**Dr. Bruce F. Smith: Molecular Genetics Of Inherited Disease And Cancer.** Several projects are available in the area of gene therapy for a variety of diseases including cancer. Cancer projects include laboratory studies and pre-clinical and clinical trials for dogs with osteosarcoma, lymphoma, melanoma, mast cell tumor and breast cancer. These studies involve the creation, evaluation and administration of gene therapy vectors and novel biological molecules, and the assessment of patient progress, as well as detailed laboratory assessments of the impact of the therapy. The latest genetic approaches may be used to understand the basis of components of the disease. Projects involve the use of a wide variety of techniques including RNA and DNA isolation, quantitative PCR amplification, cell culture and flow cytometry as well as animal handling, phlebotomy, tissue biopsy and necropsy.

**Dr. Reid Hanson: A Study of the Visco-elastic and Friction Profiles of Equine Cartilage Surfaces.** Our lab seeks to characterize and compare the material properties of cartilage located within various joints of the equine limb. Specifically, we will investigate the visco-elastic stiffness and friction coefficient of the biphasic cartilage structure. These biphasic properties affect the performance of the joint as it carries different loads and motions to determine if different types of joints with different ranges of motion possess similar or different material properties and which properties are best suited for the joint’s individual conditions. Analyzing the various cartilage surfaces within each joint and between joints will lead to a better understanding of the mechanisms controlling the performance of healthy joints in horses and humans. This data will be used to translate into the design of better human artificial joints. Articular cartilage samples will be extracted from horses and analyzed in the Multiscale Tribology Laboratory, a multidiscipline lab between the Samuel Ginn College of Engineering and the College of Veterinary Medicine. Cartilage surface geometries will be characterized using nano-scale surface profilometry, scanning and transmission electron microscopy and mathematical/numerical modeling techniques to analyze the structure of the surfaces over many scales. The key is to mesh the geometries at multiple different scales into one complete model.

**Dr. Amarjit Mishra: Molecular mechanism of asthma pathogenesis.** The main goals of the laboratory is to identify novel pathways that regulate distinct feature of asthma pathogenesis in obesity, which then may inform us regarding the development of new treatment approaches. Obese asthmatics have a higher incidence of asthma complications and respond poorly to typical asthma medications, leading to greater healthcare utilization and a reduced quality of life. The major research theme of the laboratory centers on how obesity contributes to the proliferation and differentiation of dendritic cell (DCs) - restricted common DC progenitor cells (CDPs) and focused on understanding the imperative signals in progenitor cells involve in obesity-associated airway inflammation. The hypothesis is based on that obesity exacerbates airway inflammation in asthma by inducing the proliferation and differentiation of CDPs, which enhances the ability of DCs in the lung to promote adaptive immune responses. A specific objective of the research in the proposal is to identify novel endogenous signaling pathways and druggable targets in CDPs related to adaptive immunity that regulates airway inflammation in obesity. The proposal will utilize synergistic combination of murine models of experimental obesity induced airway inflammation and cellular investigations of immune and progenitor cell functions. The laboratory employs experimental techniques including airway hyperactivity measurements, multicolor flow cytometry, biochemical and immunological evaluation of the disease. Students may participate in both experimental procedures and laboratory research. This work is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health.
Dr. Pete W Christopherson: Inherited Diseases of Hemostasis. Our laboratory is involved with evaluating inherited platelet and coagulation disorders in dogs, horses, and cows at the functional, biochemical, and molecular level. Students working in our laboratory would have exposure to a broad array of experiences ranging from blood collection, platelet isolation, platelet function testing, DNA isolation, PCR techniques, and flow cytometry.

Dr. Robert L. Judd: Obesity is associated with colonic dysfunction, including altered composition of the gut microbiota. Hydroxycarboxylic acid receptor 2 (HCA2), is a G-protein-coupled receptor originally identified in white adipose tissue, where it functions to decrease lipolysis. Recent studies have demonstrated that HCA2 is also expressed in immune and epithelial cells. In the colon, HCA2 expression is restricted to the lumen-facing apical membrane of intestinal and colonic epithelial cells, where it mediates the immunomodulatory actions of the short chain fatty acid, butyrate. HCA2 ligands, including butyrate and niacin, inhibit dextran sodium sulfate-induced colonic inflammation and colon cancer in mouse models. However, the precise role of colonic HCA2 in diet-induced colonic dysfunction and obesity have not been determined. To address this question, wild type and HCA2-/- mice will be placed on either a normal or high fat diet (HFD). The effect of diet-induced obesity on colonic HCA2 gene and protein expression will be determined. In addition, the effect of loss of HCA2 (HCA2-/-) on diet-induced colonic dysfunction will be evaluated. Data from these studies will establish the role of HCA2 in the pathophysiology of diet-induced colonic dysfunction and lay the groundwork in support of various therapies (e.g. fiber diets, probiotics, ketogenic diets, niacin, and fecal transplants) to improve colonic function and overall health.

Dr. Douglas Martin: Molecular Therapy of Neurodegenerative Disease. The laboratory’s model of neurodegenerative disease is feline gangliosidosis, similar to human Tay-Sachs disease, a disorder in which abnormal function of lysosomes causes progressive nervous system dysfunction and death. Though first reported in 1881, Tay-Sachs disease remains virtually untreatable, and affected children die by 5 years of age after spending several years in a semi-vegetative state. However, new gene therapy strategies have been tested in mouse models of gangliosidosis with excellent results. Before inclusion in human clinical trials, new therapies are tested in the feline model for safety and therapeutic benefit. The laboratory employs a variety of experimental techniques including intracranial injection of therapeutic agents, MRI-based analyses of disease progression, and biochemical and molecular biological evaluation of therapeutic benefit. Students may participate in both experimental procedures and laboratory research. This work is part of an international effort of collaborative scientists and physicians, the Tay-Sachs Gene Therapy Consortium, whose goal is to begin gene therapy clinical trials in humans.

