



Research Committee Report

2023

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Much appreciation to the dedicated reviewers

2023 Marshall Klaus Neonatal-Perinatal Medicine

On behalf of the American Academy of Pediatrics (AAP), Section on Neonatal-Perinatal Medicine (SoNPM) and this year's Klaus Neonatal-Perinatal Research Fund supporters, we would like to congratulate the recipients of the 2023 Marshall Klaus Neonatal-Perinatal Research Award! The Research Committee received 52 very strong applications and all applicants deserve recognition for their already strong bios, outstanding mentors, and exciting projects. This year's awards are sponsored by Mead Johnson, Johnson & Johnson Pediatric Institute, Brodsky & Martin's *Neonatology Review* series, Beth Israel Deaconess Medical Center, and the AAP SoNPM. Thanks to our sponsors, this year we were able to fund the top 14 ranked fellows with the \$5,000 research award. The money will be used towards supplies etc. to support the proposed research project.

Special thank you to the award sponsors

Klaus Bench or Clinical Research Award

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Beth Israel Deaconess Neonatology Education Research Award

Brodsky & Martin's *Neonatology Review* series

Health Services Research Award

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Klaus Bench or Clinical Research Awardees




Annica Alwine, MD

Vanderbilt University Medical Center

Title: *Integrin alpha3beta1 Regulates Alveolar Basement Membrane Formation during Postnatal Lung Development*

Mentor: Erin Plosa, MD

Personal Statement: I am currently a second year Neonatal-Perinatal Medicine fellow at Monroe Carell Jr. Children's Hospital at Vanderbilt. Throughout my training, I have been committed to understanding human development and physiology to help me become a better physician to my patients and their families. Bronchopulmonary dysplasia continues to be a prominent morbidity in neonates, and I have watched many families as they have grappled with this diagnosis and/or struggled to prepare to care for their infant with BPD, for a myriad of reasons. BPD may



mean one thing to physicians, but, as I have learned throughout my training, it entails so much more to the families caring for their NICU graduate. I am both honored and humbled to receive the support of the Marshall Klaus award, which will further support my clinical and research goals to better understand the pathophysiology of lung development that occurs in extremely premature infants. Under the mentoring of Dr. Erin Plosa, I have started studying integrin $\alpha 3$ to define its role in alveolar basement membrane formation and epithelial cell interactions that occur during late lung development. By gaining a better comprehension of abnormal lung development, I hope to use this in my practice to better treat neonatal lung disease, as well as the potential to find therapies to improve lung outcomes in extremely premature infants. I am excited to continue learning new basic science techniques, research methods, and overall expanding my skillset to help set my foundation in understanding developmental biology and further my education in neonatology. The Marshall Klaus award will support me to obtain the training and knowledge to accomplish this research project with Dr. Plosa, while also helping to further my long-term career goals in academic medicine to hopefully improve the survival and outcomes for premature neonates.

Abstract: Over the last two decades, there has been improved survival of extremely premature infants with a subsequent increase in the incidence of bronchopulmonary dysplasia (BPD). Infants with BPD exhibit an arrest of saccular lung development, which is the window where the epithelium closely approximates the endothelium in the distal lung. In between these cell types is the fused alveolar basement membrane (BM) responsible for facilitating gas exchange. The alveolar basement membrane is composed of collagen and laminin. Epithelial cells connect to the basement membrane via integrins, which are protein receptors comprised of alpha and beta subunits expressed on the surface of lung epithelial cells. Integrins bind extracellular matrix (ECM) components and regulate processes critical to development. There are many variations of integrins and their roles in development, but the laminin-binding integrins important for lung development are $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 3\beta 1$. Focusing on integrin $\alpha 3\beta 1$, we created a mouse model with a lung specific epithelial deletion of $\alpha 3$ at embryonic day 9.5 (E9.5) using ShhCre. Our preliminary data demonstrated that $\alpha 3\beta 1$ begins to be expressed in distal lung epithelium around E18, and histological examination of these mice lungs at different timepoints determined normal branching but exhibited sacculation and alveolarization defects as they failed to form a fused basement membrane. Consistent with our model, other studies have shown keratinocytes and renal epithelium require $\alpha 3$ for proper organization of their simple basement membranes; however, the exact mechanisms regulating the formation of the alveolar BM and organization of alveolar

epithelial cells remain undefined. We hypothesize that $\alpha3\beta1$ integrin is required for alveolar basement membrane formation that mediates epithelial proliferation and differentiation during late lung development. This study will allow us to study integrin $\alpha3$ to define its role in assembly and organization of the alveolar basement membrane, as well as define the role of integrin $\alpha3\beta1$ -ECM interactions in regulating epithelial cell behavior. By defining this role, we hope that it will give us a more detailed understanding of the molecular mechanisms governing epithelial behavior during these critical stages of lung development to allow for the potential to develop novel therapies to potentially ameliorate neonatal lung diseases caused by disruptions in lung development.



