

Meet the Faculty of the 2022 Summer Child Health Research Internship

*University of Colorado School of Medicine, Department of Pediatrics
Children's Hospital Colorado*

1) Bruce Appel, PhD (Developmental 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 signaling 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) Petter Bjornstad, MD (Endocrinology and Diabetes)

Dr. Petter Bjornstad is a NIH and JDRF funded translational researcher. Diabetic kidney disease remains the leading cause of end-stage kidney disease and dialysis in the US. Bjornstad lab (<http://bjornstadlab.org>) focuses on metabolic and hemodynamic mechanisms underlying the development of kidney disease in youth with type 1 and type 2 diabetes, with an emphasis of renal physiology studies, mechanistic clinical trials, mathematical modeling and advanced functional

imaging (MRI and PET imaging) to quantify renal hemodynamic function, energetics and metabolism. The lab also obtains kidney biopsies for comprehensive morphometrics and single-cell transcriptomic studies.

Dr. Bjornstad has authored over 93 peer reviewed manuscripts and several in high impact journals including *Circulation*, *Lancet Diabetes and Endocrinology*, *Diabetes Care*, *Diabetologia*, *American Journal of Kidney Disease* and *Journal of Clinical Investigation*.

Dr. Bjornstad is the principal investigator of several ongoing studies, including: “Renal HEIR Study: Renal Hemodynamics, Energetics and Insulin Resistance in Youth Onset Type 2 Diabetes Study”, “IMPROVE-T2D Study: Impact of Metabolic Surgery on Pancreatic, Renal and CardioVascular HEalth in Youth with Type 2 Diabetes”, “CASPER Study: Copeptin in Adolescent Participants with Type 1 Diabetes and Early Renal Hemodynamic Function”, “Dolphin-T1D Study: Define Renal Oxygenation Levels and Perfusion in Hyperfiltration in Adolescents with Type 1 Diabetes”, “Diabetic Kidney Alarm (DKA) Study – Tubulopathy in New Onset Diabetic Ketoacidosis”, “Evaluation of Coffee Therapy for Improvement of Renal Oxygenation (COFFEE)”, “ULTRA-T2D Study: Uric Acid Lowering TRIAl in Youth Onset T2D” and “CROCODILE: Control of Renal Oxygenation COnsumption, mitochondrial Dysfunction and InsuLin rEsistance.”

6) Kristen Boyle, PhD (Nutrition)

In our lab, we study molecular metabolism in umbilical cord stem cells to identify factors that may predispose children to developing obesity or diabetes later in life. We know that mothers’ health and pregnancy exposures, such as obesity, diabetes, and environmental pollutants, can increase the child’s risk for later disease. However, in humans, little is known about how these exposures may influence child outcomes. We employ various metabolic and molecular biology techniques to identify and characterize epigenetic mechanisms for altered metabolism in umbilical cord mesenchymal stem cells (MSCs), collected at birth. Current projects include: 1) the role of maternal obesity-induced epigenetic signatures on AMP-activated protein kinase signaling and mitochondrial respiration, 2) the role of cell cycle exit on adipogenesis and adipocyte metabolism, and 3) characterizing associations between maternal, MSC, and offspring metabolic phenotypes using multi-omics approaches. Students working in our laboratory will be exposed to a variety of metabolic and molecular biology techniques, including mitochondrial respiration, radiolabeled substrate metabolism, qPCR, luciferase gene reporter assays, lentiviral transduction, and will have the opportunity to tailor their research toward metabolism, molecular biology, and/or statistical analyses using existing datasets.

7) Laura Brown, PhD (Neonatology)

Intrauterine growth restriction (IUGR) is a problem that affects 8% of all pregnancies and occurs as a result of placental insufficiency, which restricts nutrient and oxygen delivery to the fetus. In the Brown laboratory, we study the physiological, molecular, and cellular mechanisms that link fetal nutrient availability during pregnancy to skeletal muscle growth and development. We aim to understand how low muscle mass in the IUGR fetus predisposes that individual for long term health problems including sarcopenia, insulin resistance and diabetes. We perform physiological studies using large animal (sheep) models to measure nutrient uptake rates across the fetal hindlimb. We also determine how nutrient supply affects skeletal muscle-specific metabolism using stable isotopic tracer and metabolomic techniques. Finally, in vivo physiological studies are combined with in vitro experiments using muscle tissue and primary fetal myocytes to understand adaptations to nutrient restriction that occur at the cellular level. The overall goal of the Brown lab is to optimize body composition and growth in the IUGR fetus and neonate, which will ultimately preempt the complications of IUGR related to low muscle mass.

