In 1970, the Golden Retriever Foundation made its first gift to Morris Animal Foundation. The $2,250 donation was invested in the Foundation’s general research program. It was the start of a collaborative partnership that seeks to advance veterinary medicine and canine health through the funding of unbiased and impactful science.

The Golden Retriever Foundation increased its commitment to Morris Animal Foundation in 2004, when it began sponsoring specific canine health studies. From 2004 to 2021, the Golden Retriever Foundation invested over $1.2M in 32 studies, including an annual donation of $50,000 for 10 years earmarked for the Golden Retriever Lifetime Study. In addition to funds, the Golden Retriever Foundation provided crucial early support for the Study by assisting in recruitment and publicity, and by continuing to be a valued partner as the Study progresses.

The unprecedented events of 2020 and 2021 have only served to strengthen our bonds with the Golden Retriever Foundation. The partnership helped the Foundation emerge from the last year with bold new projects for the Golden Retriever Lifetime Study, which remains one of the largest studies of its kind anywhere in the world.

ACCOMPLISHMENT HIGHLIGHTS TO DATE:

• Gold Partner of the Golden Retriever Lifetime Study, with a $100,000 initial gift and a pledge of $50,000 per year for 10 years. Now entering its ninth year, the Study seeks to identify environmental, nutritional, lifestyle and genetic risk factors for cancer and other major diseases in dogs.
• Invested in 22 experienced investigator studies, advancing canine health in diverse subjects such as cancer and orthopedic disease.
• Sponsored eight Veterinary Student Scholars, increasing awareness in veterinary students about research opportunities and the impact of research in veterinary medicine.
• Co-sponsored a fellowship for a promising young veterinary researcher.
• Sponsored studies have resulted in more than 56 publications in scientific journals to date, adding to the body of veterinary knowledge.
**SCOPE OF RESEARCH**

- Improvements in basic understanding of disease and disease mechanisms
- Clinical trials of existing pharmaceuticals and new drugs
- Development of new pharmaceuticals and drug delivery systems
- Genetic basis for heart disease
- Cancer immunotherapy development
- Cancer biology, diagnosis and treatment
- Stem-cell biology and use
- Genetic basis for hereditary cataracts

**Partners on the Path**

The path to scientific breakthroughs in veterinary diagnostics, treatments, preventions and cures typically is long, with incremental findings along the way to keep science moving forward. Long-term, sustained investment is required to make meaningful advances – the type of investment made by the Golden Retriever Foundation through its support of Morris Animal Foundation. Without this support, the advances we have seen to date simply would not be possible.
GOLDEN RETRIEVER LIFETIME STUDY
Janet Patterson-Kane, DVM, PhD | Morris Animal Foundation | 3/1/2010–2/29/2024

Morris Animal Foundation's Golden Retriever Lifetime Study will help identify major nutritional, genetic and environmental risk factors for cancer and other important diseases in dogs. It is the largest prospective, longitudinal study in veterinary medicine in the United States, following a cohort of more than 3,000 purebred golden retrievers throughout their lifetime.

SCIENTIFIC PUBLICATIONS

PLOS ONE
Endoparasitism of Golden Retrievers: Prevalence, risk factors, and associated clinicopathologic changes (2022)

BMC GENOMICS
Genome-wide association analysis of canine T zone lymphoma identifies link to hypothyroidism and a shared association with mast-cell tumors (2020)

JOURNAL OF VETERINARY INTERNAL MEDICINE
The Golden Retriever Lifetime Study: Assessing factors associated with owner compliance after the first year of enrollment (2020)

PLOS ONE
Age at gonadectomy and risk of overweight/obesity and orthopedic injury in a cohort of Golden Retrievers (2019)

CONN’S HANDBOOK OF MODELS FOR HUMAN AGING
The dog as a model for aging research (2018)

CANINE GENETICS AND EPIDEMIOLOGY
Population characteristics of Golden Retriever Lifetime Study enrollees (2017)

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B: BIOLOGICAL SCIENCES

DISSECTING THE ROLE OF MIR-9 IN CANINE MAST CELL DISEASE
Cheryl London, DVM, PhD – Established Investigator | The Ohio State University | 10/1/2012–11/6/2015

Mast cell tumors (MCTs) are the most common skin tumors in dogs, and they often are fatal. Previous studies in dogs with aggressive tumors found that the small microRNA (miR-9) expressed in those tumors was more likely to spread and kill affected dogs. This study provides a molecular framework for understanding how tumors with miR-9 spread.

IMPACT
Researchers found evidence that miR-9 plays a critical role in promoting mast cell invasion. This study furthered our understanding of the factors leading to aggressive canine MCTs. This new information may help in the development of new diagnostic tools for specific therapeutic targets involving miR-9s.

ANTI-CD20 AND ANTI-CD47 PASSIVE IMMUNOTHERAPY FOR CANINE LYMPHOMA
Jaime Modiano, VMD, PhD – Established Investigator | University of Minnesota | 11/1/2012–7/19/2015

This study evaluates the efficacy of two antibodies to treat canine B-cell lymphoma. The investigators theorize...
that either antibody alone will kill lymphoma cells and delay tumor progression, but that the combined effect of the two antibodies will be more effective as a treatment for dogs with lymphoma.

**IMPACT**

Researchers confirmed that the antibody combination promoted the killing of canine lymphoma cells in a laboratory setting. The research team then used a pre-clinical model to test the combination. Highly encouraging data suggested that this immunotherapy combination is both safe and effective in treating diffuse large B-cell lymphoma. The next research step is to shepherd these antibody therapies through regulatory approval and into canine clinical trials.

**SCIENTIFIC PUBLICATIONS**

**CANCER IMMUNOLOGY RESEARCH**

Eradication of canine diffuse large B-cell lymphoma in a murine xenograft model with CD47 blockade and anti-CD20 (2016)

**VETERINARY IMMUNOLOGY AND IMMUNOPATHOLOGY**


**LEUKEMIA & LYMPHOMA**

Development of a novel anti-canine CD20 monoclonal antibody with diagnostic and therapeutic potential (2014)

**DI3CA-044**

**OPTIMIZATION OF OSTEOSARCOMA THERAPY USING GENE EXPRESSION MODELS**

Daniel L. Gustafson, PhD | Colorado State University | 10/1/2012–9/30/2014

Cancers are generally treated with the same chemotherapy drugs even though it is known that different cancers respond in different ways to different drugs. This study uses gene signature patterns to determine whether a cancer from an individual dog is more or less sensitive to a specific chemotherapy drug. If the researchers are successful, canine patients could be treated with the drug that would be most effective for their particular cancer.

**IMPACT**

By comparing gene signatures to known outcomes of therapy, the researchers were able to gauge how accurately they could predict if a specific chemotherapeutic agent would have a positive or negative response in an individual dog based on the dog's gene signature. They found that gene-expression models to search drug databases for optimal treatments developed for human medicine could be used in a cross-species manner and could significantly predict chemosensitivity for some, although not all, drugs in canine osteosarcoma cell lines and tumors. Follow-up research is underway to verify the study findings, which will then be used to design a clinical trial to prospectively test drug outcome predictions. If the follow-up studies are successful, canine patients could be treated with the drug that is most effective for their particular cancer. This type of approach, known as precision medicine, uses tailored therapy designed to better control cancer growth and spread while minimizing toxicity and avoiding ineffective drugs.