Michael Cookson, MD

University of Colorado

Title: *Antenatal vitamin D treatment improves sFlt-1 induced abnormal lung and vascular development in infant rats*

Mentor: Erica Mandell, DO

Personal Statement: My introduction to developmental pulmonary vascular biology was as a first-year medical student in the Pediatric Heart Lung Center at the University of Colorado, and I am excited to continue towards a career as a neonatal physician scientist as a recipient of the 2023 AAP Marshall Klaus Award. As a neonatal-perinatal medicine fellow I am driven to understand how we can improve management and ultimately decrease the burden of bronchopulmonary dysplasia (BPD) and pulmonary hypertension in the preterm infants I care for clinically. I intend to spend my career as an academic neonatologist committed to studying how perinatal events contribute to neonatal cardiopulmonary disease. In preparation for my transition to an independent physician scientist after my fellowship, I continue to dedicate my time in the lab to improve my ability to leverage animal, cellular, and molecular laboratory techniques to understand the role of endothelial cell biology in various disease states. Support from the Marshall Klaus Award will extend my previous work demonstrating that vitamin D has proangiogenic properties in an inflammatory model of BPD. The current studies will elucidate the proangiogenic effects of vitamin D in an animal model of disrupted angiogenic signaling leading to abnormal lung and vascular development. My goal is that this work improves our understanding of the interactions between maternal and fetal disease to improve the long-term outcomes of the neonates we care for in the neonatal ICU.

Abstract: The incidence of bronchopulmonary dysplasia (BPD) remains over 40% in preterm infants born before 28 weeks gestation, yet there are few interventions to improve outcomes for this vulnerable population due to large gaps in our understanding of the mechanisms underlying BPD pathogenesis. The pathogenesis of BPD is multifactorial and disease severity is modulated by the adverse effects of both antenatal and postnatal insults. Preterm infants born to mothers with preeclampsia (PE), a pregnancy specific vascular disorder, are at increased risk for BPD, and are more likely to develop BPD associated PH, suggesting that abnormal maternal angiogenesis contributes to aberrant fetal vascular development. Work from our lab has developed the vascular hypothesis of BPD which illustrates that disruption of proangiogenic signaling, such as the vascular endothelial growth factor (VEGF) pathway, alters endothelial-epithelial cell cross talk, “angiocrine” signaling. We have previously shown that intraamniotic injection of the soluble VEGF antagonist, (soluble fms-like tyrosine kinase-1 [sFlt-1]), which is elevated in both amniotic fluid in mothers with PE and in neonatal tracheal aspirates of infants who go on to develop BPD, is sufficient to cause decreased alveolarization and vascular development associated with BPD. Prior work from our lab has demonstrated that Vitamin D (VD) has proangiogenic effects in the developing lung and placenta in an inflammatory model of BPD and that VD increases pulmonary endothelial cell growth and function during endotoxin exposure. However, whether VD can directly attenuate sFlt-1 induced abnormalities in lung development and function is not known. Using the sFlt-1 model, we will investigate the effectiveness of antenatal VD treatment of antenatal sFlt-1 exposed fetal rats in attenuating persistent abnormalities of lung development and function. These investigations will give us insight into the cellular effects of VD on lung endothelial cells responsible for coordination of distal lung development and improve our understanding of pulmonary endothelial cell signaling mechanisms.



Tristan Dear, MD
University of Colorado

Title: *The regulation of vascular growth and architecture within skeletal muscle of the growth restricted fetus*

Mentor: Laura Brown, MD

Personal Statement: I have incorporated research into all stages of my education and these experiences have solidified my choice to pursue a career as a physician scientist. After

finding my passion in pediatrics, I sought experiences in basic science to bridge disease pathophysiology to bedside clinical medicine. During residency, I worked in Dr. Laura Brown's laboratory at the Perinatal Research Center and embarked on an exciting project examining the microvascular structure in skeletal muscle from the intrauterine growth restricted (IUGR) fetus as a mechanism for reduced muscle mass. This experience fueled my passion for neonatology basic science research and helped me become a better physician, allowing me to apply what I learned in the lab to the patients I cared for. As a Neonatal-Perinatal Medicine Fellow, I have come to appreciate the profound impact that growth restriction has on both the short- and long-term outcomes for affected infants. This observation is a constant motivator to continue pursuing research around IUGR fetuses. With support from the Marshall Klaus Award, I will continue to expand my work to interrogate the molecular mechanisms that regulate vascular growth in IUGR fetal skeletal muscle.

