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2011 GRANTS

01425 Identification of epilepsy-causing mutations from the associated loci by next-generation resequencing

Dr. Hannes T Lohi, PhD

University of Helsinki and the Folkhälsan Institute of Genetics

9/12/2010 $86,400.00 - ASCF $3,000.00 matched funds

Epilepsy is the most common neurological disease in dogs and affects almost all breeds. Epilepsy runs often in families suggesting the risk for having the disease is genetic. Only a few recessive genes have been found in dogs with progressive myoclonus epilepsies, a specific type of epilepsy. For the more common idiopathic epilepsy, the genetic background is unknown. The investigators have identified several new disease genetic loci in many breeds for epilepsy. They propose to look more closely at these genetic loci in three breeds, Belgian Shepherds, Kromforhrlanders and Border Terriers. They will examine the actual DNA sequences of these candidate genes and the surrounding DNA (where the control regions for gene expression are often found) for the specific mutation that predisposes a dog to epilepsy. The identification of the mutation will allow the investigators the ability to develop genetic tests for perhaps many dog breeds and will provide insight into the pathogenesis of the disease. This will lead to better diagnosis and treatments. It is likely that if the genes are found to have mutations for these three breeds, other breeds, as well as human epilepsy patients, can be tested for the same mutations.

The investigators have identified genetic loci for epilepsy and will examine the specific DNA sequences for the mutations that may be responsible for the disease. This work may benefit Spaniels and other breeds that are prone to epilepsy.

01424 Genetic analysis of Cleft Palate/lip

Primary Investigator: Dr. Danika L Bannasch, DVM PhD

Institution: University of California, Davis - School of Veterinary Medicine

Total Grant Amount: $50,000.00 - ASCF $3,000.00 matched funds

Project Abstract: Cleft palate is a birth defect that occurs at a relatively high frequency in the Nova Scotia Duck

Address: 221 Baker Street
Phone: 727-455-7337
Email: info@ascf.com.org

Tolling Retriever (NSDTR) dog breed. Cleft palate causes inadequate sucking and swallowing and many puppies die of starvation due to their inability to nurse. In breeds of dogs with a known predisposition and high prevalence of cleft palate, cleft palate puppies are identified at birth and euthanized to prevent further suffering. We have performed a genome wide search and identified a chromosomal region that causes cleft palate/lip in the NSDTR. It is likely that this mutation causes cleft palate in other breeds since many mutations are shared across breeds. We propose to determine if other breeds affected with cleft palate share the same region of the genome and to use this information to identify the gene responsible. Identification of the causative gene or mutation for cleft palate in dogs will allow a genetic test to be designed and offered to breeders so that they will be able to make informed breeding decisions. In addition, finding the mutation in dogs could identify a good candidate gene for human cleft palate.

The investigators will have the research materials available to perform this proposal. If successful, the results will provide a genetic test to identify carriers of a mutation that predisposes the occurrence of cleft palate in hopefully multiple breeds. The use of the Nova Scotia Duck Tolling Retriever, a rare breed, has already identified a chromosomal region that is associated with cleft palate/lip and if other breeds share the same region it will allow the investigators to target this region to identify the causative mutation.

MORRIS ANIMAL FOUNDATION

6 MADGiC: Making Advanced Discoveries in Golden Cancers

Golden retrievers have been one of the most popular breeds in America for decades, but unfortunately these dogs also have one of the highest incidences of cancer. Hemangiosarcoma and lymphoma account for more than 30 percent of the deaths in this breed. Although breed susceptibility to cancer was first reported 30 years ago, the relationship between inherited traits and susceptibility for these cancers is still not known. The Golden Retriever Foundation and Morris Animal Foundation are funding MADGiC (Making Advanced Discoveries in Golden Cancers), a study that aims to discover and characterize heritable and somatic cancer mutations in golden retrievers. The three-year, $1 million project will examine heritable (genetic) traits that contribute to risk and progression of hemangiosarcoma and lymphoma in golden retrievers. The long-term goal is to understand what causes these diseases. Because both cancers occur with such high frequency, reducing their incidence (while retaining the positive phenotypes of the breed) will be a complex task, but the development of reliable genetic tests would allow breeders to build programs whereby high-risk combinations of factors could be avoided. In addition, effective strategies could be developed to control and treat hemangiosarcoma and lymphoma in golden retrievers and other dogs, and as importantly, what is learned from this research also may be applicable to develop effective prevention and treatment strategies for these diseases in people.

