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. Sarah Zohdy: *Parasite ecology in free-ranging lemurs.* The island of Madagascar is home to thousands of species (including lemurs) that live nowhere else. With a growing human population in Madagascar and the introduction of invasive species, lemurs are considered the most endangered group of mammals on earth. On the island, they are being exposed to invasive pathogens and vectors that have the potential to threaten species survival. In an effort to understand how invasive vectors and pathogens influence the health of lemurs, this project will take place at the Duke Lemur Center (DLC) in Durham, North Carolina. The DLC houses the largest collection (15 species) of lemurs outside of Madagascar. These lemurs have indoor enclosures, but are also allowed to free range in nine outdoor forests where they have the potential to encounter wildlife, domestic species, and mosquitoes native to North Carolina. The goal of this project is to examine whether native (US) mosquito-borne parasites have the potential to cause infection and/or pathology in free-ranging lemur species. I am looking for students to travel to the DLC to combine lemur health assessments with mosquito trapping/identification/pathogen detection, and historical medical record evaluations to gain a better understanding of the conservation risks that invasive vector-borne species present to the endemic lemurs in Madagascar.

Disease ecology in Madagascar. The island of Madagascar is home to thousands of species (including lemurs) that live nowhere else on earth. However, the growing human population relies on slash-and-burn agricultural practices, and therefore all endemic wildlife is threatened due to habitat loss. In addition to the loss of ecosystem resources, slash-and-burn agriculture may increase vector-borne disease risk by altering nutrient enrichment and watershed dynamics on a local scale. The goal of this project is to examine the ecological drivers of disease at the human-animal interface in this ecosystem, and to evaluate interventions that may simultaneously improve human health and wildlife conservation, through a One Health approach. I am looking for students to participate in survey design and implementation, field work in Madagascar, and data entry and analyses.

Dr. Jey Koehler: *Effects of fenbendazole and mebendazole in conjunction with pitavastatin on canine glioma cells.* High-grade gliomas are primary brain tumors with extremely high morbidity and poor survival times despite therapy. The benzimidazole drugs fenbendazole (FBZ) and mebendazole (MBZ) are most commonly used as anthelmintics; these drugs readily cross the

blood-brain barrier and produce target cell death via binding to tubulin subunits and disruption of the cellular cytoskeleton. Microtubule components are well-known targets for anticancer therapy, and several studies (including work from our own laboratory, accepted for publication) have shown variable efficacy of benzimidazoles against a variety of neoplasms both in vitro and in vivo, with little to no negative effects on non-neoplastic cells. Statin drugs inhibit cell proliferation by decreasing cholesterol within the cell making it extremely difficult for the cell to carry out many functions. Gliomas, like many different types of cancer, exploit the properties of cholesterol rafts within the plasma membrane to increase invasion and migration, suggesting that these rafts may be an attractive anti-cancer target. We propose a project to study the effects of FBZ and MBZ in conjunction with pitavastatin on canine glioma cell lines in vitro. We hypothesize that pitavastatin plus FBZ or MBZ treatments will negatively impact the growth of canine glioma cells in a synergistic fashion. To test our hypothesis, we will treat the canine glioma cell lines J3T, G06A, and SDT-3G with pitavastatin, FBZ, and MBZ at a range of concentrations. The specific aim is to assess cytotoxicity of these drugs using plate-based cell viability assays, from which we will determine the half-maximal inhibitory concentration (IC50). This work will directly impact dogs by providing initial experimental evidence for a therapeutic adjunct therapy with statins and chemotherapy in canine glioblastoma patients. Additionally, it will support our future long-term goals of: 1) performing gene expression experiments through PCR, immunocytochemistry of cholesterol-associated proteins, and Western blot of relevant pathway-related proteins if results vary among cell lines and to also further study pharmacokinetics between benzimidazole chemotherapeutic agents and statins; and 2) validate the use of the dog as a preclinical model for human brain tumor therapies through clinical trials in dogs with spontaneous gliomas.