Abstract: Growth restricted infants face both short- and long-term health consequences, including alterations in early life organ growth as well as metabolic consequences in later life. Among the many fetal organ systems affected by growth restriction, skeletal muscle is particularly vulnerable. In response to placental insufficiency, the fetus preferentially shunts blood away from skeletal muscle as a survival mechanism to preserve perfusion of the vital organs. Thus, the intrauterine growth restricted (IUGR) fetus and neonate suffer from decreased muscle mass and a reduced muscle to fat ratio. These deficits persist into adult life in the form of persistently lower muscle mass, increased insulin resistance, and a higher risk of developing type 2 diabetes mellitus. Our lab has previously demonstrated that hindlimb blood flow is similar between late gestation control and IUGR fetal sheep when normalized to hindlimb weight, indicating that hindlimb muscle growth slows to match blood supply. However, oxygen delivery rates were reduced per gram of hindlimb due to chronically lower blood content. Our preliminary data demonstrated that protein expression of the angiogenic regulator, vascular endothelial growth factor A (VEGFA) is 45% lower in IUGR hindlimb muscle. Acute hypoxemia is known to stimulate angiogenesis, but how chronic hypoxemia affects angiogenesis is less well delineated. To fill this knowledge gap, we will test the hypothesis that chronic hypoxemia associated with placental insufficiency results in downregulation of VEGFA signaling pathways and disruption of microvascular architecture to limit oxygen delivery in skeletal muscle of the IUGR fetus. By using skeletal muscle from our sheep model of chronic placental insufficiency and IUGR, we have the ability to perform immunofluorescence studies, western blots, and real-time qPCR to better understand differences in microvascular growth,

protein expression, and gene expression to elucidate differences in IUGR skeletal muscle development. This proposal will identify, for the first time, key factors involved in microvascular growth that may contribute to reduced fetal skeletal muscle mass in the IUGR fetus.



**Benjamin Fensterheim,
MD, PhD**
Children's Hospital of
Philadelphia

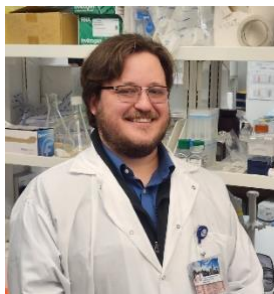
Title: *Longitudinal immune profiling of preterm infants*

Mentor: E. John Wherry, PhD

Personal Statement: I am so thankful to have received the Marshall Klaus Research Award to support my goal of becoming an independent physician-scientist. I have long been fascinated by how complex biologic systems generate health and disease, from neuronal circuits to immune networks. In graduate school, I solidified core scientific training through studying how disruption of innate immune networks, such as in murine sepsis, can result in severe systemic and organ-specific disease. When I became a neonatal-perinatal medicine fellow, it was apparent that many of the diseases impacting preterm infants resulted from immune maladaptation to medical care, but that relatively little was known about the human neonatal immune system. Expanding knowledge of the neonatal immune system to create new tools and therapeutics for infants became the goal of my fellowship work and my career. This project will be conducted with Dr. John Wherry and the Immune Health Project at Penn, both of whom provide me with the mentorship and resources needed to conduct human immunology research in preterm infants with state-of-the-art resolution, and the infrastructure needed to translate discoveries to patients. This project will provide a foundation to establish myself as an expert in neonatal immunology and will spur further research opportunities in the field. My fellowship research is a time to advance my training as a physician-scientist and move towards scientific independence, and support from the Marshall Klaus Award brings me closer to that goal.

Abstract: Preterm birth is the leading cause of infant mortality worldwide. Many of the morbidities that impact preterm infants, including bronchopulmonary dysplasia (BPD), stem from maladaptation of the immune system to an unexpected and medicalized post-natal life. This inflammation is systemic, and inflammatory cytokines can be found elevated in the blood

before BPD diagnosis. However, it has proved difficult to use the immune system to stratify infants by BPD risk because knowledge of the preterm immune system is murky. This study aims to detail the complete preterm immune network with a combination of deep cellular analysis and immune proteomics to identify immune profiles of infants who ultimately develop BPD. We will use novel small-volume 41-marker cytometry by time of flight (CyTOF) and 92-protein oligonucleotide-linked (Olink) proteomics to analyze cells and protein from soon-to-be-discarded clinical labs every two weeks as they are sent during a preterm infant's Neonatal Intensive Care Unit (NICU) admission. Then, in concert with the biostatistics team in the Immune Health Project at the Penn, we will use non-parametric statistical modelling to identify commonalities and variation over time, across age, corrected gestational age, weight, compared to 10 control healthy term infants, and compared to healthy adults. We will also collect clinical diagnosis data for the infants in the study, identify immune profile signals that correlate with graded BPD diagnosis, and determine the earliest time point which they appear. Through robust longitudinal detail of the preterm infant immune cell and protein network, this work aims to deepening our knowledge of neonatal immunity and lay a foundation to use immune profiling as a predictive tool for preterm infants. If preterm infants at high-risk of BPD could be identified early in life, it would open them to more intensive early inventions or trials of new treatments that might reduce their risk of BPD.




