Meet the Faculty of the 2018 Summer Child Health Research Internship

1) Bruce Appel, PhD (Stem Cell Biology)

We investigate how the nervous system forms during embryonic development, with the hope that that such information will help us repair nervous systems damaged by disease or injury. We use zebrafish embryos as a model system because they are transparent and develop outside the mother, permitting us to use time-lapse microscopy to watch neural cells as they migrate and differentiate into neurons and glia. We also study the effects of mutations that disrupt neural development in zebrafish, with the expectation that they will help us understand the basis of genetic diseases that cause neurological disorders in humans. Finally, we are using zebrafish to learn how to promote regeneration of neural cells that are lost as a consequence of birth defects.

2) Emily Bates, PhD (Developmental Biology)

We study the molecular mechanisms underlying human genetic disorders. For example, we use human genetics to find a mutation that may cause a genetic disorder. We make that same mutation in a mouse or a fly and then we figure out how the mutation could lead to clinical manifestations. We have used this approach to uncover interesting biological principles like how cells signal to one another during embryonic development. Right now, our projects focus on structural birth defects, brain defects, and neurodegeneration.

3) Tim Benke, MD, PhD (Neurology/Neuroscience)

The Benke lab studies the long-term consequences of early life seizures on the developing brain. These changes may not necessarily result in epilepsy, but are known to lead to cognitive and behavioral impairments. Understanding the molecular mechanisms leading to cognitive and behavioral impairments is meant to segue into new and novel treatments for all causes of intellectual disability and even autism. Students working in the Benke lab will use animal models of early life seizures to probe these underlying molecular mechanisms. Techniques that will be used include electrical recordings in living rat brain slices, stereotactic injection of interesting antisense viral vectors, electroencephalogram (EEG) and video monitoring in freely moving rats, western blotting and immunohistochemistry.

4) Richard KP Benninger, PhD (Bioengineering/Barbara Davis Center)

The islets of Langerhans are multi-cellular micro organs located in the pancreas which play a central role in maintaining blood glucose homeostasis through secretion of hormones insulin and glucagon. We study the regulation of insulin and glucagon secretion and specifically how different cellular populations within the islet interact to enhance the overall regulation of hormone secretions. We follow an approach whereby precise perturbations in signalling activity are introduced into a well-defined population of cells in the islet, utilizing transgenic mouse models, microfluidics and optogenetics. Quantitative confocal and two-photon microscopy, together with biochemical and physiological approaches, are applied to measure the effect of these perturbations across the islet and how they manifest in the overall islet dynamical response. Predictive mathematical models are then used to describe these results. We are applying this approach to understand several aspects of how islet connectivity is important for glucose homeostasis and how it is disrupted during the development of diabetes. The overall goal is to be able to manipulate cell-cell communication within the islet to improve the regulation of insulin and glucagon secretion and to optimize islet transplantation approaches to treat and cure diabetes.

5) Kristen Boyle, PhD (Nutrition)

Our research focuses on the obesity during pregnancy may increase obesity risk for the child later in life. We know that factors related to mother's obesity, such as insulin resistance and inflammation may all play a role in

her child's future risk for obesity, but we do not know how this occurs. We hypothesize that in utero exposures, such as inflammation, may alter the baby's DNA structure and function. In order to address this hypothesis, we use stem cells cultured from umbilical cord tissue of babies born to obese or normal weight mothers. These cells have the ability to differentiate into several cell types, including fat cells and muscle cells. Specifically, we are interested in how the epigenetic signatures of these cells, acquired in utero, alters their ability to become either fat or muscle cells and once they become either cell type, whether changes to the DNA structure alter cellular metabolism. Results from these experiments may give critical insight into how in utero exposures may affect obesity risk later in life.

6) Brian Branchford, MD (Hematology/Oncology)

Brian R. Branchford, MD is a pediatric hematology physician-scientist at Children's Hospital Colorado (CHCO) and an Assistant Professor at the University of Colorado School of Medicine. He takes care of patients at the University of Colorado Hemophilia and Thrombosis Center (UC-HTC) and also leads the inpatient hematology service at the CHCO Center for Cancer and Blood Disorders. In terms of research Dr. Branchford engages in 3 types of work to study the impact of genetic and environmental risk factors and prevention strategies for pediatric blood clots.

First, in the Quality/Process Improvement realm, he is the physician leader for the local CHCO Target Zero efforts to develop safe and effective thromboprophylaxis strategies. He fills the same role for Children's Hospital Solutions for Patient Safety – a network of over 100 children's hospitals nationwide.