**SCIENTIFIC PUBLICATIONS**

**COMMUNICATIONS BIOLOGY**

Immune pathways and TP53 missense mutations are associated with longer survival in canine osteosarcoma (2022)

**BMC BIOINFORMATICS**

Intra- and interspecies gene expression models for predicting drug response in canine osteosarcoma (2016)
D13CA-071
IDENTIFICATION OF GENETIC MARKERS FOR FAMILIAL SUBVALVULAR AORTIC STENOSIS IN DOGS
Kathryn Meurs, DVM, PhD | North Carolina State University | 9/1/2012–4/1/2014

Subvalvular aortic stenosis (SAS), a congenital heart disorder in dogs, is particularly common in Rottweilers and golden retrievers. This study looks for a causative genetic mutation for subvalvular aortic stenosis in these breeds, which will help researchers develop a genetic screening test to reduce disease prevalence in other at-risk breeds.

IMPACT
The team searched the DNA of Rottweilers and golden retrievers using specially designed, custom-made DNA sequencing chips that allowed them to look for mutations in a shared genetic region of interest. Using this screening tool to analyze banked DNA samples, they compared DNA from SAS-affected golden retrievers and Rottweilers to DNA from dogs without the disease. Unfortunately, final data analysis did not pinpoint a common causative mutation for SAS in Rottweilers and golden retrievers within the specific genetic region studied. However, the research team was able to rule out many genes not associated with this heart disorder in these two breeds and is continuing to search in areas not yet examined.

SCIENTIFIC PUBLICATIONS
HUMAN GENETICS
A single codon insertion in PICALM is associated with development of familial subvalvular aortic stenosis in Newfoundland dogs (2014)

JOURNAL OF SMALL ANIMAL PRACTICE
Familial subvalvular aortic stenosis in golden retrievers: inheritance and echocardiographic findings (2012)

D13CA-400
SLUG AND INTERLEUKIN-8 IN SELF-RENEWAL OF CANCER STEM CELLS IN CANINE HEMANGIOSARCOMA
Jong Hyuk Kim, DVM, PhD | University of Minnesota | 9/1/2012–11/12/2014

Hemangiosarcoma is a common and fatal cancer that is particularly deadly to golden retrievers and Portuguese water dogs. This study examines how molecular signaling helps cancer stem cells undergo self-renewal. Investigators are evaluating the potential to control the activity of hemangiosarcoma stem cells by altering these molecular signals to slow tumor growth and to enhance sensitivity to conventional and targeted therapies.

IMPACT
The researchers found that IL-8 influences stem-cell signals and helps create a microenvironment that supports hemangiosarcoma tumor formation in the early stages of this cancer. Continuing research will investigate whether hemangiosarcoma development can be altered by interfering with the actions of IL-8 and cancer stem-cell signals.

This study has provided valuable insight into the properties of cancer stem cells and how they contribute to hemangiosarcoma tumor growth. Discovery of potential therapeutic targets, such as the mechanisms of IL-8-mediated cancer stem-cell regeneration, will help in the development of new treatments to slow tumor growth.
and to enhance sensitivity to conventional and targeted therapies.

**SCIENTIFIC PUBLICATIONS**

**MOLECULAR CANCER RESEARCH**
Genomically complex human angiosarcoma and canine hemangiosarcoma establish convergent angiogenic transcriptional programs driven by novel gene fusions (2021)

**VETERINARY AND COMPARATIVE ONCOLOGY**
Interactions between CXCR4 and CXCL12 promote cell migration and invasion of canine hemangiosarcoma (2015)

**THE AMERICAN JOURNAL OF PATHOLOGY**
Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization (2014)

**EXPERIMENTAL CELL RESEARCH**
Interleukin-8 promotes canine hemangiosarcoma growth by regulating the tumor microenvironment (2014)

**D13CA-604**

**COMBINING PAC-1 AND DOXORUBICIN FOR IMPROVED SENSITIZATION OF OSTEOSARCOMA CELLS TO APOPTOTIC SIGNALS**
Julie Song, PhD | University of Illinois | 6/1/2012–7/31/2012

Canine osteosarcoma accounts for approximately 90% of primary bone cancers in dogs. Conventional treatment for these dogs consists of limb amputation, followed by chemotherapy, for which doxorubicin is commonly used. This student project will test whether PAC-1, a synthesized chemical compound that induces cell suicide in cancer cells, is able to improve or restore the sensitivity of canine osteosarcoma cells to treatment with conventional anticancer drugs, such as doxorubicin. The student will administer PAC-1 in combination with doxorubicin in vitro using osteosarcoma cells. The data could provide necessary evidence as to whether treatment of osteosarcoma cells with PAC-1 improves outcomes.

**IMPACT**
This study was performed using an osteosarcoma cell line, which was treated with various concentrations of PAC-1 and doxorubicin. The viability of the treated cells was measured after treatment with PAC-1 alone, doxorubicin alone and as a combination therapy. Our results demonstrate that when PAC-1 or doxorubicin was used as single agent drugs, they had toxic effects but, unexpectedly, this effect was attenuated when the drugs were combined. Similar experiments also were conducted using cells that had become resistant to low levels of doxorubicin, which also revealed an attenuation of cytotoxic effects upon combination of PAC-1 with doxorubicin. These experiments reveal that combining PAC-1 with doxorubicin may inhibit cell toxicity to some degree, rather than enhance it. This study provides important information for practicing oncologists.

**D13CA-608**

**TARGETING THE METASTATIC PHENOTYPE IN CANINE SOFT TISSUE SARCOMA CELL LINES**
Leanne Magestro | North Carolina State University | 6/1/2012–7/31/2012

The incidence of canine cancer has risen in recent years. Despite more sophisticated and specialized treatment methods that control primary tumors, treatment for metastatic disease remains ineffective. This student project builds on work previously funded by Morris Animal Foundation that is determining the genomic changes that lead to metastasis of canine soft-tissue sarcomas. The student already has performed gene expression profiling and has determined different pathways for nonmetastatic and metastatic tumors. This student research project will test the effectiveness of different doses of drugs in inhibiting the various pathways identified.
D12CA-026
DEVELOPMENT OF A CD20-SPECIFIC ANTIBODY FRAGMENT FOR TARGETED THERAPY OF CANINE B-CELL LYMPHOMA

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% 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 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 outcomes for dogs with B-cell lymphoma.

IMPACT
The research team worked to develop canine-derived antibody fragments, similar to rituximab, that would recognize and specifically target canine B cells while escaping rejection by the dog’s immune system. Using various laboratory techniques, the researchers generated cells containing canine CD20. They also created three libraries of antibody fragments from dogs with B-cell lymphoma to screen for fragments that will bind tightly to these cancer cells.

Although the researchers have not yet identified a canine antibody fragment that targets CD20, they have generated important tools for detecting antibodies that cross-react with canine B cells. This information will be made available to other researchers and should prove valuable in future studies.