Daniel Goldenberg, MD
Saint Louis University

Title: *Role of intestinal microbiota transplantation in mitigating liver and gut injury in short bowel syndrome model*

Mentor: Ajay Jain, MD

Personal Statement: I am a second-year Neonatology-Perinatology Fellow at Saint Louis University with a strong interest in the field of gut microbiology and gut-systemic signaling, and their effect on neonatal nutrition, immune system development and modulation, and neurodevelopment. My fascination and passion for neonatology began in medical school, and my gastrointestinal research interests evolved during my pediatric residency as I reviewed the discoveries of gut microbiomes' influence on physiology. Fortunately, I had the opportunity to join the lab of Dr. Ajay Jain, my research mentor, who shared these interests. With his support, I have been contributing to innovations in the prevention and mitigation of adverse outcomes related to short bowel



syndrome. My professional goal is to become a physician-scientist practicing clinical neonatology and conducting research in a lab focusing on the role of gut-systemic signaling in fetal and neonatal development. I am honored and humbled to have my project selected to receive the 2023 Marshall Klaus Neonatal-Perinatal Research Fund award.

Under Dr. Jain's mentorship and in collaboration with lab partners, I have been using a novel piglet model of short bowel syndrome (SBS), developed by Dr. Jain's lab, to develop a novel approach to mitigating the hepatic and intestinal sequelae associated with prolonged parenteral nutrition use in short bowel syndrome. We hypothesize that in SBS animals, scheduled Intestinal Microbiota Transplantation (IMT) obtained from EN animals will prevent gut microbiota changes and mitigate gut injury. We will use our SBS model and achieve IMT by delivering it in defined aliquots via an externally accessible duodenal catheter (available in our novel model) to SBS animals. To ascertain the impact of IMT, we will assess serological markers of gut injury, gut and liver histology, cytokine profiles, as well as classify and quantify stool microbiota using culture-independent targeted amplicon sequencing and shotgun metagenomics to identify mechanistic pathways.

Abstract: Short Bowel Syndrome (SBS) is a devastating condition characterized by insufficient remaining intestinal length to allow sustainable nutritional absorption from enteral nutrition. SBS patients are dependent on Parenteral Nutrition (PN) to survive. In addition to the expected health risks of continuous intravenous access for prolonged PN, such as the risk of central line infections and thrombosis, PN itself can induce potentially lethal liver and gut injury. We hypothesize that the lack of intestinal exposure to enterally administered nutrition, as occurs in PN-dependent SBS patients, alters gut-systemic signals driving injury mechanisms. Our lab has shown gut microbial shifts in SBS, with a significant increase in the Bacteroidetes phylum and a decrease in the Firmicutes phylum, as well as significant subphylum changes. We hypothesize that restoration of gut microbiota in SBS animals through intestinal microbiota transplant (IMT), obtained from EN animals, will mitigate injury. Using our model as a proof of concept, we have observed mitigation of hepatic and gut injury in SBS upon IMT, attesting to its therapeutic role.



Rachel Hu, MD

Boston Children's Hospital

Title: *Optimizing genetic diagnosis in the NICU: a pooled analysis*

Mentor: Monica Wojcik, MD

Personal Statement: I am currently a second-year neonatology fellow. My research interest in genetics was first sparked clinically, where I saw firsthand how impactful a genetic diagnosis can be on an infant's care in the NICU as well as the care of a patient over an entire lifespan. My initial work in clinical genetics research involved obtaining and analyzing precise information about the physical characteristics of patients in order to answer questions about the full phenotypic spectrum related to an exposure or genetic disorder – I worked on a project describing the craniofacial findings associated with valproic acid in utero, as well as one describing distinct inner ear findings in patients with Kabuki syndrome and a related newly described disorder. More recently, I worked with my current mentor, Dr. Monica Wojcik, to better understand the mortality burden of genetic disorders in NICU infants as well as to describe how the yield of commonly used genetic testing modalities varies by phenotype. I am honored and thankful to receive the Marshall Klaus award which will support me in building on these prior experiences in order to answer a variety of important clinical questions using a comprehensive database of infants that I have worked to build and refine.

Abstract: Many infants admitted to the NICU after birth are suspected to have genetic disorders, and these infants contribute considerably to morbidity and mortality in this population. Despite its importance, genetic diagnosis in this population remains difficult with the optimal approach poorly defined. Prior studies have demonstrated the high yield of exome sequencing (ES) for genetic diagnosis in the NICU, though the yield is dependent upon phenotype selection and certain infants may go undiagnosed. The overarching goal of this project is to determine the optimal diagnostic approach for critically ill infants with suspected genetic disorders. In particular, the impact of integrating ES into routine clinical care in the NICU will be evaluated in terms of its effect on diagnostic yield and other clinical outcomes. The availability and utilization of ES has dramatically increased over the past 10 years, which provides us a valuable opportunity to use the year of NICU admission as an instrumental variable in order to investigate the causal effect of the use of ES on multiple outcomes. In addition, though it has not been previously described, our preliminary data indicates that diagnostic yield was significantly

lower for preterm infants and appeared to decrease successively with earlier gestational age. We will therefore test the hypothesis that the likelihood of obtaining a molecular genetic diagnosis increases with increasing gestational age, and that infants with lower gestational ages are more likely to receive a diagnosis with ES than with targeted testing since ES is less reliant on accurate phenotyping to guide the choice of molecular test.