Second, he leads a clinical research program that includes the co-founding and ongoing development and expansion of the first national registry for pediatric hospital-acquired venous thromboembolism. The Children's Hospital-Acquired Thrombosis (CHAT) study involves over 1,000 HA-VTE cases and 1,000 controls in an effort to develop an evidence-based HA-VTE risk scoring system. This score will then be validated in another group of patients. Finally, a randomized controlled trial will be designed to evaluate the safety and efficacy of various intervention strategies to reduce the incidence of pediatric HA-VTE.

A subset of the risk factor evaluation involves use of over 1,000 frozen patient plasma samples in the UC-HTC Thrombo-PICS (prospective inception cohort study) to evaluate the levels of inflammatory mediators – various interleukins, cytokines, etc. that may contribute to thrombotic risk. Additionally, he is utilizing a novel genetic array to evaluate 146 genes associated with bleeding and clotting to study the VTE patients for enrichment of variants beyond the known standard thrombophilia traits (deficiencies of prot C, prot S, and antithrombin, as well as mutations in factor V or prothrombin).

Third, Dr. Branchford has a basic/translational science laboratory that focuses on the study thromboinflammation (how inflammation affects thrombosis). His laboratory studies the impact of specific platelet activation signaling pathways on aggregate stability and thrombus formation. He uses several murine induced-thrombosis models (arterial, venous, ischemia-reperfusion, microvascular injury, etc.) to study the effect of different activation pathway components using pharmacologic inhibitors in conjunction with several types of transgenic mice. Specifically, he is interested in the evaluation of platelet-leukocyte aggregates, platelet activation assays, and neutrophil extracellular trap formation in various types of knockout mice will help him to investigate the impact of inflammatory mediators on platelet activation responses and determine whether platelet activation serves as a bridge between clinical inflammation and thrombus formation.

7) Amy Brooks-Kayal, MD (Neurology/Neuroscience)

The Brooks-Kayal lab studies the changes in the brain that occur after a brain injury that lead to the development of acquired epilepsy. These cellular and molecular changes are then used as targets for development of new treatments to prevent and/or treat epilepsy. Students working in the Brooks-Kayal lab will use animal models of acquired epilepsy to test potential new treatments to see if they reduce occurrence of seizures after brain insults. Techniques that will be used include electroencephalogram (EEG) and video monitoring in rodents, western blotting and immunohistochemistry.

8) Colm Collins, PhD (Gastroenterology and Hepatology)

The Collins lab works to identify novel therapeutic approaches to treat inflammatory bowel diseases (IBD), chronic inflammatory diseases of the digestive tract including Crohn's Disease and Ulcerative Colitis. We use a combination of mouse models, cell lines and isolated human cells to test our hypotheses. Currently the lab is focused on the role of cannabinoids in the regulation of intestinal inflammation. Cannabis use is increasing nationwide and has been reported to alleviate symptoms of IBD such as visceral pain, loss of appetite and frequent bowel movements. Our interest is in understanding how targeting cannabinoid receptors alters immune function in general and regulatory T cell function in particular. We use a combination of immunohistochemistry and flow cytometry to assess protein changes as well as real time PCR to assess transcriptional changes.

9) Jorge DiPaola, MD (Hematology/Oncology)

The DiPaola lab is interested in studying the genetics and physiology of blood clotting (also known as hemostasis). The process of platelet binding and aggregation is highly regulated such that the platelets rapidly stem the flow of blood at the site of vessel injury while not causing vessel occlusion. In addition, upon binding and activation, platelets release granule contents that include clotting proteins and numerous growth factors that are involved in tissue growth and wound healing. Thus platelets play a central role in blood vessel repair and have both physical and biochemical properties that are essential for normal hemostasis. We are also interested in Von Willebrand Factor (VWF), which is multimeric protein present in platelets and endothelial cells. Our current studies of VWF mutations are primarily focused on identifying genetic factors that give rise to the clinical variability seen in the patients with von Willebrand Disease (VWD) and to develop assays to better characterize and understand this bleeding disorder. Association and linkage analysis, along with next generation sequence strategies, are being used to study families with VWD and other congenital bleeding disorders. Also, in collaboration with the Neeves lab at the Colorado School of Mines, we are testing a state of the art microscopy system to further examine platelet function under different flow rates and to characterize the effects of shear on platelet binding and aggregation in normal individuals and those with bleeding disorders. By applying both genetic and biochemical approaches we hope to expand our scope of understanding of platelet development and function, and to be better able to diagnose and treat related bleeding disorders.