Address: 221 Baker Street
Phone: 727-455-7337
Email: info@ascf.com.org

Principal Investigator: Principal Investigator: Drs. Jaime F. Modiano, Matthew Breen and Kerstin Lindblad-Toh, Institutions: North Carolina State University, University of Minnesota and Uppsala University, Sweden

Total Study Cost: $1,109,688 - ASCF $3,000.00

Fully Sponsored: Golden Retriever Foundation & Morris Animal Foundation

1 Identifying Genetic Mutations for Cataracts in Australian Shepherds

Australian Shepherds depend heavily on their eyesight when herding stock animals such as cattle and sheep. Unfortunately, this breed has an increased risk of developing hereditary cataracts (HC), the most common eye disease leading to blindness in purebred dogs. This study investigates the genetic basis of HC in Australian Shepherds. Although recent studies have identified a mutation in the HSF4 gene that partially accounts for HC in this breed, about 10 percent of affected dogs do not carry this mutation while 15 percent of dogs reported to be clear of cataracts are carriers of this mutation. Consequently, the inability to accurately determine a dog's genetic risk for cataracts has led to difficulties for the breeding community. Researchers aim to identify additional genetic mutations that contribute to HC in Australian Shepherds by comparing the DNA of affected and unaffected dogs over 8 years old. If successful, the research could benefit Australian Shepherds and other breeds and could also help prevent this debilitating eye disorder.

Principal Investigator: Dr. Sally Ricketts, Animal Health Trust and the Centre for Preventive Medicine, United Kingdom, First Award Grant

Co-sponsor: Orthopedic Foundation for Animals; The Australian Shepherd Health & Genetics Institute, Inc.

Study ID: D10CA-303

Total Study Cost: $62,193 - ASCF $3,000.00

Review: Cataracts are one of the major health concerns for Cocker Spaniels and although this study is focused on Australian Shepherds, the research could benefit other breeds, including the Cocker Spaniel. Both breeds have an increased risk of developing hereditary cataracts (HC). Recent research has identified a mutation in the HSF4 gene,

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but this accounts for only 10% of HC in Australian Shepherds and another 15% carry this mutation but are clear of the disease. It is highly probable that other genetic mutations are responsible for HC. The grant proposes to identify additional genetic mutations that afflict Australian Shepherds. If successful, this may be applicable to many breeds with HC, including the Cocker Spaniel. The Orthopedic Foundation for Animals and the Australian Shepherd Health and Genetics Institute are supporting this grant, which reflects its importance and relevance to the health of many dog breeds.

5 Treating Canine Paralysis with Stem Cells

Most dogs who suffer from a severe spinal fracture that causes paralysis of the hind legs and loss of sensation will remain permanently paralyzed and unable to urinate. Numerous studies have shown that transplantation of a variety of cell types into an injured spinal cord is safe and can produce improvement. However, for the therapy to be clinically practical, transplantation of cells derived from the patient (autologous cells) is ideal, and combining different therapies is needed to improve the host regenerative response and survival, and integration of transplanted cells. With the recent explosion of stem cell therapy research, poorly controlled studies have resulted in contradictory results, making it unclear whether transplantation is effective. Investigators will compare the effect of three different therapies in chronically paraplegic dogs. This blinded clinical trial will rigorously compare a novel cellular transplantation therapy with different control groups. A positive result will provide a clinically applicable stem cell therapy for chronic canine paralysis.

Principal Investigator: Dr. Natasha J. Olby, North Carolina State University

Total Study Cost: $297,578 - ASCF $3,000.00

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Phone: 727-455-7337
Email: info@ascf.com.org

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2012 GRANTS

01633: Phase I S100B Inhibitor Clinical Trial for Canine Melanoma Therapy

Principal Investigator: Dr. Heather M. Wilson, DVM

Institution: Texas A&M University

Total Grant Amount: $80,000.00

Grant Period: 1/1/2012 - 12/31/2013

Project Abstract:

Spontaneous melanoma strikes an estimated 50,000 dogs each year. Even with aggressive treatment, the median survival time is < 1 year. Our 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.
01424 Genetic analysis of Cleft Palate/lip

01585: Phase I Study of Involved-Field Radiotherapy (IFRT) for Advanced Stage

Canine Lymphoma

Principal Investigator: Dr. Michael Deveau, DVM, MS

Institution: Texas A&M University

Total Grant Amount: $93,140.00

Grant Period: 1/1/2012 - 12/31/2013

Address: 221 Baker Street
Phone: 727-455-7337
Email: info@ascf.com.org

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Project Abstract:

Lymphoma is one of the most common neoplasms in canine companion animals accounting for upwards of 25% of all canine cancer and incident rates continue to rise. Chemotherapy results in high remissions rates but poor overall survival durations even with aggressive therapy. Lymphoma is extremely radiosensitive, however, incorporating full and half-body radiation therapy has demonstrated a quid pro quo effect between treatment-related toxicities and tumor control. In human medicine, this approach has been abandoned for advanced IFRT techniques utilizing advanced radiotherapy systems designed to kill residual disease 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, we propose a phase I study in which patients with advanced stage lymphoma will be treated with IFRT using helical tomotherapy. Canine patients identified will be treated with our current standard of care, a 19 week multi-drug chemotherapy protocol. Upon completion, they will be anesthetized to undergo CT examination for radiation therapy planning. Enlarged lymph nodes and the spleen and liver will be contoured as targets and treated to a predetermined dose level. Patients will be subjected to rigorous evaluation at each treatment and at one month intervals for dose limiting toxicities and/or adverse events.

01678-A Apoptosis - not just for Nucleated Cells: the Contribution of Programmed Cell Death to Red Cell Destruction in Immune-Mediated Hemolytic Anemia

MORRIS ANIMAL FOUNDATION

Developing a New Delivery System for Lymphoma Treatment

Blood cell lymphomas affect about 30 of every 100,000 dogs. Current treatment consists of a combination of cytotoxic drugs that induce remission in about 75 percent of patients. However, most dogs relapse within six to nine months of diagnosis. In human medicine, rituximab, an antibody-targeting drug, has substantially improved survival times for people with various types of B-cell lymphoma. Rituximab cannot be used in dogs, however, because it is a foreign protein and will therefore be rapidly destroyed by the dog’s immune system. Furthermore, rituximab does not recognize or bind to canine B cells. The researchers in this study will use a novel system to develop a canine-derived antibody fragment similar to rituximab that will recognize canine cancer cells and can be used repeatedly in dogs to specifically target B cells. Development of such a canine-derived antibody fragment may then allow targeted delivery of cytotoxic agents to the malignant B cells, thereby allowing for increased chemotherapy doses, reduced side effects and improved outcome for dogs with B cell lymphoma.

Address: 221 Baker Street
Phone: 727-455-7337
Email: info@ascf.com.org

Principal Investigator: Dr. Nicola Mason, University of Pennsylvania

Co-sponsors: The Emma-Jolie Cancer Foundation for Animals; The Yorkshire Terrier Club of America Foundation, Inc.; Portuguese Water Dog Foundation, Inc.; Australian Shepherd Health & Genetics Institute, Inc.

Study ID: D12CA-026

Evaluating a New Cell Therapy for Osteoarthritis in Dogs

An estimated 20 percent of adult dogs suffer from osteoarthritis. Many drug therapies are available, but some dogs do not respond to these medications or cannot tolerate them. One option would be to try to repair the connective tissue of the arthritic area, but cell therapies for connective tissue development need further exploration and validation before they are ready for mainstream clinical practice. This study will evaluate canine mesenchymal stromal-cell formulations for their effect on the immune system and ability to generate cartilage. Data gathered will contribute to a greater understanding of cellular reprogramming events and could be used to develop advanced treatments for repairing damaged tissue in dogs.

Principal Investigator: Dr. Thomas G. Koch, University of Guelph, Canada, First Award Grant

Co-sponsor: Ms. Ann Campbell

Study ID: D12CA-313

Developing Stem Cells to Treat Spinal Cord Injuries

Up to 2 percent of the dogs admitted to the hospital arrive with spinal cord injury, and 77 percent of these injuries are due to intervertebral disc disease. Long- backed breeds, especially Dachshunds, have the highest incidence. Currently, there is no restorative treatment for canine spinal cord injuries. The use of induced pluripotent stem cells (iPSCs) offers a potential solution; however, efforts to establish a platform for canine ipSC generation, neural differentiation and cell transplantation have been limited. Previously, the researchers generated canine ipSCs from adult fibroblasts of a German Shorthair Pointer and derived canine neural stem cells from those cells. In this study, they will attempt to do the same with Dachshunds. If successful, the study could demonstrate that derivation of canine ipSCs and canine neural stem cells is feasible, thereby opening the window for studies into inherited central nervous system diseases in dogs.

Principal Investigator: Dr. Jose Cibelli, Michigan State University

Study ID: D12CA-066

Address: 221 Baker Street
Phone: 727-455-7337
Email: info@ascf.com.org