Nazli Kuter, MD

John Hopkins University

Title: *Targeting p75NTR for rescue of cholinergic neurons after neonatal hypoxic ischemia*

Mentor: Frances J. Northington, MD

Personal Statement: I have been interested in neonatal brain injury since my first pediatric residency in Turkey where I studied the effects of hypothermia on bilirubin neurotoxicity in cell cultures. That experience also reinforced my desire to continue basic science research throughout my career and eventually led to my decision to pursue Neonatology fellowship in the U.S. My goal is a career in academic medicine where I can continue mechanistically based research that will lead to the introduction of novel biologically plausible treatments for the long-term consequences of neonatal HIE. As a Neonatology fellow, I joined Dr. Frances Northington's lab at Johns Hopkins University. Our proposed research is aiming to study cholinergic brain injury after neonatal hypoxic-ischemia (HI) and to investigate a novel agent for cholinergic neuron rescue that can be administered as a delayed therapy after neonatal hypoxic ischemic encephalopathy (HIE). A therapy that is targeting the memory, learning and executive function deficits in the child survivors or a therapy that can be effectively and easily given after the acute phase of the HI injury is yet to be found. This research is an immensely valuable experience for me as it gives me an opportunity to improve my knowledge in HI brain injury targeting neuroprotective cellular mechanisms, and also gain a solid foundation in laboratory techniques, translational research models and tissue/cell imaging that will be useful in every part of my career as a physician-scientist. I am honored to have received the Marshall Klaus Award which will be of invaluable support to my research.

Abstract: Hypoxic-ischemic encephalopathy (HIE) affects over 1 million neonates every year and is a leading cause of lifelong disability. Neurodevelopmental follow up of HIE patients shows executive dysfunction, learning and memory deficits, and lack

of cognitive flexibility starting from early childhood. Forebrain cholinergic systems efferently modulate these functions and our lab has previously shown that these systems are damaged after neonatal HI. p75NTR is a receptor expressed in cholinergic neurons and modulates survival of adult cholinergic basal forebrain (cBF) neurons. LM11A-31 is an orally bioavailable, brain penetrant small molecule p75NTR ligand with neuroprotective effects in mouse models of adult neurodegenerative disease and acute stroke. We have shown that p75NTR are present in ChAT+ neurons in neonatal mice with HI injury and we have also shown that intranasal administration of LM11A-31 achieves brain levels at or above therapeutic levels after neonatal HI. We hypothesize that treating with LM11A-31 after neonatal HI will rescue cholinergic neurons in cBF and result in improved learning, memory, and executive function. We will address this hypothesis with immunohistochemistry, immunofluorescence studies and high throughput put behavioral touchscreen testing. We will use modified Vannucci HI model in mice and will administer the drug as a delayed intranasal therapy after neonatal HI. This is a novel study in both targeting the cBF systems after neonatal HI, in investigating a late and technologically simple therapeutic agent and in following outcomes well into adulthood.



Betty Pham, MD

University of California, San Diego

Title: *The Role of GATA4 in Lung Hypoplasia and Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia*

Mentor: David McCulley, MD

Personal Statement: I am currently a second-year Neonatal-Perinatal Medicine fellow at the University of California, San Diego-Rady Children's Hospital. As the eldest sibling to former premature triplet brothers, I am honored to receive the Marshall Klaus Research Award to conduct research to further neonatal care. I was inspired to become a pediatrician by my family's experience with one brother's early medical challenges and prolonged NICU hospitalization with later chronic, complex needs. Prior to my medical training, I pursued a Master of Science degree during which I conducted research on natural killer cell receptor expression in pediatric liver transplant patients. This work deepened my interest in understanding the underlying mechanisms of disease and led to my career goal of becoming a physician-scientist. To develop the skills and techniques required for that path, I have been mentored by Dr.

David McCulley in the study of genetic etiologies of congenital diaphragmatic hernia (CDH) using a murine model. While there is increasing usage of advanced cytogenetic analysis to determine genetic etiologies of NICU pathology, there is still little known about the role of genetic mechanisms in CDH pathogenesis. We hope to make an impact on the high rates of mortality and morbidity in CDH patients by elucidating the pathways in which the genetic mechanisms lead to a phenotype. With this experience, I aim to develop a research career in developing targeted therapies for genetic etiologies of pulmonary hypertension and to further define phenotypes previously thought to be idiopathic in nature.

Abstract: Congenital diaphragmatic hernia (CDH) is a common and severe structural malformation affecting 1/2,000 births with a 10-50% mortality rate. The range in mortality is due to varying severity of lung hypoplasia and pulmonary hypertension. Through work completed by the Diaphragmatic Hernia and Research and Exploration; Advancing Molecular Science (DHREAMS) study, common variants associated with CDH have been identified in up to 30% of cases. Variants causing GATA4 loss-of-function (LOF) are among the most common in CDH patients and are associated with a high mortality rate and need for oxygen and pulmonary vasodilators at discharge. To understand the role of GATA4 in lung and pulmonary vascular development, our lab utilizes an inducible and tissue-specific gene deletion approach in a murine model. The conditional deletion of a gene of interest during embryologic development allows us to study the resulting molecular and physiologic phenotype. This study aims to add to our current understanding of CDH genes which may serve as possible therapeutic targets.