10) Karim El Kasmi, MD, PhD (Gastroenterology and Hepatology)

The SOKOL/EL-KASMI lab is a basic science and translational research lab within the section of Gastroenterology, Hepatology and Nutrition and focuses its research program on the identification of pathways that are involved in the pathogenesis of cholestatic liver disease.

The lab investigates how liver macrophage activation and inflammatory cytokines regulate expression of bile transporters in the hepatocyte. The main research animal involves infusion of i.v. nutrients (parenteral nutrition) into mice that have intestinal injury, thereby replicating the clinical scenario in which human infants with intestinal injury, malformations and other pathologies require i.v. nutrition for survival; however this benefit comes at the cost of liver disease that eventually requires transplantation for the only cure. Therefore our

laboratory aims at elucidating cellular and molecular pathways that promote this liver injury in order to better our understanding toward how to design novel prevention and treatment options for this childhood disease.

The student will learn all basic science and clinical aspects related to this liver injury and will be introduced to immunology and macrophage biology; the student will learn lab techniques such as cell culture, PCR, RNA and protein isolation; the student will learn experimental design and interpretation of data and how to develop and test a scientific hypothesis.

11) Nick Foreman, MD (Hematology/Oncology)

The goal of the Foreman laboratory is to better understand the biology of pediatric brain tumors. In particular, we are interested in identification of biological characteristics of these tumors that have clinical relevance, such as drug sensitivity, diagnosis and prognosis. To identify novel clinically relevant factors, we screen patient surgical samples using gene expression microarray tools. Gene expression microarray technology allows us to simultaneously measure tens of thousands of genes in a tiny sample of tumor, an extremely powerful and efficient approach that provides huge amounts of novel data. Analysis of this microarray data is performed by our laboratory, and students working in the Foreman lab would be encouraged to be involved with this. Students would then further explore the results of microarray analyses using protein expression analyses including flow cytometry, Western blot and immunohistochemistry.

12) Jed Friedman, PhD (Neonatology/Reproductive Sciences)

The prevalence of obesity has been increasing dramatically in the United States over the past decades and obesity is now present at increasingly younger ages, indicating that risk factors for this condition start operating very early in life. Fetal life is considered one of the critical (or sensitive) periods when an exposure may have lifelong effects on the structure or function of organs, tissues, and body systems through biological programming. We are interested in investigating the metabolic and genetic causes and consequences of nutrition on the early developmental origins of childhood obesity. This involves novel animal models (mice, non-human primate) together with invasive clinical investigation of human pregnancy. Since 2012, we have focused on understanding how maternal diet impacted infant microbiome (MB) in human neonates and in germ-free (GF) mice. An important goal of this work is to identify the mechanisms whereby dysbiosis in mothers and infants born to obese or GDM mothers promotes inflammation and metabolic disease, and how it can be prevented or reversed. Our team's interventional studies focus on longitudinal randomized control trials (RCT)s of fixed diets in pregnant women and infants, and new approaches to halting inflammation, obesity, and Non Alcoholic Fatty Liver Disease (NAFLD) in Non-Human Primate model of maternal obesity.

13) Eva Grayck, MD (Critical Care/Developmental Lung Biology)

The overall mission of the Grayck lab is to understand the role of oxidative stress in the development of pulmonary arterial hypertension in the immature lung. Our work focuses on an important antioxidant enzyme, extracellular superoxide dismutase (EC-SOD), which is highly expressed in the lung and vessels under normal conditions and is impaired in vascular and lung diseases, leading to inflammation and fibrosis. We utilize a number of genetically engineered mouse strains with alterations in EC-SOD expression along with cell culture systems to test how EC-SOD modulates pulmonary vascular remodeling and inflammation in models of pulmonary hypertension. Ultimately our long-term goal is to provide a foundation for the development of novel cell-targeted antioxidant therapies to treat pediatric pulmonary arterial hypertension.

14) Adam Green, MD (Hematology/Oncology)

We investigate novel targets and therapeutic strategies in the treatment of a set of aggressive pediatric brain tumors called high-grade gliomas (HGG), and in particular, a subtype called diffuse intrinsic pontine glioma (DIPG). These tumors do not respond well to chemotherapy or targeted drugs, and they are among the most difficult childhood cancers to cure. We use a variety of genomic, epigenomic, and drug screening techniques to identify weaknesses in these tumors. We then work to exploit these weaknesses in cell culture and mouse models and then bring the most effective new therapies to rationally-designed early-phase clinical trials in children. We are also interested in the mechanisms of action of new therapies, as well as the challenge of getting medicines to reach these tumors in patients.

