

MADGiC: Making Advanced Discoveries in Golden Cancers Study ID: D10CA-501

Identifying Genetic Mutations for Cataracts in Australian Shepherds Study ID: D10CA-303

Treating Canine Paralysis with Stem Cells Study ID: D10CA-040

I have received updates for two of the Morris Animal Foundation grants and the updates are in layperson's terms so require no input on my part. The most exciting part is each grant is making significant progress. The researchers for MADGiC have identified several significant locations in the genome for both hemangiosarcoma and lymphoma! They are also looking at other breeds and collecting tumor samples which indicates the results may be applicable to other breeds. The second study, on canine paralysis, has significant progress as well. Two dogs have been treated with autologous stem cells and one patient appears to be improving. This patient was paralyzed for a long time, so any improvement is significant. The following are the updates:

D10CA-501: Discovery and Characterization of Heritable and Somatic Cancer Mutations in Golden Retrievers

LAY TITLE: MADGiC: Making Advanced Discoveries in Golden Cancers

Jaime F. Modiano, VMD, PhD, University of Minnesota; Dr. Matthew Breen, North Carolina State University; Dr. Kerstin Lindblad-Toh, Uppsala University, Sweden

UPDATE: 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 and are frequently diagnosed with hemangiosarcoma and lymphoma. In this three-year, multi-institutional study, researchers are examining genetic traits that contribute to risk and progression of these cancers in Golden Retrievers. So far, preliminary analysis of collected samples from more than 200 dogs has identified several significant locations on the Golden Retriever genome that are associated with each cancer. Researchers have also collected hemangiosarcoma and lymphoma tumor samples and are developing cell lines from some of these tumors to study specific traits of malignant cells and genetic abnormalities of the tumors. For breed comparisons, several tumor samples and cell lines originating from dogs of other breeds have also been acquired. Although this study focuses on Golden Retrievers, hemangiosarcoma and lymphoma tumors occur in all breeds, so the results of this study may be widely applicable to all dogs. The long-term goals are to understand what causes hemangiosarcoma and lymphoma and to develop strategies to prevent and treat these cancers.

D10CA-040: Treating Canine Paralysis with Autologous Adipose Tissue Derived Stem Cells, Schwann Cells & Inosine

LAY TITLE: Treating Canine Paralysis with Stem Cells

Dr. Natasha J. Olby, North Carolina State University

UPDATE: Most dogs that suffer from a severe spinal fracture resulting in paralysis of the hind legs and loss of sensation will remain permanently paralyzed and will experience a loss of bladder function. In the search for a new treatment, researchers from North Carolina State University are comparing the effectiveness of three different therapies in improving motor and sensory function in chronically paralyzed dogs. Of the three therapies being studied, the researchers hypothesize that transplantation of stem cells derived from the patient (autologous cells), along with an infusion of inosine (a drug effective in rewiring nerve cell fibers), will be more effective than the other two treatments: inosine alone or injections of artificial cerebrospinal fluid. Each dog participating in the study will be videotaped so an external group of researchers blinded to the treatment group can fairly evaluate the outcomes. This study is in the early stages of patient recruitment. Researchers plan to recruit 10 dogs a year over a three-year period and have so far performed cell transplantation in two dogs. Although it is too early in the clinical trial to assess outcomes, the first dog recruited into the trial appears to be improving. As this dog has been paralyzed for a long time, any improvements are encouraging. If this clinical trial demonstrates benefits from stem cell therapy, it will provide veterinarians with a new way to treat chronically paralyzed dogs.

In addition to the Morris Animal Foundation grants, the ASC-F Board funded the following AKC CHF grants for \$3,000 each:

01425 **Identification of epilepsy-causing mutations from the associated loci by next-generation resequencing** Dr. Hannes T Lohi, PhD

01424: **Genetic analysis of Cleft Palate/lip** Dr. Danika L Bannasch, DVM PhD

I have received updates for these grants and I am pleased that each have made significant progress in a relatively short period of time. The aim of the epilepsy grant was to identify epilepsy loci in three different breeds, Belgian Shepherds, Kromforhrlanders and Border Terriers. The researchers have successfully captured and sequenced the regions in two of the breeds and identified many variants across the regions. They will attempt to coordinate the variants with controls to identify those that occur in patients with epilepsy. With the Kromfohrlanders, they have not procured enough samples. They have also made progress in Schipperke and Norwich terriers.

They have also collected samples from over 400 new cases in many breeds. For the Genetic Analysis of Cleft Palate grant, the investigators have identified two regions that cause autosomal recessive cleft palate in Nova Scotia Duck Tolling Retrievers. They are looking at other breeds to determine if the same genes cause cleft palate in those breeds. They have 30 samples from nine different breeds, including the Nova Scotia Duck Tolling Retriever, Brittany, Whippet, Rhodesian Ridgeback, **Cocker Spaniel**, Dachshund, Labrador Retriever, Boston Terrier, and Weimaraner. The two genes in NDSTR do not share regions with the other breeds. They will continue to collect samples from affected, their parents, and unaffected littermates from all breeds.

I have also received updates for two AKC CHF grants funded prior to this past year. The grant, Canine Non-Hodgkin Lymphoma: Characterization and Prognostic Value of Cancer Stem Cells grant is a 30 month progress report. This completed study demonstrated that canine lymphoma has a cancer stem cell (LPCs, lymphoid progenitor cell) which give rise to the rest of the tumor cells. If these could be eliminated, it might be sufficient to cure the disease. The findings are providing a new target for finding effective therapeutic approaches to this disease. Once additional research into the basic biology of the lymphoma cancer stem cell is done, a novel approach to targeting these specific cells may be developed. This approach may reduce the number of these cancerous stem cells, or eliminate them completely. This could result in prolonged remissions or complete cures of this disease. The second AKC CHF grant is Immune Targeting of Canine Hemangiosarcoma Using a Canine Derived Single Chain Antibody Approach, by Dr. Nicola Mason. In this completed study, the investigators developed canine-derived antibody fragments that could be used to target tumor cells or their growth factors that are necessary for tumor cell proliferation and survival. An antibody fragment can be linked to toxic agents, and can deliver the toxic agent to the cancer cell. This allows for more specific drug delivery and thus reduces the side effects. For growth factors, the toxic agent is unnecessary; the antibody fragment itself is sufficient to inhibit tumor growth and survival. The researcher was successful in generating canine antibody fragments. They attempted to identify and isolate antibody fragments to canine hemangiosarcoma cells and to canine Vascular Endothelial Growth Factor (VEGF). They were unsuccessful with hemangiosarcoma cells, but were successful with VEGF. This growth factor plays an important role in ensuring that new blood vessels are generated in response to the presence of the tumor. The blood vessels are critical to tumor growth and agents that inhibit VEGF are important in the treatment of many malignancies, not just hemangiosarcoma. They are currently testing the ability of the antibody fragments to neutralize VEGF's effects on the growth of hemangiosarcoma cells in vitro. They are also attempting to generate monoclonal antibodies which will have more favorable pharmacokinetic properties in vivo. This is the development of the first canine-derived,

antigen-specific targeting approach that can be used for the treatment of many different types of cancer, including hemangiosarcoma. They have now isolated three separate antibody fragments that bind to canine VEGF. They have subsequently been awarded an AKC CHF grant to further develop the antibodies and move the work one step closer to the clinic.