8) Child Health Research Biostatistical Core

Claire Palmer, MS

Suhong Tong, MS

Lori Silveira, PhD

Laura Pyle, PhD (Acting Director)

The Child Health Research Biostatistical Core provides statistical support to child health researchers in a variety of disciplines. Our collaborative research includes work in diverse areas such as endocrinology, neonatology and cancer research. Our individual research in statistical methods and applications includes genomics, longitudinal modeling and

machine learning. Students who are placed with our group will have the opportunity to work with multiple faculty members and to participate in study design, creation and execution of analysis plans, data analysis and writing manuscripts. They will also be exposed to statistical programming and have the opportunity to develop communication skills in a collaborative research setting, including working with other students. We will engage with students to tailor their time in the program to their specific interests and encourage them to produce work for presentation at a scientific meeting.

9) eXtraordinary Kids Program

Nicole Tartaglia, MD, MS

Shanlee Davis, MD, MS

The eXtraordinary Kids program is focused on improving the lives of youth affected by sex chromosome aneuploidies through excellent clinical care and research. 1 in 400 babies are born with an extra or missing sex (X or Y) chromosome, but only a handful of centers around the world are conducting research to learn more about these conditions and how best to care for them. Our clinical-translational research program applies multiple methodologies (intervention trials, retrospective and prospective observational studies, neurodevelopmental studies, translational science, secondary data analyses, surveys, qualitative methods, etc.) to answer important clinical questions with the goal of improving patient outcomes in these genetic conditions, with a focus on neurodevelopmental, endocrine, and health outcomes. Our interdisciplinary team includes Developmental Pediatrics (Dr. Tartaglia), Pediatric Endocrinology (Dr. Davis), neuropsychology, psychology, genetic counseling, speech and occupational therapy, and study coordinators. Students play a crucial role on our team with a project suited to their experience and goals. In addition to identifying and completing a project, students will have the opportunity to assist with patient visits for our ongoing studies focused on neurodevelopment and early cardiometabolic health in infants and toddlers with sex chromosome aneuploidies.

10) 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.

11) Craig Forester, MD, PhD (Hematology/Oncology)

The Forester lab studies a unique approach to understanding how early blood development is controlled. Our lab seeks to understand why the bone marrow in certain children stops functioning leading to failed blood maturation and production; a collection of diseases known as the Inherited Bone Marrow Failure Syndromes (IBMFS). Historically, much focus has been devoted to the consequences of mutations in DNA and RNA giving rise to changes in gene expression. However, mutations discovered in these children focus on the protein synthesis machinery and delineates a clear need to study how genes can be controlled by translation in early hematopoiesis. Why mutations in the translation machinery leads to failed blood production is still poorly understood. Our lab seeks to determine how this process is able to quickly and specifically target RNA messages for translation and how this becomes dysregulated with mutations found in children with IBMFS. To this end, we have developed novel tools to identify waves of new gene expression shortly after cells encounter an array of pharmacologic inhibition and growth stimuli using mass spectrometry. Our lab employs mouse models and tissue culture models that recapitulate red blood cell production to identify specific sets of expressed genes that are aberrantly expressed with patient mutations. We then utilize RNA sequencing techniques to delineate nucleotide and structural elements encoded in the mRNA message that mechanistically yields insight into how specific mRNA are recognized by the protein synthesis manner to allow normal blood production. The overall goal of the lab is to identify how the ribosome can rapidly and specifically translate specific mRNA to allow for normal blood production in response to stresses such as growth and injury and how this process is impaired with mutations we discover in children.