15) Melanie Cree Green, MD, PhD (Endocrinology)

Dr. Melanie Cree Green is a pediatric endocrinologist who performs clinical-translational research on improving care and reducing long-term complications of polycystic ovarian syndrome. This is a condition of excess male hormone in girls, and effects up to 15% of women. The focus of her group's work is developing a better understanding early contributors to the development of fatty liver disease and pre-diabetes in these girls, including mechanisms of insulin resistance, cardiovascular and muscle dysfunction. Dr. Cree Green's lab performs studies including oral glucose tolerance tests with stable isotope tracer methodology; vascular function with carotid artery ultrasound, brachial artery ultrasound, and measures of arterial stiffness; sleep study testing; effect of circadian rhythm abnormalities on insulin resistance. The focus of the lab this year is to develop new techniques to study complex physiology in a non-invasive way which is tolerable to youth. Techniques currently being developed include modeling glucose and insulin response to excessive sugar intake, hepatic glucose uptake, and the role of brain signaling in altering metabolism. The experience is thus a true bench to bedside, with scientific methods development and bedside patient exposure for application of methods, to then following patients in a multi-disciplinary PCOS clinic for see the effect of interventions.

16) Research at the Perinatal Research Center (PRC)

William W. Hay, Jr., MD (Scientific Director of the PRC)
Stephanie Wesolowski, PhD
Paul Rozance, MD
Laura Brown, MD

Dr. Hay's research group (Drs. Thorn, Brown, and Rozance) focuses on the mechanisms by which maternal nutrition and diseases (such as diabetes) that produce different plasma nutrient substrate and hormone concentrations regulate placental uptake, metabolism, and transfer to the fetus of essential nutrients (principally glucose and amino acids), and in turn, how these processes are interrelated to fetal nutrition, metabolism of nutrient substrates, hormone balance, and growth rate. A major effort over the years has been a focus on intrauterine growth restriction (IUGR) and how this condition results in metabolic and developmental adaptations which set up an individual for long term health problems including hypertension, cardiovascular disease, pulmonary disease, obesity, and diabetes; this is known as the Fetal Origins of Adult Disease Hypothesis. Basic work is conducted in the pregnant sheep model involving fetal surgery and in vivo metabolic experiments. Cell and molecular studies focus on a variety of fetal organs including the liver (Dr. Thorn), skeletal muscle (Dr. Brown), and pancreatic beta cells (Dr. Rozance), as well as adipose tissue, heart, lungs, brain, and placenta. Through this research, it is hoped that there will be a better understanding of how to provide nutrition to the pregnant and lactating mother in order to better nourish the fetus and neonate, in order to correct or prevent acute and long-term adverse consequences of abnormal fetal nutrition.

17) Paul Jedlicka, MD, PhD (Pathology)

Our laboratory's overarching goal is to identify, understand and target new molecular pathways critical to the development and progression of common pediatric sarcomas. Most of our work focuses on Ewing Sarcoma, but we also investigate rhabdomyosarcoma and osteosarcoma. Currently, much of our focus is on epigenetic pathways controlling disease metastasis. For more information, please see our lab web page: http://www.ucdenver.edu/academics/colleges/medicalschool/departments/Pathology/research/Pages/jedlickalab.aspx

18) Nancy Krebs, MD, MS (Pediatric Nutrition)

The focus of our research program is primarily on micronutrient nutrition, especially zinc and iron, with both studies in international and local settings. Our interventions seek to refine nutrient requirements in women and children in health and disease; to examine effects of dietary and supplemental constituents on bioavailability; and determine effects of nutritional intake on the intestinal microbiome and epigenetic changes. Laboratory-based methodologies include stable isotopes; ELISA's for biomarkers of micronutrient status; and various elemental analyses. Current intervention trials involve nutritional supplementation in pre-conception period through pregnancy in women in 4 low resource international settings, with primary outcome of birth length and weight plus multiple biologic comparisons (nutritional status, microbiome, epigenetics) and with follow-up of offspring through 2 years of age; measures of zinc absorption capacity in young Bangladeshi children with environmental enteric dysfunction; and comparison of complementary feeding choices on growth and body composition of infants in Denver.