The group continues to screen their libraries for successful fragments and to test alternative approaches for binding CD20 in a way that will not be targeted by the dog’s immune system. Once the appropriate antibody is found, a canine drug similar to rituximab will be able to provide targeted delivery of cell-killing agents to the cancerous B cells, reducing side effects and improving outcomes for dogs with B-cell lymphoma.

D12CA-033
MONOCLONAL ANTIBODY THERAPY OF CANINE B-CELL LYMPHOMA
Barbara Biller, DVM, PhD | Colorado State University | 10/1/2011–7/17/2014

Lymphoma is one of the most common cancers of dogs, accounting for an estimated 25% of all canine cancers. More than 8% of dogs die of the disease within two years because chemoresistance develops. Although all types of dogs can be affected, certain breeds, such as boxers, Rottweilers, golden retrievers and cocker spaniels, appear to be at greater risk. The researchers will investigate a modified antibody (IMMU-114) that effectively kills canine lymphoma cells but does not appear to result in serious side effects when administered to healthy dogs. They will work to find the best dosage and evaluate its safety and effectiveness in dogs with B-cell lymphoma.

If successful, this research might provide a new treatment option for owners of dogs that develop this type of lymphoma. This antibody also might be effective in the treatment of malignant histiocytosis, a cancer commonly found in Bernese Mountain dogs. Therefore, a secondary aim of this project will be to conduct preliminary studies to determine if IMMU-114 could be effective in treating this aggressive disease.
IMPACT
Data showed that the antibody was well tolerated and had no serious side effects. The therapy successfully targeted B cells in dogs and decreased the B-cell population up to 50% within the first 24 hours after antibody infusion; however, in most patients, B cells returned to normal values within seven days after treatment.

Although the antibody therapy did not appear to slow down the progression of lymphoma in the study dogs, cancer was temporarily stabilized in three dogs. The longest period of stabilization was four weeks. This is significant because lymphoma usually progresses very quickly when no chemotherapy is given or when chemotherapy is no longer effective.

D12CA-302
CD40 SIGNALING PATHWAY AS A THERAPEUTIC TARGET IN CANINE DIFFUSE LARGE B-CELL LYMPHOMA
Daisuke Ito, DVM, PhD | University of Minnesota | 9/1/2011–4/1/2014

Canine lymphoma accounts for up to 24% of all canine tumors, and more than 80% of hematopoietic cell cancers. Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in dogs. Despite efforts to establish effective chemotherapy protocols, long-term remissions are rare and the median survival time for dogs with high-grade tumors ranges from six to 11 months. New strategies are required to improve survival and attain cures. One of the limitations in identifying therapeutic targets for canine lymphoma has been the lack of reliable systems to maintain and expand lymphoma cells in the laboratory. Previously, the researcher created a culture system to maintain lymphoma cells in the laboratory. In this study, he will use this system to stimulate CD40, a protein found in B-lymphocyte cells that help lymphoma cells spread and learn more about CD40's signaling pathway. The findings may highlight novel targets for developing therapies to treat diffuse large B-cell lymphoma in dogs.

IMPACT
Through his studies of canine DLBCL cells in the laboratory, Dr. Ito found that a signaling pathway is activated in DLBCL and is indeed critical for DLBCL tumor growth. Inhibiting this pathway killed canine tumor cells, which suggests that this pathway is a promising new therapy target to help combat lymphoma in dogs.

Dr. Ito and his team are continuing their research, including screening drugs to find those that can inhibit activity of this pathway. If successful, this strategy will help find potential new treatments for DLBCL, a much-needed tool for veterinary oncologists who treat patients with DLBCL. This study also has contributed to the career development of a promising young research scientist. In 2013, Dr. Ito was appointed assistant professor at the College of Veterinary Medicine at the University of Minnesota, where he will continue his research in veterinary oncology.

SCIENTIFIC PUBLICATIONS
CANCER IMMUNOLOGY RESEARCH
Eradication of canine diffuse large B-cell lymphoma in a murine xenograft model with CD47 blockade and anti-CD20 (2016)

VETERINARY IMMUNOLOGY AND IMMUNOPATHOLOGY

LEUKEMIA & LYMPHOMA
Development of a novel anti-canine CD20 monoclonal antibody with diagnostic and therapeutic potential (2014)

VETERINARY PATHOLOGY
Molecular profiling reveals prognostically significant subtypes of canine lymphoma (2013)

COMPARATIVE MEDICINE
Parenchymal signal intensity in 3-T body MRI of dogs with hematopoietic neoplasia (2013)
VETERINARY AND COMPARATIVE ONCOLOGY
Canine osteosarcoma cells exhibit resistance to aurora kinase inhibitors (2013)

LEUKEMIA & LYMPHOMA
CD40 ligand is necessary and sufficient to support primary diffuse large B-cell lymphoma cells in culture: a tool for in vitro preclinical studies with primary B-cell malignancies (2012)

D12CA-313
IMMUNOLOGICAL AND CHONDROGENIC EVALUATION OF CANINE STEM CELLS
Thomas Koch, DVM, PhD | University of Guelph | 3/1/2012–2/27/2017

An estimated 20% 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 need further development 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.

IMPACT
The team found that stem cells from both sources had similar functional properties, but different growth patterns. Each population showed an equal ability to become fat and bone cells, and suppress cells of the immune system, including cells responsible for inflammation. However, the adipose-derived stem cells grew at a much faster rate than the bone marrow-derived cells and were easier to isolate. The researchers concluded that: “Faster proliferation along with the potential for a less invasive method of their procurement makes them (fat-derived stem cells) the preferred source for canine mesenchymal stem cells.”

While the stem cells studied did form joint cartilage using standard protocols, more work still is needed before they can be used to regenerate (and possibly repair) joint cartilage. The research team has started looking at an alternative to using stem cells for cartilage formation. They are investigating ways to enhance the growth potential of chondrocytes, the normal principal cell of joint cartilage. They hope this alternative method will garner more promising results.

SCIENTIFIC PUBLICATIONS
PLOS ONE
Characterization and immunomodulatory effects of canine adipose tissue- and bone marrow-derived mesenchymal stromal cells (2016)

PLOS ONE
Canine platelet lysate is inferior to fetal bovine serum for the isolation and propagation of canine adipose tissue- and bone marrow-derived mesenchymal stromal cells (2015)

D12CA-616
EVALUATING GRADING SYSTEMS FOR ACCURATE PROGNOSIS OF CANINE CUTANEOUS MAST CELL TUMORS
Keiko Petrosky | Tufts University | 5/1/2011–6/30/2011

In dogs, mast cell tumors are one of the most common cancers, comprising up to 21% of all canine skin cancers. Clinical signs of cutaneous mast cell tumors can vary from easily cured isolated tumors to fatal metastases. Failure to accurately predict the outcome can result in patients being subjected to painful and expensive treatments unnecessarily or, conversely, to them not getting the intensive treatment they need. The student
scholar will evaluate different grading systems to determine which method will provide the most accurate prognosis for canine patients diagnosed with cutaneous mast cell tumors. More accurate grading systems will better predict outcomes and will help owners and practitioners determine the treatment options that will work best for the patient.