Puneet Sharma, MD
Boston Children's Hospital

Title: *The Role of GATA4 in lung hypoplasia and pulmonary hypertension associated with congenital diaphragmatic hernia*

Mentor: Andrew Beam, PhD

Personal Statement: I hope to establish a career as a physician-scientist investigating the intersection between artificial intelligence and neonatal intensive care. I was first exposed to artificial intelligence during my pediatrics residency at Cincinnati Children's Hospital Medical Center where I had the privilege of working on the Early Prediction Study as part of the



Parikh Lab. During this time, I learned the power of machine learning through its ability to identify subtle white matter abnormalities on MRI that were predictive of neurodevelopment impairment in preterm infants. This experience showed me the potential role artificial intelligence can have in diagnosis and management of neonates. As I transitioned to fellowship, I joined the Beam Lab at the Harvard T.H. Chan School of Public Health to continue my research in this field. With the help of my mentor Dr. Andrew Beam, I was able to craft a project that built upon the principles I established in residency to tackle another morbidity of prematurity: the patent ductus arteriosus (PDA). With additional support from neonatologists and cardiologists at Boston Children's Hospital, I hope to apply my previous experience to investigate whether machine learning can interpret echocardiograms to predict which patients will respond to pharmacologic closure of their PDA. I am honored to receive the Marshall Klaus Award. Its support will be instrumental in the completion of this project and therefore my continued development as a physician-scientist and advocate of artificial intelligence in neonatal intensive care.

Abstract: The management of the patent ductus arteriosus (PDA) is a major focus of neonatal intensive care as it is a source of significant morbidity and mortality in preterm infants. While there is variability in practice, most clinicians elect to trial pharmacologic closure prior to pursuing ligation or catheterized occlusion. However, there is currently no reliable way to predict which patients will respond to pharmacotherapy. This ambivalence can lead to delays in closure and ineffective counseling of families. Machine learning has emerged as a powerful tool for the interpretation of clinical and imaging data to predict outcomes in neonatal intensive care. One such area that machine learning has shown promise is in the interpretation of echocardiograms where it has been demonstrated to predict ejection fraction, recognize signs of volume overload, and most notably identify the presence of a PDA. However, there is yet to be a study that examines the capability of machine learning to predict pharmacologic closure of the PDA based on echocardiogram data alone. The purpose of this retrospective cohort study is to develop a novel machine learning model to predict the likelihood of PDA closure with pharmacologic management in preterm infants.



Shelby Steinmeyer, MD, PhD

Cincinnati Children's Hospital

Title: *Remodeling of nascent hematopoietic stem cell niches by early-life stressors*

Mentor: Hitesh Deshmukh, MD, PhD

Personal Statement: As a current second year neonatology fellow and developing physician scientist, my research goals focus on improving the health of neonates and setting them on the path towards a healthy life. I aim to discover cues that the immune system relies on during fetal and neonatal development to achieve long lasting homeostasis of crucial mucosal surfaces like the lungs and GI tract. From prior research experience, I have developed skills in quantitative and experimental cellular biology, with an overarching clinical problem ranging from epidemiology of infectious disease to auto-inflammatory disease at the GI mucosal interface of host and microbiota. In residency at Cincinnati Children's Hospital, as my clinical direction transitioned from general pediatrics to neonatology, I worked under the direction of Drs. Hitesh Deshmukh and Will Zacharias to investigate neonatal lung adaptation to the external environment. I leveraged my background in quantitative biology and computer science to develop proficiency in single cell RNA-sequencing (scRNA-seq) data analysis, which I used to better understand the developing lung during inflammation. As a fellow, I have found additional mentorship at Cincinnati Children's in experimental hematology with Dr. Daniel Starczynowski and Computational Biology with Dr. Emily Miraldi. I plan to further develop my "wet-lab" skills—working with hematopoietic stem cell culture and xenotransplant systems—while also refining my "dry-lab" skills—developing signaling and gene regulatory networks revealed by single cell analysis of transcriptomics, epitopes, and epigenomics. After fellowship, I will continue to work towards directing a research program that uses experimental methods in combination with bioinformatics to better understand immune development in the neonatal period and further refine our clinical approach in the NICU. I am extremely grateful to be a recipient of the Marshall Klaus Award, which will be helpful to fund my research as I develop data to support my transition towards a junior faculty position.