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 performs 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. These 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. 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 better 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. Michael Irwin: *Cellular and in vivo models of mitochondrial disease.* Our laboratory works with cellular and animal models of severely debilitating (and often lethal) human disorders caused by genetic mutations that affect mitochondrial function. These models are used to gain a better understanding of mitochondrial dynamics and pave the way for basic and translational technologies. There are two potential projects for a summer research student. The first project involves the development of an assay that will detect serum biomarkers in a mouse model of mitochondrial dysfunction. The second project uses cultured neuronal cells to study the molecular interactions of proteins (parkin and PINK1) that modulate mitophagy (removal of damaged mitochondria by autophagy) and may be important in developing therapies for Parkinson's disease.

Dr. Nancy Merner: *Purebred canine pedigrees and mammary tumors - A model for hereditary breast cancer.* The inbreeding practices of canines to observe desired traits/characteristics associated with certain breeds also results in the presence of undesirable alleles that predispose certain breeds to particular diseases. The resulting large and consanguineous pedigrees reduce heterogeneity and represent a powerful approach towards disease gene discovery. My laboratory studies purebred pedigrees with multiple cases of canine mammary tumors (CMTs) in order to understand CMT genetic susceptibility – a very understudied field. My laboratory implements sequencing approaches to identify mutations in our canine pedigrees. Such discoveries are extremely beneficial. For example, they can aid in improving overall breed health by selectively breeding dogs without the mutations. On a more broad level, they can also provide insight towards human breast cancer susceptibility, since CMTs represent very practical models for hereditary breast cancer due to the genetic overlap between the two species.

Drs. Dawn Boothe and Amelia White: *Pharmcokinetics and pharmacodynamics of Rifampin in the dog.* Rifampin (RFP) is an antimicrobial that is used commonly to treat bacterial infections including *Mycobacteria*, *Rhodococcus*, and *Staphylcoccus* organisms. Increased incidence of methicillin- and multidrug-resistant staphylococcal infections in veterinary medicine has led to increased use of RFP. Pharmacokinetic studies with RFP have been performed in several species, but RFP has not been studied in dogs despite its common use in the species. This summer, we will study the way that RFP is metabolized in the body in order to provide a scientific basis for a dosing regimen for RFP in dogs. We will be performing a pharmacokinetics and pharmacodynamics study of RFP in 12 normal dogs in a single dose (oral and intravenous) crossover and an oral multiple dose study. This will provide veterinarians a more judicious use of this drug. Additional goals are to evaluate how continued exposure to RFP changes drug metabolism, bacterial normal flora populations, and drug concentration in the skin. Our specific aims of this study are to:

1) Determine the pharmacokinetics, including oral bioavailability of RFP in healthy dogs after single intravenous and oral doses, and changes in elimination half-life after multiple oral doses.

2) Determine the influence of RFP on the normal flora *S. pseudintermedius* in dogs after multiple doses of RFP.

3) Determine if the studied dose of RFP has the potential to cause hepatotoxicity in dogs by analyzing liver enzyme values prior to and after administration of RFP.

4) Determine if auto-induction occurs with RFP administration.

5) Determine the concentration of RFP within the skin after oral dosing.

6) Determine the effects of RFP on standard bile acids assay.

Dr. Anne Wooldridge: *Combined biomaterials and stem and progenitor cells for regenerative medicine applications in the horse.* We collaborate closely with Dr. Elizabeth Lipke in the Department of Chemical Engineering. This summer we will continue work on an ongoing project that utilizes equine endothelial progenitor cells (EPCs) in combination with a hydrogel material to promote vascularization. The goal of current studies is to improve performance of the EPCs and to promote their differentiation into endothelial cells. The summer scholar will be involved in isolation of EPCs from equine peripheral blood, cell culture, cell sorting, and in vitro characterization assays of cells. The student will be working primarily with my PhD student, Dr. Randolph Winter (Clinical Sciences), and the team from Dr. Lipke's lab in Chemical Engineering.