**IMPACT**
The student evaluated the usefulness of a newer, simpler grading system with respect to outcome in patients at the Cummings School of Veterinary Medicine at Tufts University. This study showed that the newer grading system is effective for evaluating dogs with mast cell tumors, allowing for better prediction of outcomes and helping owners and practitioners determine the treatment options that will work best for the patient.

**D12CA-619**
**THE ANIMALS DEPENDENT ON PEOPLE TRAINING (ADOPT) INITIATIVE**
Rochelle Prudic | Western University of Health Sciences | 6/1/2011–7/31/2011

Each year, an estimated seven million pets are placed into shelters and four million of them are euthanized prior to adoption. Twenty percent of surrendered dogs in shelters had been previously adopted from a shelter. These return statistics are largely attributed to the owner’s inability to address the pet's behavioral, financial or physical needs. The ADOPT (Animals Dependent on People Training) initiative creates veterinary-approved, first-time owner training that will serve to reduce the number of animals returned to shelters. The ADOPT curriculum is based on information collected from top veterinarians and veterinary organizations in their specialized fields of toxicology, behavior, emergency, welfare and wellness. The student will conduct and document the training program for adoption counselors and first-time owners to monitor the success of the program in reducing animal returns. This allows for measure of the success and tangibility of the ADOPT initiative in an animal adoption center. The long-term goal will be to create a veterinary-developed program with national distribution that serves to educate animal rescue facilities and new owners about basic canine medical, behavioral and financial planning needs at the time of adoption.

**IMPACT**
The veterinary student conducted and documented the training program to monitor its success in reducing animal returns. Shelter staff received training on emergency management, behavioral factors of adoption and potential toxin exposures in the home environment, among other topics. They also were a consistent message to give first-time owners. Use of the program at the pilot shelter led to a reduction in animal returns. This project also succeeded in using veterinary-taught shelter training programs to encourage collaboration among animal facilities and veterinary professionals and highlighted the importance of bridging the gap between veterinary medicine and adoption facilities to reduce animal returns.

**D12CA-803**
**DERIVING CANINE-INDUCED PLURIPOTENT STEM CELLS FOR FUTURE THERAPEUTIC USE AND DISEASE MODELING**
Debbie Guest, BSc, PhD | Animal Health Trust | 9/1/2011–11/1/2013

Dogs suffer from many orthopedic, neurological and cardiovascular injuries and diseases that could be treated with cell replacement therapies. One potential therapy is the use of induced pluripotent stem cells (iPSCs), which are artificially produced by reprogramming adult cells back to an embryonic state, thereby giving them the ability to grow indefinitely in culture and the potential to turn into any cell type. These iPSCs have enormous therapeutic potential because they can be used to grow genetically identical cells for use in transplantsations without risk of being rejected by the dog's immune system. To date, iPSCs have been successfully derived from adult human, mouse, monkey, pig, horse and sheep cells, but little has been done in dogs. The researcher will determine the factors and culture conditions required to generate canine iPSCs. This study will form the basis of future work to further characterize iPSCs and determine their potential to be used therapeutically in dogs and as a novel tool for studying canine inherited diseases.
IMPACT
With Morris Animal Foundation funding, researchers from the Animal Health Trust successfully determined the conditions required to generate canine iPSCs from clinically normal canine adult cells in the lab. By establishing the methods required to generate canine iPSCs, this research has formed the basis for future work to assess the therapeutic potential of canine iPSCs. These data stand to improve the health and welfare of dogs suffering from a wide range of conditions and injuries. Important next steps will include work to turn iPSCs into specific cell types with therapeutic relevance to dogs. Researchers also hope to generate iPSCs from dogs with inherited diseases, leading to a greater understanding of these diseases and their treatment.

SCIENTIFIC PUBLICATIONS
REPRODUCTION IN DOMESTIC ANIMALS
Derivation of Canine-Induced Pluripotent Stem Cells (2015)

D10CA-002
SAFETY AND EFFICACY OF A NOVEL ANTHRACYCLINE, AD198 IN DOGS WITH REFRACTORY LYMPHOMA
Alfred Legendre, DVM | University of Tennessee | 12/1/2010–1/1/2013

Lymphoma is a common tumor of the lymph nodes of dogs that is rarely cured because the tumor becomes resistant to chemotherapy. AD198 is a new anthracycline drug that is similar to doxorubicin, which is used in chemotherapy. Though very effective, doxorubicin causes heart toxicity, which limits the total amount that can be safely given. AD198 shows promise in treating lymphomas that are resistant to doxorubicin, and it does not produce heart toxicity. An injectable formulation of AD198 has been developed and evaluated in healthy dogs. This study will determine the best dose for dogs with lymphoma, and researchers will study how well AD198 affects cancer cells so that an alternative treatment option can be available to owners and veterinarians.

IMPACT
The researchers tested the safety and effectiveness of AD198 in tissue cultures. In these laboratory tests, the lymphoma cells that were resistant to doxorubicin also were resistant to AD198. This finding is contrary to similar studies done in mice with doxorubicin-resistant lymphomas.

Researchers also concurrently evaluated the effectiveness of AD198 in dogs with resistant lymphoma. Along with other drugs commonly used to treat lymphoma, increasing doses of AD198 were given to dogs with doxorubicin-resistant lymphoma. Similar to the results of the laboratory tissue-culture experiments, canine lymphomas that were resistant to doxorubicin chemotherapy also were resistant to AD198. Given these findings, the researchers do not recommend AD198 as an alternative treatment option for dogs with drug-resistant lymphomas.

D10CA-047
PHASE I/II CLINICAL TRIAL OF ATTAXOL® IN TUMOR-BEARING DOGS
Kim Selting, DVM | University of Missouri | 10/1/2010–12/5/2017

Many treatments for cancer work well in both humans and animals; yet taxane chemotherapy is too toxic for dogs and causes massive allergic reactions. The reaction, however, is to the liquid in which the drug is dissolved rather than to the drug itself. Paclitaxel, which is derived from the yew tree, is one of the most active drugs in this class. When paclitaxel is reformulated into nanoparticles, it is unlikely to cause reactions in dogs because the toxic liquid is not needed to deliver the drug. Nanoparticles also have the advantage of being so small that they are easily taken up in cancer cells. Attaxol, a reformulation of paclitaxel that allows it to be mixed with water, is safe when given intravenously to dogs. This study will assess whether Attaxol works well for treating canine tumors. If proven effective, Attaxol could be a new treatment option that would improve the quality and length of life for companion animals.
IMPACT

Although the newer formulation was generally safe, the team found inconsistent blood level measurements of the drug in study subjects. They also found rapid clearance of the drug from the blood, and variable tumor response. Overall, the drug was well tolerated by the patients enrolled in the study, with only one dog having a severe reaction.

Because of the wide range of toxicity data noted in dogs and the finding of rapid clearance from the blood, the team shortened the dose escalation study and investigated injecting the drug under the skin for slow release. No drug could be detected in the blood when it was administered in this manner. Researchers have proposed future investigation into the potential use of Crititax as an intra-lesional therapy (injected directly into the tumor).