Abstract: Chorioamnionitis is characterized by inflammation at the maternal-fetal interface of the placenta and activation of both maternal and fetal inflammatory pathways. Fetal inflammation enhances risks both acutely for infection as well as long term for poor vaccine response, asthma, and chronic

inflammatory diseases. This concept of “*fetal origins of health and disease*” is powerful because it suggests that intervention early in life could alter the course of a patient’s chronic illness and reduce healthcare needs for their lifetime. Due to major differences in murine bone marrow development and limited human tissue availability, there is little information about how fetal inflammation alters the development of immune and hematologic systems in human bone marrow. This proposal addresses that knowledge gap by studying bone marrow and the effects of fetal inflammation during clinically relevant third trimester time points in a nonhuman primate model. Our overall hypothesis is that fetal inflammation imprints epigenetic changes in hematopoietic stem cells and associated stromal cells, disrupting the intrinsic developmental program of the bone marrow niche leading to stem cell exhaustion and immune dysregulation. Using single cell sequencing data analysis, we have identified key changes in hematopoietic stem cell gene regulation and associated signaling in the bone marrow niche. Using cryo-preserved bone marrow samples from our nonhuman primate model, we will perform *in vitro* experimental testing of these gene regulatory and cell signaling pathways to determine the role of altered cell signaling to promote emergency myelopoiesis and ultimately hematopoietic stem cell exhaustion after exposure to chorioamnionitis.



Alyssa Thomas, MD
Boston Children's Hospital

Title: *The Arch Watch Study: An Integrated Evaluation of Hemodynamics during Monitoring of Ductus Arteriosus Closure in Infants with Suspected Coarctation of the Aorta*

Mentor: John Kheir, MD

Personal Statement: I am second year neonatology fellow at the Harvard neonatal-perinatal medicine fellowship program. I am inspired by a goal of using translational initiatives to study neonatal cardiac physiology and improve how we provide care for this high-risk population of infants. My project proposes to integrate multiple types of physiologic data, including a novel resonance spectroscopy-based measure of tissue oxygenation and compromised blood flow, to better characterize the evolving hemodynamics of neonates with possible critical coarctation of the aorta (CoA) during ductus arteriosus closure. My past research, mentored in collaboration with a neonatologist and a cardiologist, similarly focused on building bridges between these two fields, by investigating oxygen

physiology in infants with congenital heart disease during the hemodynamic transition immediately after birth. During my fellowship I have cared for many infants admitted for evaluation for possible CoA (the 'arch watch'), including infants who have developed severe morbidities related to their diagnosis. Relying on imperfect tools and protocols to monitor for signs of developing arch obstruction increases the risk of poor outcomes and uncertainty for families. Through this project I hope to identify hemodynamic patterns indicating critical CoA to better serve this population. I am honored and humbled to receive the Marshall Klaus Award to support my fellowship research in the lab of Dr. John Kheir.

Abstract: Coarctation of the aorta (CoA) is a potentially life-threatening form of congenital heart disease (CHD) in which an anatomic narrowing of the aortic arch may cause critical aortic obstruction following closure of the ductus arteriosus. CoA accounts for 6-8% of all CHD and occurs in about 1 in every 1800 babies born in the United States each year. Despite this prevalence, CoA frequently eludes detection on prenatal imaging and remains the critical CHD most likely to be missed on standard newborn pulse oximetry screening. If undiagnosed, infants may present with catastrophic shock, often leading to mortality or severe morbidities. In the days following delivery, constriction of the DA creates dynamic changes in arch anatomy, dimension, and physiology, complicating postnatal detection and necessitating hemodynamic monitoring of infants at risk of CoA. The goal of this project is to evaluate the sensitivity and specificity of the multimodal monitoring currently used during the 'arch watch' in detecting a developing critical aortic obstruction, including blood pressure, pulse oximetry and photoplethysmography waveform features, and cerebral-renal near-infrared spectroscopy gradient. In addition, we will test Resonance Raman spectroscopy as a novel measure of tissue oxygenation and mitochondrial reduction state indicating critical impairments in oxygen delivery.

Health Services Research Awardees




Nikita Kalluri, MD

Boston Children's Hospital

Title: *Characteristics of communication in interpreted and non-interpreted NICU family meetings*

Mentor: Margaret Parker, MD, MPH



Personal Statement: I am currently a post-graduate year 5 physician completing my neonatal-perinatal clinical fellowship in the Harvard Neonatal-Perinatal Medicine Fellowship Program. Concomitantly with my clinical training, I am completing a two-year Harvard Pediatric Health Services Research Fellowship and a Master of Public Health. Afterwards, it is my goal to practice clinically and perform health services research to reduce disparities in NICU parental engagement.

My interest in this topic has been built upon prior research experiences investigating disparities in neonatal care. As a resident, I performed a retrospective analysis of infants admitted to local NICUs to evaluate NICU infant morbidities (including late-onset sepsis, necrotizing enterocolitis, growth, and length of stay) based on maternal primary language. In our specific evaluation of length of stay, we found significant differences in length of stay between infants of English-speaking vs. non-English speaking mothers. To further understand the difference in quality of care and engagement for infants of non-English speaking mothers, I assessed differences in NICU bedside presence based on maternal sociodemographic factors, including primary language. Through this study, we found that mothers of minority race and non-English primary language were less likely to be present at the NICU bedside and when present were less likely to be active in their infant's cares. Performing this retrospective work has illuminated the difference in parents' experience in the NICU and has led me to become interested in the mechanisms behind these disparities. In my current fellowship scholarship, I hope to gain a greater understanding of the characteristics of communication between clinicians and families during family meetings during the NICU stay, a critical part of NICU communication, and further understand mechanisms of communication disparities.