Dr. Dawn Boothe: The role of cannabinoids in the treatment or prevention of disease in animals. Our laboratory is interested in generating evidence regarding the safe and effective use of cannabinoids, and particularly cannabidiol, in animals. Our efforts include studies that are molecular to clinical in application. Molecular studies are focusing on characterization of the cannabinoid receptors in the tissues of dogs and cats. Additionally, this summer, we would like to begin to pursue affinity binding study with endogenous and exogenous cannabinoids. Clinically, we will be working with an online survey directed toward clients whose pets are receiving cannabinoids and will be submitting for funding a clinical trial targeting the use of cannabidiol in epileptic dogs.

Dr. Stuart Clark-Price, Dr. Seung-Woo Jung, and Dr. Jacob Johnson: Evaluation of intracoelomic alfaxalone in turtles. Reptiles as pets, and turtles in particular, are a rapidly growing area of the pet industry. As such, research into the anesthetic care of these species must continue to...
grow to provide veterinarians with information on the uses of different anesthetic drugs for facilitation of diagnostic and therapeutic procedures. Alfaxalone is a newer anesthetic agent that has the unique property of being a neuro-steroid that easily crosses biologic membranes. This allows for alfaxalone to be administered via multiple routes including intravenous and intramuscular. Intracoelomic administration of alfaxalone has been described in snakes but no published data is available for intracoelomic administration in turtles. We propose to study the effect of different dosages of alfaxalone administered into the coelomic cavity of turtles on anesthetic depth and cardiovascular function. Anesthetic depth will be determined based on loss of righting reflex, response to stimulation and response to Semmes-Weinstein monofilaments and cardiovascular parameters will be assessed via cardiac ultrasound examination.

**Dr. Rachel Moon:** Auditory environmental effects on canines undergoing abdominal ultrasound. The goal of this project is to assess effects of different auditory environments on canine subjects undergoing abdominal ultrasound. One of the advantages of ultrasound as a diagnostic tool is lack of invasiveness however sedation is often necessary to reduce stress and increase degree of cooperation in some canine patients undergoing ultrasound evaluation. Environmental manipulations, including auditory, could potentially prove valuable to reduce stress and decrease incidence of sedative use in clinical ultrasound patients. Both quantitative physiologic parameters and qualitative assessments will be collected during experiments. The student will gain experience with both data collection and evaluation.

**Dr. Maninder Sandey:** Melanoma is the most common malignant oral neoplasm in dogs. Canine oral melanoma (OM) is characterized by a highly aggressive biological behavior with rapid progression from localized to advanced-stage disease. Current treatment strategies, including surgery and radiation therapy provide transient relief from the local disease. However, chemotherapy or the Oncept vaccine yield no tumor control for the metastatic disease (<3 months median survival for stage III). Thus, alternative therapeutic approaches are needed for the control of primary and metastatic oral melanoma. Melanoma differentiation association gene-7/Interleukin-24 (mda-7/IL-24) is a member of the interleukin-10 gene family based on its predicted structure, chromosomal location and a small conserved signature sequence. Ectopic expression of human MDA-7 (HU-MDA-7) selectively induces cell death in a spectrum of human cancers, including melanoma, without harming normal cells or tissues. In a Phase I/II clinical trial, intratumoral injection of HU-mda-7 by means of a replication incompetent adenovirus (INGN 241; Ad.mda-7) in patients with advanced melanomas, was found to be safe and clinically effective. We have recently cloned the canine ortholog of human mda-7 gene, CN-mda-7, which encodes a protein that is 75% similar to HU-MDA-7. Like human MDA-7, canine MDA-7 is also a secreted protein in the IL-10 gene family, and is constitutively expressed in cultured normal canine epidermal keratinocytes. When tested against canine and human cancer cells, canine-MDA-7 displays similar cancer-selective killing and potent “bystander” anti-cancer activity. In this research proposal, we will explore the basic properties and activities of CN-mda-7 in the context of *in vitro* models of canine oral melanoma (OM). To achieve this, we will develop a non-replicating Ad5 in which CN-mda-7 will be under the transcriptional control of a CMV promoter (Ad.5-CN-mda-7). We will elucidate the molecular mechanism of antitumor activity of canine MDA-7 and its “bystander” antitumor properties in *in vitro* studies using canine melanoma cells. We will use several techniques including cell proliferation assay, cell cycle analysis and apoptosis assay to study the antitumor properties of canine MDA-7. These studies will provide fundamental knowledge about the mechanism of action of canine MDA-7 and will also provide a pathway to implement of effective MDA-7 based therapy for canine oral melanoma. Melanoma in dogs shares many clinical and histopathological features with the human disease,
including tumor genetics, molecular phenotypes, histologic appearances, disease duration, and responses to conventional therapies. Thus, using a “one health” approach, our ultimate aim is to develop a novel cancer-specific replicating virus that produces MDA-7 for the therapy of canine oral malignant melanoma, which would then be advanced for the treatment of humans with metastatic melanoma.