The drug did show promise as a potential treatment with some evidence of drug efficacy in the treatment of cancers in the study dogs. The team also made a dose recommendation based on this study but emphasized the need for further research. They plan to use their findings as the basis for expanded Phase II Crititax drug trials.

Finding and adapting new cancer drugs for use in veterinary patients can be challenging. This applied research study provided critical baseline information for the future use of Crititax in dogs and highlighted the difficulties that confront researchers in this field. Preliminary findings of the study were presented at the 2013 Veterinary Cancer Society meeting, and a manuscript of the study results is in preparation.

SCIENTIFIC PUBLICATIONS

VETERINARY AND COMPARATIVE ONCOLOGY

Evaluation of intravenous and subcutaneous administration of a novel, excipient-free, nanoparticulate formulation of paclitaxel in dogs with spontaneously occurring neoplasia (2018)

DIOCA-060

PHARMACOKINETICS OF SINGLE ORAL DOSE LEVETIRACETAM EXTENDED-RELEASE TABLETS IN HEALTHY ADULT DOGS

Dawn Boothe, DVM, PhD | Auburn University | 2/1/2011-3/1/2012

Epilepsy is a serious seizure disorder that affects a large number of breeds and usually requires lifelong treatment. Dogs often develop a tolerance to therapy, so increasingly higher doses of anticonvulsants are needed. Previous studies showed that levetiracetam (commercially known as Keppra®), a human antiepileptic drug, is well tolerated by dogs, even at concentrations that exceed the maximum therapeutic range for humans. The drug also shows promise in controlling seizures. However, the half-life of levetiracetam is short in dogs. An extended-release Keppra® product was recently approved for humans and may allow for twice- or once-daily dosing in dogs. This study will determine the efficacy of levetiracetam as a safe, convenient anticonvulsant drug that can be given to dogs in a single oral dose. These data should be directly applicable to canine epilepsy patients, allowing the use of levetiracetam as a sole anticonvulsant drug.

IMPACT

Researchers at Auburn University studied the potential effectiveness in dogs of the new extended-release formulation of the levetiracetam. Results of the study showed that the new extended-release version of levetiracetam is a safe and convenient anticonvulsant drug that can be given to dogs once or twice daily rather than every eight hours for the standard formulation. Monitoring is suggested to determine which duration is best for each dog. These data suggest that the new drug may be a better treatment option for providing long-term management of seizures in dogs with epilepsy.
Golden retrievers have one of the highest incidences of cancer among dog breeds, with hemangiosarcoma and lymphoma accounting for more than 30% of the deaths in this breed. This study 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. 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, study results could inform treatment of these cancers in golden retrievers and other dogs.

**IMPACT**

The multi-institutional research team from the University of Uppsala & Broad Institute, the University of Minnesota, and North Carolina State University, examined genetic traits that contribute to the risk and progression of hemangiosarcoma and lymphoma in golden retrievers. Using recent technological advances to study heritable mutations in the golden retriever genome, the research team identified two regions that together explain part of the risk for these two diseases in this breed. They also showed that the disease progression and response to treatment are very heterogeneous in both hemangiosarcoma and lymphoma. At least some of these differences could be related to heritable traits.

The identification of genomic regions associated with these two cancers constitutes a critical step to designing rational strategies to diagnose these cancers earlier and more accurately. The recognition that disease heterogeneity could be due at least in part to genomic alterations is similarly important in the process of developing more effective treatments for golden retrievers and for the many other dogs diagnosed with hemangiosarcoma or lymphoma. Continuing research by this team will involve validating these key genomic regions in golden retrievers from more families to increase the representation of global pedigrees. If successful, potential outcomes would include tests that could be used to make informed breeding decisions and to guide treatment for dogs diagnosed with hemangiosarcoma or lymphoma.

**SCIENTIFIC PUBLICATIONS**

**JOURNAL OF VETERINARY INTERNAL MEDICINE**

Disposition of extended release levetiracetam in normal healthy dogs after single oral dosing (2015)

**D10CA-501**

**MADGIC: MAKING ADVANCED DISCOVERIES IN GOLDEN CANCERS**

Jaime F. Modiano, DVM, PhD | University of Minnesota | 1/1/2011–9/1/2014

Exome sequencing of lymphomas from three dog breeds reveals somatic mutation patterns reflecting genetic background (2015)

PLOS GENETICS

Genome-wide association study identifies shared risk loci common to two malignancies in golden retrievers (2015)

**CHROMOSOME RESEARCH**

Genomic profiling reveals extensive heterogeneity in somatic DNA copy number aberrations of canine hemangiosarcoma (2014)

**THE AMERICAN JOURNAL OF PATHOLOGY**

Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization (2014)
EXPERIMENTAL CELL RESEARCH
Interleukin-8 promotes canine hemangiosarcoma growth by regulating the tumor microenvironment (2014)

INTERNATIONAL JOURNAL OF CANCER
Hemangiosarcoma and its cancer stem cell subpopulation are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors (2013)

VETERINARY PATHOLOGY
Molecular profiling reveals prognostically significant subtypes of canine lymphoma (2012)

D09CA-029
GLUTATHIONE-S-TRANSFERASE POLYMORPHISMS IN DOGS: ASSOCIATION WITH RISK FOR LYMPHOMA AND RESPONSE TO CHEMOTHERAPY
Lauren Trepanier, DVM, PhD | University of Wisconsin-Madison | 9/1/2009–4/1/2012

Lymphoma is one of the most common cancers in dogs and fatal in most patients. Though the underlying causes of the disease aren’t understood, exposure to industrial pollutants and commonly used herbicides may increase a dog’s risk of lymphoma. Research shows that humans exposed to environmental chemicals have a higher risk for developing lymphoma, and genetic defects in the enzymes that remove environmental chemicals from the body increase this risk. This study will determine whether dogs with genetic defects in an important detoxification enzyme, called GSTT, are more likely to develop lymphoma. The results will provide insight into the genetic and environmental risk factors for lymphoma in dogs.

IMPACT
Glutathione-S-transferase (GST) enzymes play an important role in the detoxification of environmental carcinogens. People with defects in the gene that produces this enzyme are at higher risk for lymphoma, probably because of an inability to detoxify environmental pollutants. Researchers at the University of Wisconsin identified 27 variants of the GST gene in dogs. Dogs with one particular variant showed more than a six-fold higher risk for lymphoma. As a result of this finding, researchers are planning future studies to screen additional dogs. If researchers can link this genetic variant to a defective enzyme, it would suggest that the risk of lymphoma is related to an inability to detoxify environmental toxins in some dogs. This information could be used to better identify and minimize environmental risk factors for this common cancer.