Dr. Beth Spangler: *Multiplate™ for assessment of platelet aggregation in horses*. This work will be completed under my direction, in collaboration with Dr. Chris Lanier (resident in Clinical Pathology). The goal of his study is to determine how platelet aggregation in horses is affected by decreased blood pH. For this study, blood will be collected from healthy horses, the blood pH will be adjusted *in vitro* and platelet aggregation will be assessed using an impedance platelet function analyzer (Multiplate™). Many basic questions regarding use of the Multiplate™ in horses have not been answered, and the summer student will play a key role in collecting that information. This work will be completed in the Clinical Pathology laboratory and may include the opportunity to use other methods for analysis of coagulation and platelet function.

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. Satyanarayana Pondugula: *Mechanisms of PXR-mediated adverse drug interactions and chemoresistance.* Altered levels of drug metabolizing enzymes and drug-efflux pumps can lead to adverse drug interactions and chemoresistance. The pregnane X receptor (PXR) plays a central role in regulating the expression of major drug-metabolizing enzymes and drug-efflux pumps. We are interested in understanding the mechanisms of PXR-mediated adverse drug interactions and chemoresistance. Additionally, we are interested in identifying antagonists of PXR to prevent adverse drug interactions/chemoresistance.

Dr. Chengming Wang: *Molecular diagnostics and transmission mechanisms of vector-borne agents.* Several projects are available in the establishment of highly sensitive and specific qPCR-based platforms for detection and differentiation of pathogens, including *Bartonella* spp., *Mycoplasma* spp., Porcine Reproductive and Respiratory Syndrome virus and bovine leukemia virus. In addition, my laboratory investigates the pathogenesis of *Chlamydia* spp. and the transmission mechanisms of vector-borne agents with zoonotic importance, as well as the interrelationship between bovine leukemia virus and human breast cancer.

Dr. Heather Gray-Edwards: *Evaluation of AAV gene therapy in the Tay-Sachs Sheep*. Tay-Sachs disease is an invariable fatal and untreatable neurodegenerative disease in people. Children affected with this disease die by five years of age and suffer from swallowing difficulties, seizures and eventually progress to a vegetative state. Like many other human diseases, Tay-Sachs disease also exists in animals and the only relevant laboratory animal model in the world is available for study here at Auburn. Tay-Sachs sheep suffer from neurodegeneration and exhibit progressive neuro signs that include cognitive alterations, proprioceptive deficits, ataxia and seizures. Our group has tested AAV gene therapy in sheep and has extended survival in the Tay-Sachs sheep to nearly 2 years, compared to a ~9 month survival in untreated sheep. In these studies we will continue to look at biomarkers in live animals, which include ultra-high field MRI based modalities, electrodiagnostics and CSF evaluation and post-mortem evaluation including therapeutic and vector biodistribution, histopathology and other biochemical techniques. Research opportunities in all areas of the project are potentially available, with special focus on MRI analyses and benchtop lab work. Participation in aspects of the live animal testing (neurologic exams, MRI, etc.) are also possible.

Dr. Lindsey Boone: Lameness due to joint or tendon/ligament related injuries is the leading cause of performance loss in horses resulting in significant economic hardship to the equine industry. Regenerative medicine therapeutics, including stem cell therapy, are gaining popularity in the equine industry for treatment of musculoskeletal related injury. Mesenchymal stem cells are cells derived from the mesoderm (connective tissue) that are capable of enhancing musculoskeletal repair resulting in reduced re-injury rates and/or slowed progression of disease. In addition to their reparative effects, MSCs are considered to be immunomodulatory and can exert ant-inflammatory effect upon activation. Further enhancing their reparative effects. In the proposed research we will evaluate priming (activation) or equine bone marrow derived mesenchymal stem cells (BMSCs) by several known danger signals (IFNy, TNFa, LPS, Poly I:C) then test their immunomodulatory capacity using a mixed lymphocyte reaction. Bone marrow will be collected and cultured for establishment of BMSCs from six healthy, adult horses. Blood will be harvested from an additional six horses for peripheral blood mononuclear cell isolation. BMSCs will be exposed to the above danger signals during an 18 hours activation period, media will be harvested for mediator analysis. BMSCs will be harvested, irradiated, then added to mitogen activated peripheral blood mononuclear cultures (mixed lymphocyte reaction). Peripheral blood mononuclear cell proliferation will be measured.