19) Katherine Lee, PhD (Infectious Diseases)

The Lee lab is interested in better understanding the interactions of the human alphaherpesvirus, varicella-zoster virus (VZV), with human cells. In particular, we would like to identify host factors important to VZV infection and pathogenesis. We have developed novel tools, such as genetic libraries and in vitro model based on induced pluripotent stem cells, to address questions concerning VZV replication, latency and reactivation. We have recently initiated a translational project directed at elucidating the immunopathology involved in VZV-associated uveitis, an important cause of blindness in the world.

20) Cara Mack, MD (Gastroenterology)

Biliary atresia is a devastating disease that leads to liver transplant in the majority of children. The etiology of biliary atresia is not known and the Mack lab investigates the role that the immune system plays in the bile duct damage. The overall hypothesis is that the bile duct injury is initiated by a virus infection, followed by an autoimmune inflammatory process targeting bile ducts. The Mack lab investigates the pathways of the adaptive immune response (cellular- T cell and humoral- B cell) in order to determine the key players involved in bile duct destruction. The majority of studies utilize a mouse model of biliary atresia and limited research on human liver tissue is performed as well. The Mack lab is affiliated with both the Department of Pediatrics, Division of Pediatric GI, Hepatology & Nutrition and the Department of Medicine, Division of Allergy & Immunology.

21) Ken Maclean, PhD (Clinical Genetics and Metabolism)

The Maclean lab studies the etiology and pathogenesis of cystathionine beta-synthase deficient homocystinuria (HCU), Down syndrome and a range of hepatic disorders. Our research uses a range of transcriptomic and proteomic platforms coupled with, biochemical, behavioral, genetic and molecular approaches to study mouse

models of these diseases with a view towards delineating pathogenic mechanisms and the rational design of novel treatment strategies. With regard to HCU we have generated a novel transgenic mouse model of the disease and using behavioral analysis, hippocampal microarrays and proteomic analysis have elucidated a number of novel pathogenic mechanisms that we have subsequently confirmed in human HCU tissue samples. This work has led to the discovery of a novel treatment for HCU, for which an FDA funded clinical trial is currently running at the Children's hospitals of Denver and Philadelphia.

22) Shelley Miyamoto, MD (Cardiology)

Pediatric Cardiovascular Research Laboratory (PCRL)
Shelley Miyamoto, MD
Brian Stauffer, MD
Kika Sucharov, PhD

The mission of this multidisciplinary research group is to perform translational and molecular research focused on children with heart disease. Expertise within the laboratory spans the cardiovascular field from pediatric to adult disease and from basic molecular biology to cardiovascular physiology and clinical translation. Our research utilizes a pediatric and adult heart tissue bank as well as animal models. Our current projects include study of: (1) the beta-adrenergic system and downstream signaling pathways; (2) regulation of phosphodiesterase expression and activity; (3) tissue and circulating microRNA profiling; and (4) the role of histone deacytelases in hypoplastic left heart syndrome. Currently, treatment of pediatric heart failure is largely extrapolated from the results of trials performed in adults with heart failure. Our results demonstrate that children with heart failure have a unique molecular adaptive response that warrants specific targeted therapy. Students working in our laboratory would be exposed to a variety of molecular biology techniques including RT-PCR, Western blotting, various activity assays and basic biostatistics.

23) Peter Mourani, MD (Critical Care)

Our clinical-translational research program has several areas of focus: 1) we conduct NIH funded research projects utilizing molecular microbiome, transcriptomic, and proteomic analyses to investigate the contribution of airway microbiome and the host immune responses to the risk for ventilator associated pneumonia and acute lung injury in order to facilitate improved prevention and treatment methods; 2) we conduct clinical studies and trials as part of the NIH sponsored Collaborative Pediatric Critical Care Research Network, including studies investigating sepsis, traumatic injury, acute respiratory failure, resuscitation after cardiac arrest, and critical care outcomes; and 3) as part of the Pediatric Heart Lung Center, a multidisciplinary group of collaborators who promote the translation of research into clinical care for newborns, infants and children with severe cardiopulmonary diseases, we conduct clinical-translational studies investigating mechanisms of lung and lung blood vessel growth and injury in prematurely born infants. Projects in this area explore prenatal and postnatal risk factors for impaired lung blood vessel growth and development of chronic lung disease called bronchopulmonary dysplasia (BPD) and pulmonary hypertension. We have collected a wealth of data and clinical specimens from these ongoing clinical studies for students to identify and work on their own project with support from our collaborative research team with the goal of producing a first-author manuscript. Students would also attend regular research meetings and participate in both clinical and laboratory based activities depending on their identified project.