SCIENTIFIC PUBLICATIONS
VETERINARY AND COMPARATIVE ONCOLOGY
Characterization of a low expression haplotype in canine glutathione S-transferase (GSTT1) and its prevalence in golden retrievers (2017)

VETERINARY AND COMPARATIVE ONCOLOGY
Positive association between a glutathione-S-transferase polymorphism and lymphoma in dogs (2014)

D09CA-405
ENRICHMENT FOR CANINE CANCER STEM CELLS BY IN VITRO MANIPULATION AND CHEMOTHERAPY
Aric Frantz, DVM, PhD | University of Minnesota | 9/1/2009–10/1/2012

Cancer therapy for dogs has become more common, but treatment doesn’t always lead to long-term remission, and some therapies have debilitating side effects. A major reason for failure of conventional treatments may be their inability to eradicate cancer stem cells. These cells are self-renewing, can spread to new areas of the body and can give rise to daughter cells, which can rapidly divide. This means that even one cancer stem cell left behind after treatment can cause the cancer to return. Cancer stem cells appear to be less susceptible to traditional cancer therapies, such as chemotherapy. Researchers will study cancer stem cells to help them develop therapeutic strategies that target these cells and generate new, more effective treatment approaches with fewer side effects for dogs with cancer.
IMPACT
The team first developed a single method to culture, enrich and maintain cancer stem cells from the three tumor types. These cells were then used to demonstrate that a shared set of characteristics defines cancer stem cells within the different tumor types. More specifically, they were able to identify groups of genes that interact via common pathways that are essential to produce cancer stem cells. Pathways are communication lines that cells use to work together to control one or more cell functions, such as cell division or cell death. Abnormal activation of signaling pathways can lead to cancer development and spread. Researchers suspect that these genes and pathways are potential drug targets and hope that further research may lead to treatments that will reduce or eliminate cancer relapse, benefiting most patients with these diseases.

Breeds represented in the tumor studies included golden retriever, German shepherd, Rottweiler, Saint Bernard, Great Pyrenees and boxer, all high-risk breeds for hemangiosarcoma, osteosarcoma and glioblastoma. All breeds stand to benefit from this work because any dog can develop these tumors.

This Fellowship Training Grant also has provided valuable training and career development opportunities for a new and promising cancer researcher.

SCIENTIFIC PUBLICATIONS

**VETERINARY AND COMPARATIVE ONCOLOGY**
Modulation of fatty acid metabolism and immune suppression are features of in vitro tumor sphere formation in ontogenetically distinct dog cancer (2017)

**THE AMERICAN JOURNAL OF PATHOLOGY**
Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization (2014)

**EXPERIMENTAL CELL RESEARCH**
Interleukin-8 promotes canine hemangiosarcoma a growth by regulating the tumor microenvironment (2014)

**GENOME BIOLOGY**
Genome-wide analyses implicate 33 loci in heritable dog osteosarcoma, including regulatory variants near CDKN2A/B (2013)

**INTERNATIONAL JOURNAL OF CANCER**
Hemangiosarcoma and its cancer stem cell subpopulation are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors (2013)

**LEUKEMIA & LYMPHOMA**
CD40 ligand is necessary and sufficient to support primary diffuse large B-cell lymphoma cells in culture: A tool for in vitro preclinical studies with primary B-cell malignancies (2012)

**VETERINARY PATHOLOGY**
Molecular profiling reveals prognostically significant subtypes of canine lymphoma (2012)

**D09CA-909**
**IDENTIFICATION OF A GENETIC MARKER FOR FAMILIAL SUBVALVULAR AORTIC STENOSIS IN THE GOLDEN RETRIEVER**
Joshua A. Stern, DVM, PhD | Washington State University | 9/1/2009–8/15/2013

Subvalvular aortic stenosis (SAS), the second most common congenital heart defect in dogs, is characterized by a ridge of fibromuscular tissue below the aortic valve. Mildly affected dogs may have a normal life span, but moderate to severely affected dogs are at risk for developing severe complications, such as congestive heart failure and infections of the heart muscle; they also are at risk for sudden death. Golden retrievers are one of the most frequently affected breeds, making them good subjects for study.
IMPACT
The team identified and mapped a chromosomal region that appears to contain the causative mutation for SAS in golden retrievers. The researchers are continuing to analyze these data and perform genetic research to precisely identify the causative mutation within this targeted chromosomal region and the data are now being used in genetic investigations of SAS in other breeds. The study team also identified a mutation associated with SAS in Newfoundlands. This information will help veterinarians and breeders make informed decisions regarding SAS in breeding lines and has brought researchers closer to developing a genetic screening test that would reduce the incidence of this often-devastating condition. Upon completion of his fellowship training program, Dr. Stern accepted a tenure-track faculty position at the University of California, Davis, as an assistant professor of cardiology. He now operates a molecular genetics laboratory there.

SCIENTIFIC PUBLICATIONS
HUMAN GENETICS
A single codon insertion in PICALM is associated with development of familial subvalvular aortic stenosis in Newfoundland dogs (2014)

MAMMALIAN GENOME
Extent of linkage disequilibrium in large breed dogs: chromosomal and breed variation (2013)

JOURNAL OF SMALL ANIMAL PRACTICE
Familial subvalvular aortic stenosis in golden retrievers: Inheritance and echocardiographic findings (2012)

D08CA-050
TYROSINE KINASES IN CANINE HEMANGIOSARCOMA
Stuart Helfand, DVM | Oregon State University | 10/1/2008–6/1/2012

Hemangiosarcoma remains one of the deadliest canine cancers. Despite treatments such as chemotherapy, immunotherapy and surgery, dogs rarely live beyond six months after diagnosis. New approaches are needed to improve the survival time of dogs afflicted with this devastating disease. This study will expand on the research team’s previous research into a novel class of drugs called tyrosine kinase inhibitors that may have the potential to control the growth of hemangiosarcoma. The results will help to clarify abnormalities that contribute to hemangiosarcoma proliferation and may ultimately lead to new treatment options for this aggressive cancer.

IMPACT
The research team investigated a novel class of drugs, tyrosine kinase inhibitors, which have the potential to control the growth of HSA cells. They learned that inhibiting certain tyrosine kinases effectively suppresses the growth of cancer cells. In addition, when tyrosine kinase inhibitors were combined with standard chemotherapy, the combination was significantly better at killing cancer cells. Researchers have begun to treat several dogs with HSA using dasatinib, a tyrosine kinase inhibitor identified as effective through this Morris Animal Foundation–funded study. Although it is too early to determine whether dasatinib is making a difference, the researchers hope to validate it as a therapy for dogs with hemangiosarcoma.

SCIENTIFIC PUBLICATIONS
TRANSLATIONAL ONCOLOGY
Imatinib and dasatinib inhibit hemangiosarcoma and implicate PDGFR-β and Src in tumor growth (2013)

VETERINARY AND COMPARATIVE ONCOLOGY
Phosphotyrosine enrichment identifies focal adhesion kinase and other tyrosine kinases for targeting in canine hemangiosarcoma (2012)

D08CA-620
EFFECT OF ALTERNATIVE AND COMPLEMENTARY TREATMENTS ON DOGS WITH OSTEOARTHRITIS OF THE HIP OR STIFLE
Osteoarthritis is a common, crippling orthopedic problem affecting an estimated one in five adult dogs. While many pharmacological therapies, including non-steroidal anti-inflammatory drugs, are currently used to alleviate the pain of osteoarthritis, pet owners are increasingly using alternative and complementary treatments. Little is known about the efficacy of these alternative treatments in dogs, however. This study evaluated the efficacy of three alternative treatments commonly used to alleviate chronic pain in humans with osteoarthritis – transcutaneous electrical nerve stimulation, low level laser therapy and acupuncture – to determine their effectiveness in helping dogs with osteoarthritis of the hip or stifle. This veterinary scholar project is part of a larger Morris Animal Foundation-funded grant. Results may provide scientific proof as to whether these treatments work in dogs.