12) Gregory Forlenza, MD (Pediatric Endocrinology/Bioengineering/Barbara Davis Center)

The Pediatric Artificial Pancreas Research Team works with children with type 1 diabetes conducting clinical trials to investigate the role of advanced technologies to improve clinical care in this population. Our team works with engineers, computer scientists, psychologists, clinicians, nurses, and regulators to develop, refine, and approve advanced medical technologies. Our work has included the development and approval of factory calibrated continuous glucose monitors, the first automated insulin delivery systems, and high-level machine learning algorithms to tune dosing. Students working with this team will have the opportunity to learn clinical care for children with diabetes, work on FDA-monitored clinical trials, and understand the process of bringing engineering concepts to commercial use

13) Eva Grayck Nozik, 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) 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.

15) Masanori Hayashi, MD (Solid Tumor Program)

The main goals of the Hayashi lab is to investigate the biology of pediatric sarcoma metastasis in order to develop specific anti-metastasis therapy, as well as develop biomarkers to identify who will fail conventional therapy and relapse with metastasis. Currently, we are studying the role of Wnt signaling in the metastatic cascade, by focusing on how individual sarcoma cells use activated Wnt signaling to manage to intravasate into the circulation, survive the blood stream, and eventually grow in the distant target organs. Additionally, we have been working on developing cell-free plasma tumor DNA as a sensitive and patient specific method of early detection of relapse.

16) 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.

17) Siddhartha Mitra, PhD (Hematology/Oncology)

The Mitra lab is part of the Morgan Adams Pediatric Brain Tumor Research Program within the Department of Pediatrics Hematology/Oncology/Bone Marrow Transplantation section of the University of Colorado School Of Medicine based in Denver, Colorado, USA. The Mitra lab brings together three distinct fields of research: Immuno-Oncology, neurodevelopment, and brain tumor oncology. The lab focuses on the mechanisms of immune-surveillance in brain tumors by cells of the innate immune system. As one of the earliest immunologic defense mechanisms developed in the body, is independent of mutational load and provides a unique effector mechanisms of macrophages and brain resident microglia that are often present in high numbers within the brain tumor microenvironment. While most studies have demonstrated tumor-associated macrophages to promote tumor growth, we have recently shown that inhibiting the myeloid checkpoint pathway (the CD47-SIRP α signaling axis) suppresses the "don't eat me" signal and allows for efficient macrophage-mediated phagocytosis of different types of brain tumors (Science Translation Medicine, 15 Mar 2017) and are now continuing our investigations on understanding the immune microenvironment and immune-evasion pathways in brain tumors. A major interest of the laboratory focuses on translational immune-Oncology to understand and leverage the mechanisms of efferocytosis and immunogenic cell death to develop better immune modulating drugs against adult and pediatric brain tumors. The members of the lab will be part of a unique brain tumor research program which encompasses seven labs whose expertise ranges from single cell RNA sequencing, autophagy and oncogenic signaling pathway.

18) Shelley Miyamoto, MD (Cardiology)

Pediatric Cardiovascular Research Laboratory (PCRL)

Shelley Miyamoto, MD

Anastacia Garcia, PhD

Brian Stauffer, MD

Stephanie Nakano, MD

Kika Sucharov, PhD

Katie Chatfield, MD, 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 and primary cell culture models. Our current projects include study of: (1) the study of mitochondrial function in the failing hearts of children with cardiomyopathy and single ventricle heart disease; (2) regulation of phosphodiesterase expression and activity in pediatric heart failure; (3) tissue and circulating microRNA profiling; and (4) myocyte mechanics of the failing heart. 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.