24) Jean Mulcahy-Levy, MD (Hematology/Oncology)

My laboratory research focus is the study of autophagy, a multi-step cellular catabolic process that contributes to cell and organism survival during nutrient deprivation and other stresses. Autophagy has been shown to be important in the development of cancer and is a promising target for manipulation to improve cancer treatment and survival. My goal is to determine how to utilize autophagy to improve therapy for patients with malignant central nervous system tumors. I am laying the groundwork for determining the importance of the connection between BRAF mutations and autophagy addiction in brain tumors.

25) Kristen Nadeau, MD, MS (Endocrinology and Diabetes)

Dr. Kristen Nadeau is a Pediatric Endocrinologist and the Director of Research for Pediatric Endocrinology, who performs clinical-translational research on reducing long-term complications of pediatric obesity, type 1 diabetes, type 2 diabetes, and prediabetes. The focus of her group's work is better understanding early contributors to cardiovascular disease (CVD), including mechanisms of insulin resistance, cardiovascular and muscle dysfunction. Dr. Nadeau's lab performs human studies including measures of insulin sensitivity and pancreatic function (IV hyperinsulinemic clamps with isotopes, hyperglycemic clamps, arginine stimulation tests, hypoglycemic clamps, mixed meal tolerance tests and oral glucose tolerance tests); assessment of liver, visceral and muscle fat deposition via MRI/MRS; heart function via resting and exercise-stress echocardiography and cardiac MRI; measures of endothelial function, arterial stiffness, blood flow and arteriosclerosis via MRI and other vascular techniques; exercise function via VO2max and physical activity monitoring; sleep and circadian rhythm monitoring; carbohydrate oxidation via metabolic cart; and muscle mitochondrial function via exercise MRI/MRS. Dr. Nadeau's research also includes several large longitudinal studies, including studies in youth and young adults with type 2 diabetes (TODAY), a trial to improve pancreatic function in youth and adults with prediabetes/early type 2 diabetes (RISE), and medication trials to reduce cardiovascular disease and improve insulin sensitivity in youth and young adults with type 1 diabetes. Finally, Dr. Nadeau's work includes several studies of American Indian youth with obesity, including a gestation diabetes prevention project. Thus, students would have a rich exposure to clinical/translational research in youth with obesity and diabetes.

26) Maki Nakayama, MD, PhD (Barbara Davis Center for Childhood Diabetes)

Type 1 diabetes is an organ-specific autoimmune disease caused by lymphocytes that mistakenly destroy cells in the pancreas, called "beta cells." Pancreatic beta cells secrete insulin to regulate the blood glucose level, and as a result of beta cell destruction, patients develop hyperglycemia. We have discovered that a peptide contained in insulin itself is an essential antigen targeted by autoreactive lymphocytes causing type 1 diabetes in the animal model. If we can identify such essential antigens required for the development of human type 1 diabetes, blocking or regulating lymphocytes targeting those antigens will enable us to prevent diabetes. Thus, one of our current goals is to define antigen specificity of human autoreactive lymphocytes that target pancreatic beta cells in patients having type 1 diabetes and to elucidate whether and how antigen specificity determines the fate of lymphocytes (i.e. pathogenic or regulatory). Techniques used in in my laboratory include molecular biology techniques (e.g. high-throughput sequencing), cellular engineering (e.g. transfection), and immunoassays (e.g. ELISA) using both animal models and human samples. Our long-term goal is to understand the molecular mechanism of beta cell autoimmune-destruction and ultimately to develop robust diagnostic and therapeutic tools for type 1 diabetes.

27) Yogendra Raol, PhD (Neurology)

The main focus of Raol lab is to study the changes that occur following an injury in early-life, such as caused by neonatal seizures, and finding a treatment that can prevent or reverse these changes and alleviate injury-induced

long-term neurologic disability. Although seizures can occur at any age, the risk is high in the neonatal period. Currently available drugs to treat neonatal seizures, which were originally developed to treat seizures in adult, are sub-optimally effective and are associated with side effects. Further, these drugs do not alter the later neurological outcome that may occur following an injury in early-life. Due to developmental differences, the immature brain responds differently to insult and treatment than the mature brain. Therefore, to find the most efficacious treatment for early childhood diseases, it is imperative to target age-specific mechanisms and test new therapies in neonatal disease models. Our current studies aim to identify age-specific therapies for neonatal seizures and determine if treatment of early-life seizures can alter long-term neurological outcome. We use a wide variety of methods including video-EEG monitoring, MRI, immunohistochemistry, western blotting and behavioral testing to investigate these effects.