**IMPACT**
The student helped in the recruitment of dogs into the study. At the conclusion of her summer program, she had learned several techniques used in orthopedic trials as well as learning more about the conduct of research and the challenges faced by scientists. The program also stimulated her interest in canine rehabilitation.

---

**DO7CA-620**
**STEREOTACTIC RADIOSURGERY FOR CURATIVE-INTENT TREATMENT OF APPENDICULAR OSTEOSARCOMA IN DOGS**

Osteosarcoma is the most common primary bone tumor in dogs, and it commonly affects large breed dogs such as Rottweilers. The current standard of care therapy is removal of the primary tumor via amputation, or surgical limb salvage of the distal radius, followed by chemotherapy.

**IMPACT**
Complications associated with limb spare surgery include local tumor recurrence and infection, which can occur in as many as 30% to 50% of patients. Stereotactic radiosurgery (SRS) is a new type of radiation available in veterinary medicine that can deliver high doses of radiation to the tumor while minimizing the radiation to the surrounding normal tissues. The investigators evaluated the possibility of using SRS as a novel, non-surgical limb salvage option for a variety of anatomic sites to treat the primary tumor in canine osteosarcoma.

Results showed improvement in patient lameness, significant pain palliation and no incidence of tumor recurrence. Fracture of the affected limb is the most common complication of SRS and occurred in five of the 17 dogs in this study. All of these dogs have been managed appropriately for their fractures. SRS promises to be a viable treatment option that can be offered to owners with dogs suffering from osteosarcoma, and expands the arsenal that veterinarians have to fight this devastating disease.

---

**DO7CA-627**
**DEVELOPMENT OF A GENOMIC ASSAY TO PROFILE ARCHIVAL CANINE HEMANGIOSARCOMAS**
Stephanie Montgomery, PhD | North Carolina State University | 6/1/2008–9/30/2008

Hemangiosarcoma is one of the most devastating cancers diagnosed in dogs. Because the tumors grow slowly and painlessly but aggressively spread throughout the body, the cancer progresses to advanced stages before a dog shows any signs of disease. Cancer is caused by mutations to DNA, but the precise mutations responsible for canine hemangiosarcoma are unknown. The student will compare the DNA found in hemangiosarcoma to the complete DNA sequence of a typical, healthy dog. This approach will allow the researchers to identify the precise location of the genetic mutations that lead to canine hemangiosarcoma. Ultimately, this knowledge may lead to new cancer therapies and the ability to identify dogs susceptible to this disease before they get sick.
IMPACT
The student and her mentor have identified a technique to isolate and use the DNA from existing archival samples, rather than having to collect fresh samples from thousands of newly diagnosed cases. This approach will allow them to rapidly identify the location of the genetic mutations leading to hemangiosarcoma. Ultimately, this knowledge may lead to new cancer therapies and allow them to identify dogs susceptible to this disease before they get sick.

DO6CA-027
TRANSCRIPTIONAL PROFILING OF CANINE MAST CELL TUMORS
Cheryl A. London, DVM, PhD | The Ohio State University | 9/1/2006–11/30/2008

Mast cell tumors (MCTs) are one of the most common tumors in dogs. Although many MCTs are benign, others can behave in a highly aggressive manner (malignant), spreading to distant skin sites, lymph nodes and the spleen and ultimately resulting in death. Scientists at The Ohio State University were interested in establishing a more accurate method to distinguish MCTs more likely to behave in a malignant manner and, therefore, identify dogs in need of aggressive treatments. They theorized that certain genetic factors, specifically a subset of genes called microRNAs, would be differentially altered in the malignant tumors. Scientists successfully profiled microRNA changes in benign and malignant MCTs and have identified a set of microRNAs preferentially expressed at high levels in the malignant tumors. Further research now is needed to use this new information to develop earlier diagnostic tools and better treatments for this deadly cancer in dogs.

IMPACT
Scientists successfully profiled microRNA changes in benign and malignant MCTs and have identified a set of microRNAs preferentially expressed at high levels in the malignant tumors. Further research now is needed to use this new information to develop earlier diagnostic tools and better treatments for this deadly cancer in dogs.

DO6CA-065
RECIPROCAL RELATIONSHIP OF PTEN AND P21 IN CANINE CANCER
Jaime F. Modiano, DVM, PhD | University of Minnesota | 10/1/2006–6/30/2009

An estimated one out of every two dogs alive today will get cancer in its lifetime, and as many as 50% of those will die from the disease. Despite significant gains in cancer treatment, a thorough understanding of why cancers arise and why they behave as they do is essential to improving prevention and treatment. For this project, researchers will investigate two proteins whose interactions appear to be intimately tied to the behavior of two serious cancers, melanoma and hemangiosarcoma. What they learn may help to test targeted therapies for these cancers and significantly improve the lives of affected dogs.

IMPACT
Scientists at the University of Minnesota and the University of California, Davis, found that using compounds to lower the levels of p21 in some tumors decreased resistance to conventional chemotherapy drugs. They also concluded that chemotherapy resistance is sometimes unrelated to abnormalities of PTEN, though it often is associated with elevated p21 levels. The results from this Morris Animal Foundation-funded project allowed the investigators to justify efforts to move these compounds to the next step of clinical development.
SCIENTIFIC PUBLICATIONS

MOLECULAR CANCER THERAPEUTICS
Sorafenib has soluble epoxide hydrolase inhibitory activity, which contributes to its effect profile in vivo (2009)

JOURNAL OF UROLOGY
Antisense attenuation of p21 sensitizes kidney cancer to apoptosis in response to conventional DNA damaging chemotherapy associated with enhancement of phospho-p53 (2008)

CANCER BIOLOGY AND THERAPY
High-throughput screening of a small molecule one-bead-one-compound combinatorial library to identify attenuators of p21 as chemotherapy sensitizers (2008)

MOLECULAR CANCER

EXPERT REVIEW OF ANTICANCER THERAPY
Targeting the PI3K-Akt pathway in kidney cancer (2007)

DOGCA-624
ACTIVITY OF DECITABINE, A DEMETHYLATING AGENT, ON TUMOR SUPPRESSOR GENES IN CANINE LYMPHOMA
Hillary Voris | The Ohio State University | 6/1/2007–9/30/2007

In this study, the student used a canine lymphoma cell line to examine the effect of a new drug, decitabine, which currently is being tested in humans with cancer. Treating the lymphoma cells with decitabine resulted in cell death and decreased growth of cancer cells. Additionally, treatment with decitabine restored the expression of one of the tumor suppressor genes examined. Though the drug will need to be tested further, the results from this study suggest that decitabine could one day be another tool veterinarians can use to treat canine cancer.