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

I have a broad background in oncology research with specific training and expertise in pediatric brain tumors. My research is focused on the development of new brain tumor therapies with a special interest in therapy resistance mechanisms. One goal of my lab is to determine how to utilize autophagy, a cellular recycling program, to improve therapy for patients with central nervous system (CNS) tumors. As a Fellow and early investigator, I laid the groundwork for targeting autophagy in CNS tumors, identifying the connection between BRAF pathway alterations and autophagy addiction in brain tumors. My work demonstrated the effectiveness of autophagy inhibition when tumors become resistant to BRAF/MEK inhibitors. A *first in pediatrics multi-institutional trial* of autophagy inhibition based on my work opened in 2019 in collaboration with the Pediatric Brain Tumor Consortium and Novartis. We also recently published the largest series of paired pediatric CNS tumor samples used to investigate other resistance mechanisms to BRAF/MEK inhibitors. Together, we are using this work as a basis for additional work in my lab focused on the development of novel, rapidly translatable treatments for pediatric CNS tumors. Our work has continued to identify biologically driven therapies for AT/RT and other tumors using genome and pharmacologic screening. Here we combine these techniques and identified

CDK7 as a key vulnerability in AT/RT. We will build on these findings to investigate the mechanistic relationship of CDK7 and the SWI/SNF complex in AT/RT and the potential for inhibiting CDK7 alone and in combination with available AT/RT chemotherapies.

20) 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.

21) 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 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.

22) Christopher Ng, MD (Hematology/Oncology)

Our research is focused on the study of coagulation factors as they pertain to bleeding and clotting. Currently, we are investigating why certain individuals have different set points of coagulation factors, such as von Willebrand factor (VWF) and how this can be predictive of bleeding risk. We suspect that this variation in bleeding can be explained by biologic and possibly even epigenetic changes in the regulation of VWF. We hope this work will help develop a more personalized therapy that balances clinical risk with therapeutic intervention based on the biology of each individual patient. Students on our lab will learn molecular biology techniques, cellular culture, and also novel technologies such as microfluidic patterning that simulates blood as it courses through blood vessels.

23) Sarit Polsky, MD, MPH (Barbara Davis Center for Childhood Diabetes)

Dr. Polsky is the director of the Pregnancy & Women's Clinic at the Barbara Davis Center (BDC) for Diabetes. The BDC is a specialty center for type 1 diabetes. The main focus of Dr. Polsky's work is to improve the health of women with diabetes through clinical research trials and excellence in clinical care. Pregnancies associated with type 1 diabetes are increased risk of adverse health outcomes, such as fetal loss (miscarriage, stillbirth), abnormal fetal size (babies born too large or too small), pre-term delivery, cesarean delivery, gestational hypertensive disorders, and babies being born with

low glucose (sugar) levels, low oxygen, and/or needing admission to the neonatal intensive care unit. In order to reduce the risks of the adverse outcomes, it is recommended that women obtain and maintain normal to near-normal blood glucose levels throughout pregnancy, which is challenging for women on intensive insulin therapy. Dr. Polsky's research examines how advanced diabetes technologies (insulin pumps, continuous glucose monitors, and artificial pancreas systems) impact glycemic control and health outcomes in pregnant women with type 1 diabetes. Dr. Polsky also examines how some adverse maternal outcomes in pregnancy (such as preeclampsia) impact long-term cardiovascular and renal health in women with type 1 diabetes. Students working with our group will take part in research team meetings, learn about and participate in data collection and reporting, learn responsible research conduct for human clinical trials, and may have an opportunity to help prepare abstracts for scientific meetings.

24) 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).

25) Stacey L. Simon, PhD (Pulmonary & Sleep Medicine)

Dr. Simon is a pediatric sleep psychologist with a research focus on mechanisms underlying the negative cardiometabolic consequences of insufficient sleep and circadian misalignment in adolescents. Short sleep duration and circadian misalignment are believed to contribute to health problems, including obesity and insulin resistance. Adolescence is a time of chronic short sleep duration and a propensity for delayed circadian phase. However, imposed early school start times mean that adolescents are often unable to avoid going to bed late, yet are woken early in the morning and out of synchronization with their circadian rhythm. Dr. Simon's current projects are evaluating the impact of increased sleep duration on insulin resistance in short-sleeping adolescents; and examining associations between sleep and glycemic control in youth with type 1 diabetes.

26) 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.

27) 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, ubiquitin 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 modification 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 in vitro 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.

28) 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.