28) Tamim Shaikh, PhD (Human Genetics and Genomics)

The Shaikh lab investigates the genetic basis of neurodevelopmental and neuropsychiatric disorders. Their main focus is on identifying the genetic mutations that underlie multiple congenital anomaly syndromes (MCAS), which includes phenotypes like global developmental delay, intellectual disabilities and deficits, other neurological phenotypes such as seizure disorders, behavioral issues, etc., cranio-facial differences, cardiac defects and/or defects in other tissues and organs. Dr. Shaikh's group uses high resolution genomic technologies including microarrays and high-throughput sequencing to identify genetic mutations in these patient samples. They have identified novel, pathogenic mutations in several candidate genes and are now beginning to analyze the effect of mutations in these genes using functional genomics approaches and animal models (mainly zebrafish).

29) Ronald J. Sokol, MD (Gastroenterology and Hepatology)

Dr. Sokol is the Chief of the Section of Pediatric Gastroenterology, Hepatology and Nutrition and is an expert on childhood liver disease and liver transplantation. His laboratory is currently investigating the role of innate immunity and the intestinal microbiome in liver injury in mouse and rat models of childhood liver diseases. The disease now being studied in a mouse model is parenteral (intravenous) nutrition associated cholestasis, a condition that is the leading indication for pediatric intestine and combined liver-intestine transplantation in children. The laboratory uses a unique mouse model in which the intestine is injured and a central venous catheter is placed for total nutrition for 7 to 28 days. The role of the liver macrophage, the intestinal microbiome, plant sterols, cytokine signaling pathways, hepatocyte transport protein gene expression and epigenetics; and cell injury pathways are being investigated in this mouse model to identify new targets for potential therapeutic strategies. We use a variety of model systems, including whole mouse models, cultured hepatocytes and macrophages, and isolated organelles to study these pathways. Students will work on a project along with members of the Sokol Lab, attend regular laboratory meetings and participate in related research activities.

30) Danielle Soranno, MD (Nephrology)

The Soranno lab bridges research in kidney disease and bioengineering. We use a mouse model of acute kidney injury (AKI) to study the effects of kidney injury on long-term health. We use injectable hydrogels to deliver therapeutics (such as stem cells) locally to the kidney after AKI. The hydrogels are biocompatible, and can be tuned to degrade quickly or slowly. As the hydrogels degrade, their cargo is released locally in a sustained fashion. When used to deliver stem cells, the hydrogels protect the cells during injection, optimize delivery to the kidneys, and keep the stem cells in place so they can secrete helpful proteins to help the kidneys heal following injury. To-date, we have shown that even delivery of the hydrogels alone (without any therapeutics)

improves outcomes. We hypothesize that the hydrogels adsorb pro-inflammatory cytokines, decrease oxidative stress, and improve autophagy in the kidneys following injury. Techniques used over the summer will include animal studies, histology, ELISA's, western blots, hydrogel formulation, and others. Students working in the Soranno lab can tailor their research experience to their specific interests (animal work, bench work, bioengineering techniques).

31) Kurt R. Stenmark, MD (Pediatric Critical Care)

Pulmonary arterial hypertension (PAH) is a syndrome in which pulmonary arterial obstruction increases pulmonary vascular resistance, which leads to right ventricular (RV) failure and a 15% annual mortality rate. The Stenmark laboratory is interested in determining the cellular and molecular mechanisms that contribute to structural remodeling and resultant obstruction of the pulmonary vasculature and to right heart failure in the setting of pulmonary hypertension. Most work in this field has focused on changes in the behavior or resident vascular cells believing that these cells alone are the primary determinants of the vascular remodeling. However, several years ago, we were among the first to report that cells expressing progenitor cell markers appeared in the remodeled pulmonary hypertensive vessel wall along with a variety of other cells of hematopoietic origin (monocytes, macrophages, lymphocytes), in a variety of experimental models of pulmonary hypertension. We are thus extremely interested in determining the mechanisms that are involved in the recruitment of progenitor cells to the vessel wall and the right ventricle, their differentiation potential and fate, and ultimately their specific roles in vascular stiffening and remodeling and right heart failure.