DOGCA-019
CANINE LYMPHOMA - THE PROGNOSTIC SIGNIFICANCE OF CYTOGENETIC CHANGES
Matthew Breen, PhD | North Carolina State University | 1/1/2006–2/20/2009

Lymphoma accounts for nearly 25% of all cancers in dogs, with some breeds particularly susceptible. Untreated cases rarely survive beyond three months after diagnosis. Some dogs respond to chemotherapy, but overall response and survival time vary widely, indicating a need to develop more refined modes of classification. Studies have shown that the presence of certain chromosome changes in humans with lymphoma has both diagnostic and prognostic significance. Investigators in this study have identified recurrent chromosome changes in canine lymphoma and will determine whether these changes show prognostic significance for dogs with this cancer.

They also may be able to determine whether these changes are associated with specific dog breeds at higher risk for lymphoma.

IMPACT
The study population used for this project was a set of archival lymph node specimens from dogs with lymphoma that were part of a multi-center clinical trial and had been treated with the same chemotherapy protocol. Each dog had been followed from the time of their diagnosis of lymphoma to the time of death and so provided a key resource to allow us to determine if genetic changes were of any prognostic value. Cells from each patient were isolated from the archival specimens and interrogated subsequently using multicolor molecular cytogenetics. In these experiments, regions of each of the five chromosomes were labeled with a
fluorescent dye and then used to probe cells isolated from each specimen. Using fluorescence microscopy, the number of copies of each of the five chromosomal regions was assessed in a population of cells from each patient. The mean copy number of each locus in the lymph node cell population was then evaluated using appropriate statistical methods. The data revealed that one of the five aberrations tested correlates significantly with the time that the lymphoma patients went into remission following first chemotherapy treatment. Further analysis of this chromosome aberration is underway and early data indicate that assessment of this chromosomal region may provide a means to reliably and accurately predict how long canine lymphoma patients will respond to their first series of chemotherapy treatments.

D05CA-049
CANDIDATE GENE ANALYSIS IN DOGS AFFECTED WITH HEREDITARY CATARACTS
D.J. Sidjanin, PhD | The Medical College of Wisconsin | 12/1/2005–12/31/2008

Cataracts are one of the top 10 diseases of concern for dogs, and hereditary cataracts are the most common hereditary eye disorder in purebreds, affecting nearly 125 breeds. Mutations in at least 26 genes in humans and mice already have been associated with the development of hereditary cataracts, but no such mutations have been identified in canine genes. The investigators hypothesize that the mutations that cause cataracts in humans and mice also are responsible for causing hereditary cataracts in dogs. In this study, they hope to identify the mutations responsible for hereditary cataracts in dogs. Such findings would allow scientists to develop a blood-based DNA test that could predict at a young age if a dog is normal, a carrier or will be affected with cataracts. Through selective breeding, the mutant gene could be ultimately eliminated from dog breeds.

IMPACT
The research team 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. Despite 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.

SCIENTIFIC PUBLICATIONS

MOLECULAR VISION
Cloning and characterization of canine PAX6 and evaluation as a candidate gene in a canine model of aniridia (2007)

MOLECULAR VISION
Radiation hybrid mapping of cataract genes in the dog (2006)

ANIMAL GENETICS
Cloning of canine galactokinase (GALK1) and evaluation as a candidate gene for hereditary cataracts in Labrador retrievers (2005)

D04CA-026
GENOME SCANNING FOR ABERRANT DNA METHYLATION IN CANINE LYMPHOMA
Laura Rush, DVM, PhD | The Ohio State University | 1/1/2004–12/31/2007

This study was discontinued due to the unexpected departure of the Principal Investigator from the institution. Below is a summary of progress from the most recent progress report.
DNA-promoter methylation occurs frequently in human cancers and enhances tumor survival by inactivating genes necessary for normal growth control. We hypothesized that methylation plays a key role in canine lymphoma. Using a technique called Restriction Landmark Genomic Scanning, we have shown that canine lymphoma samples exhibit widespread abnormalities in their genomic DNA methylation patterns which are very similar to human tumors. We also have investigated individual genes for a more comprehensive assessment of their promoter methylation and found that the promoter regions of some genes could be demethylated and reactivated after exposure to a demethylating drug. Our approach is to identify these genes based on a computational “in silico” computer program, an approach that has been successful for the human, mouse and rat genomes.

Thus far, the project has shown that dogs with lymphoma have abnormal DNA methylation in their cancer cells, just as humans do. Some of the same genes methylated in humans are methylated in dogs, and our studies in cell culture show that the methylation can be partially reversed by treatment with a demethylating drug. This treatment has been used with success in human cancer and we hope that our work leads to clinical trials in pet dogs.

SCIENTIFIC PUBLICATIONS
BMC GENOMICS
Restriction landmark genomic scanning (RLGS) spot identification by second generation virtual RLGS in multiple genomes with multiple enzyme combinations (2007)
MORRIS ANIMAL FOUNDATION IN THE NEWS

The Foundation consistently recognizes Zoetis in communications regarding sponsored research, including the Golden Retriever Lifetime Study, such as press releases, social media posts, email communications and advertising.

In 2021, the marketing team continued to work with numerous media outlets to promote our research and mission.

IN FY21, IN EARNED MEDIA:

• 34,000 total stories
• Total unique page views/viewership/circulation of 2 billion
• Advertising value of $1.5M

GOLDEN RETRIEVER LIFETIME STUDY:

• 267 stories
• Viewership of 95,000,000
• Advertising value of $668,000

We continue to have our sponsored research featured on numerous media platforms in prestigious outlets, including ESPNews, the Pittsburgh Post-Gazette Online, the Arizona Republic Online, Mile High Living, The Miami Herald, Veterinary Practice News Online and Psychology Today, to name a few.

Our team is building a solid reputation as consistent and thoughtful commentators and are sought after by radio programs, online magazines and television stations across the United States. We continue to be featured guests on local radio stations such as KOSI and KOOL, as well as other regional and national stations such as WHYY Philadelphia and KSCO Santa Cruz.

During 2021, Foundation spokespeople made several television appearances in a number of outlets, including KUSA (Colorado and Company) and KMGH (Mile High Living).

The death of Betty White on December 31, 2021, brought unprecedented attention to the work of the Foundation. The marketing team responded quickly, fielding media requests from around the country, sending out press releases and engaging with our digital audiences. CEO, Tiffany Grunert, appeared on Good Morning America to discuss Betty’s legacy and long support of the Foundation.

In addition, the Foundation benefited from the #BettyWhiteChallenge, a global effort to promote donations to local shelters and Betty White’s favorite charities.
LOOKING FORWARD TO 2021

As we move into 2022, we recognize the ongoing challenges faced by our researchers, donors, partners and staff. The Foundation continues to adapt and innovate to fulfill our mission to bridge science and resources to advance the health of animals.

Our marketing and development teams continue to strategize ways to leverage exposure to the Foundation that resulted from Betty White's passing and to honor Betty's extraordinary love of animals by highlighting her accomplishments and bond with the Foundation.

In the latter half of 2022, depending on COVID-19 conditions, we plan to attend conferences and meetings that were put on hold due to the pandemic. Outreach efforts to veterinarians, veterinary students and other veterinary personnel remains a top priority in 2022 as we expand our outreach efforts with these audiences. As always, our valued sponsors and partners are highlighted in our communications.