29) Sujatha Venkataraman, PhD (Peds Neuro-Oncology)

Dr. Venkataraman's lab research is focused on identifying novel therapeutic strategies for a fatal brain tumor in children called DIPG (Diffuse Intrinsic Pontine Glioma). Treatment options for DIPG are limited as chemotherapy is largely ineffective and surgical resection is not possible due to the tumor's location in the pons, a region of the brain responsible for multiple vital functions like heartbeat and respiration. Ionizing radiation is the current standard of care for DIPG but provides only a temporary relief as the tumor becomes resistant to radiation at recurrence. Our lab is currently studying the radiation resistant mechanisms at the single cell level to identify new targeted treatments that are directed towards enhancing radiation efficacy in DIPG. In addition, Dr. Venkataraman lab have also been working on immunotherapy, both CAR-T cell and antibody-based therapies to effectively target DIPG, which is otherwise a refractory disease.

30) Livia Veress, MD (Pulmonology/Critical Care/Translational Drug Development Research)

Dr. Veress leads research efforts at the University of Colorado Pediatric Airway Research Center (UC-PARC) where she investigates the mechanisms and potential novel therapies for plastic bronchitis, bronchiolitis obliterans, pulmonary fibrosis, acute and late neurotoxicity, and other systemic injuries after several different insults, particularly chemical inhalation. The UC-PARC focuses on studies all the way from molecular signaling pathways to whole animal drug dosing efficacy studies. Studies related to the basic mechanisms of airway injury and aberrant repair during the acute and chronic phases of injury are evaluated with the aid of animal models to mimic human disease, as well as cell culture, histopathological and molecular techniques to pinpoint promising target pathways for treatment. After screening in vitro, novel therapeutics are tested in vivo using animal models, often in a pre-clinical animal intensive critical care unit setting, and efficacious drugs are developed under FDA guidelines for future use in human patients. Employing novel inhalation engineering systems to create models for drug screening, the center currently focuses on animal models related to toxic vapor and gas inhalation. The lab's future directions include testing of cell-based therapies (stem cells) for various lung diseases in animal models, particularly bronchiolitis obliterans. In addition, a rodent lung transplantation model is being developed to study bronchiolitis obliterans, in which promising therapies could be evaluated for efficacy prior to human clinical trials.

31) 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.

32) Christine Vohwinkel, MD, PhD (Critical Care)

Our lab is housed in the Division of Critical Care. The lab is focused on acute lung injury-its clinical manifestation, the acute respiratory distress syndrome (ARDS), is a highly-morbid critical illness characterized by acute onset of hypoxemia, pulmonary edema, and chest X-ray with bilateral opacities. We are specifically interested how metabolism of the alveolar epithelium is regulating inflammation that is central of the pathogenesis of acute lung injury and how the lung epithelium “communicates” with macrophages. We work with several mouse models of acute lung injury (ventilator induced acute lung injury, acid aspiration and pneumonia) and in cell cultures. Other techniques we use in our lab are PCR, Western Blotting, ELISA and enzyme activity assays and histology.

33) Stephanie Wesolowski, PhD (Neonatology)

Our lab studies how altered nutrient supply programs fetal metabolism and how these changes may persist after birth and increase susceptibility to adult metabolic disease. Our primary research is aimed to understand the effects of intrauterine growth restriction (IUGR) on liver metabolism and function using integrative approaches in physiology and metabolism combined with novel molecular techniques in cell biology, epigenetics, and metabolomics. Current studies in our research program are focused on understanding the mechanisms for the early activation of fetal hepatic glucose production and development of hepatic insulin resistance, specifically the role of reduced glucose versus oxygen supply to the fetus, both key features of placental insufficiency and resulting IUGR. This is important in understanding why IUGR offspring have increased susceptibility to diabetes across their lifespan. We also have projects investigating the effects of maternal high fat diet and obesity on offspring metabolism, specifically the early development of non-alcoholic fatty liver disease (NAFLD) and immune cell reprogramming.

34) 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- κ B. Clinical studies have correlated NF- κ B activation in the preterm lung to an increased risk of developing BPD. Our lab is working to define how NF- κ B activation modulates hyperoxic injury in the newborn lung.