32) Frederick Suchy, MD (Gastroenterology)

Our lab is interested in understanding the multiple crosstalk signals that are present in the promoter region of FXR (nuclear receptor) target genes. Our current work is focused on understanding how epigenetic factors regulate the expression of FXR target genes as part of normal hepatobiliary physiology and as a response/adaptation to experimental cholestasis.Many co-regulators associated with FXR have been identified as histone modifying enzymes that are capable of attaching organic groups onto nucleosomal histones such as acetyltransferases, methyltransferases, kinases, ubiqutin ligases, etc after translation. It is confirmed in only a few cases that the modification of nucleosomal histones through FXR result in an active transcriptional response. Despite the fact that FXR has the capacity to integrate multiple histone modifying enzymes simultaneously, little is known about how nuclear receptors orchestrate changes in chromatin structure through histone modification. Furthermore, it remains unclear how each modifications of the histone residues, and the crosstalk between them, achieve transcriptional activation of specific target genes.Our work relies on well established methods in our laboratory including promoter analysis in liver cell lines and human hepatocytes, siRNA knockdown of coactivators and histone modifying enzymes, mutational analysis of coactivator binding sites, in vivo and invitro methylation of histones and transcription factors, mammalian two hybrid and co-immunoprecipitation, in vivo and in vitro chromatin immunoprecipitation (ChIP) and reChIP assays, and mouse models of experimental cholestasis.

33) Lori Sussel, PhD (Developmental Biology)

Dr. Sussel is the Research Director of the Barbara Davis Diabetes Center. Her research focuses on the molecular regulation of islet cell differentiation and function, with a focus on understanding pancreatic diseases such as diabetes and pancreatic cancer. Her research program combines advanced molecular biology techniques, mouse genetics, histology and mouse embryology and physiology to understand the molecular mechanisms that determine the differentiation of the pancreas during fetal development and maintained beta cell function in the adult. These studies have identified several novel proteins and molecular mechanisms that are involved in islet cell fate decisions during pancreas development and in maintaining the function and/or identity of the beta cell in the adult. Current research in the lab continues to explore how pancreas development and function are regulated by transcriptional and epigenetic modifications. More recently the lab has embarked on a

set of ground-breaking studies to identify and characterize pancreas-specific long non-coding RNAs (lncRNAs) in physiological and pathophysiological conditions, including diabetes and pancreatic cancer. Students would work on their own project with mentorship from senior members of the Sussel lab.

34) Johan Van Hove, MD, PhD (Medical Genetics and Metabolism)

The field of medical genetics is rapidly advancing with the advent of whole exome sequencing. My laboratory examines disorders that affect the mitochondrion. The mitochondrion contains about 1000 proteins, and performs a very large number of biochemical reactions. We examine patients with genetic disorders of mitochondrial enzymes with an emphasis on either disorders of energy generation, or disorders of neurochemistry such as infantile seizures. We identify new genetic causes of disease, we then examine the way in which the gene leads to the symptoms, and develop new treatments focused on the specific cause. Students have been involved in either the identification and proof of a new genetic cause for a mitochondrial disease, or in the development of a new treatment for a specific neurological disorder affecting babies. A specific example of a mitochondrial function could be the development of a new test for mitochondrial structural abnormalities. A specific example of a treatment project involves the development of a treatment that restores the amount of the cofactor lipoic acid for patients that cannot synthesize this essential compound.

35) Rajeev Vibhakar, MD, PhD (Hematology/Oncology)

The Vibhakar lab is interested in studying the Biology of childhood brain tumors. We have several projects underway. One line of research understands the role of microRNAs in regulating tumor cell growth and control of brain tumor stem cells. Another major line of research involves identifying new molecular targets for potential therapy.

36) Clyde Wright, MD (Neonatology)

Dr. Wright's lab investigates the effects of Bronchopulmonary dysplasia (BPD) in very low birthweight infants. BPD affects 25% of the very low birthweight infants and leads to significant long term morbidity. BPD results in part from multiple inflammatory and oxidant insults encountered in the perinatal period. Exposure to hyperoxia is thought to contribute to the pathogenesis of BPD. The major focus of our research is to further define how the neonatal lung responds to toxic exposures of oxygen. Over 100 genes orchestrating the cellular response to these insults are regulated by the transcription factor NF-κB. Clinical studies have correlated NF-κB activation in the preterm lung to an increased risk of developing BPD. Our lab is working to define how NF-κB activation modulates hyperoxic injury in the newborn lung.