levels of all three oxidative tyrosine modifications were increased in plasma and lung tissue. Cellular models support a critical role for a heme peroxidase and enzymatic source(s) of reactive oxygen species (ROS) in the generation of these oxidized products.

CONCLUSIONS:

We demonstrate an increase in oxidized tyrosine moieties within proteins in the circulating plasma of ILD patients. These data support the potential for development of oxidative stress-related biomarkers in early diagnosis, prognostication, and/or in evaluating responsiveness to emerging therapies for ILD.

Targeting the Cancer Epigenome: The Effect of Specific Histone Lysine Methyltransferase Inhibition in Canine B-Cell Lymphoma 02309

Principal Investigator: Dr. Angela McCleary-Wheeler, DVM, PhD; Cornell University TotalGrantAmount: $78,069 Grant Period: 1/1/2017 - 12/31/2018 Project Abstract:

While often treatable, canine lymphoma can rarely be cured. A continued understanding of the mechanisms causing lymphoma in dogs and identification of novel therapies are needed to improve survival. Research that has been actively explored and provided exciting breakthroughs for human lymphoma is epigenetics, or alterations in how genes are turned on and off independent of the DNA sequence. One way this occurs is through modifications of proteins that interact with DNA called histones. Modifications

to these histones can result in genes being turned on or off, leading to the development of cancer. One enzyme that modifies histones, EZH2, has been found to play a role in some human lymphomas. Given the striking similarities between human and canine lymphoma, the objective of this study is to characterize the function and role of EZH2 in canine lymphoma. The investigators will utilize an EZH2 inhibitor to study EZH2 in canine lymphoma cells, and help guide the future development of this targeted inhibitor for use as a novel therapy for canine lymphoma.

The Role of Complex Translocations Associated with TP53 Somatic Mutations for Aiding Prognosis of Canine Diffuse Large B-cell Lymphoma 023717

Principal Investigator: Dr. Matthew Breen, PhD; North Carolina State University TotalGrantAmount: $177,327 Grant Period: 1/1/2017 - 12/31/2018 Project Abstract:

Lymphoma accounts for up to 24% of all cancers diagnosed in pet dogs; diffuse large B-cell lymphoma (DLBCL) is the most common subtype. The response to treatment for canine lymphoma remains highly variable with no reliable means to predict response. Studies of lymphoma in people have identified characteristic genome changes that have both diagnostic and

prognostic significance. In human DLBCL, mutations in the TP53 gene, and genome rearrangements involving the MYC, BCL2 and BCL6 genes have been shown to confer particularly poor prognosis in cases treated with standard of care multi-agent (CHOP- based) chemotherapy. The investigator's previous CHF-funded studies have shown that canine cancers, including lymphoma, exhibit genomic changes that are conserved with those observed in the corresponding human cancers, and have identified MYC and BCL2 rearrangements and a high frequency of TP53 mutation in canine DLBCL. This research will screen a well-defined collection of over 450 pre-treatment, canine DLBCL samples to determine accurate frequencies of these genome changes. The researchers will investigate the correlation of these target aberrations with duration of first remission, and identify key genomic signatures that may aid prognosis of prospective canine lymphoma cases. The data generated should assist owners and veterinarians with decisions regarding treatment, and patients with signatures predictive of poor response to CHOP chemotherapy may benefit from more aggressive treatment to improve outcomes.