Abstract: This proposed research endeavor seeks to explore the previously unstudied relationship between parental primary language, interpreter use, and communication during family meetings (a crucial component communication during NICU stay). We aim to use audio recordings of family meetings to assess elements of high-quality family meetings and subsequent parental satisfaction.



Blair Simon, MD

Ann & Robert H. Lurie

Children's Hospital of Chicago

Title: *Preterm birth rates among infants of US-born and foreign-born Latinx women in the United States: An analysis of how self-identified Black race effects preterm birth rates*

Mentor: James Collins Jr. MD, MPH

Personal Statement: I have always aspired to be a well-rounded physician, with an overall goal of advancing the field of neonatology. My interest in outcomes research was initiated during medical school as I worked on projects that outlined the clinical outcomes of surgical patients based in respect to social demographics. As a resident physician at Ann & Robert H. Lurie Children's hospital of Chicago, I had the opportunity to join the research team of Dr. James Collins Jr. This opportunity allowed me to see the utility of health services research and its potential impact on the field of neonatology. I have been able to continue my work under the mentorship of Dr. Collins during fellowship, while also honing my research acumen in the Northwestern master's program in Health Services and Outcomes Research. My time is allocated to both clinical and academic excellence alike, with a focus on using my education to narrow the gap in healthcare for at risk populations. I plan to focus on utilizing large population-based datasets to analyze neonatal outcomes, with emphasis on their connection with health disparities. My intellectual curiosity is stimulated by the utilization of large-scale data to inform future decisions. I envision myself using my academic work to implement productive change in how we ultimately care for our patients. Further evaluation of vulnerable populations is critical to facilitate evidence-based interventions. The goal of my proposed research project is to gain a deeper understanding of the nuances between different Latinx populations by evaluating the effect of black race on differing neonatal outcomes. I am honored to receive The Marshall Klaus Research Award, which will support my goal of evaluating the relationship between racial identification and preterm birth rates. Previous research studies have attempted to elucidate causal linkages between preterm birth rates and socioeconomic factors in the Latinx population. However, the racial identification (black vs. white) within the Latinx population and its linkage with preterm birth rates are still poorly understood. Support from the Marshall Klaus award will aid in bolstering the understanding of this potential linkage.

Abstract: Preterm birth is the second leading cause of infant mortality in the US. Infants that are born prematurely and survive have an increased risk of neurological, visual, and hearing deficits, with an overall increased risk of chronic disease. Prior research has shown a distinct discrepancy in preterm birth rates with non-Latina black mothers having the highest preterm birth rates, followed by women of Native American and Latina descent. The Latinx population of the United States continues to grow, accounting for almost 19% of the total US population according to the US Census Bureau. The US Census Bureau uses ethnicity to define Hispanic/Latinx origin. This classification is distinct from race. Three central racial backgrounds exist in national census data – white, black, and Native Indian. Within these three racial backgrounds, there are different subgroups. These proportions and combinations create nuances within the population that are not always considered in health services research. As a result, the relationship between black race and preterm birth rates in the Latinx population remains incompletely understood. The goal of my project is to study preterm birth rates in the Latinx population, evaluating the differences in outcomes (preterm birth) with respect to maternal country of origin (nativity) and self-identified race. As we strive to serve a diverse patient population it is our duty to thoroughly evaluate relevant outcomes for our patients. This project is important in that it will serve to augment our understanding of the effect modification of race and its interplay with ethnicity, as the two are not necessarily mutually exclusive. This research may serve as the framework for potential to positively affect maternal outcomes, in turn affecting neonatal outcomes. My long-term goal is to utilize outcomes research to create the framework for policy and intervention that will improve discrepancies in neonatal outcomes.

Newborn Medicine Education Awardee




Jessica O'Neal, MD

University of Pittsburgh Medical Center

Title: *Education and implementation of joint perinatal counseling*


Mentor: Christine Bishop, MD, MA

Personal Statement: I am a second-year neonatal-perinatal medicine (NPM) fellow at the University of Pittsburgh Medical Center (UPMC). My career goals are to become an academic neonatologist. I have a strong interest in medical education, quality improvement and palliative care. I realized my interest



in medical education and quality improvement early on in residency. I began working on several quality improvement projects including umbilical line placement training and improvement of resident education. As a senior resident, I was chosen to be a part of the Academic Clinician Educator Program, which facilitated growth as an academic instructor and culminated in teaching newly matched medical students. As a chief resident, I grew as an educator, mentor, and leader. I was able to be involved in the hospital quality improvement committee. My interest in palliative care peaked when I was a first year NPM fellow and I realized the importance of communication skills when having a difficult discussion. As fellows we had no formal training on joint perinatal counseling, which led me to connect with my mentor Dr. Christine Bishop, Director of Perinatal Supportive Care. We developed a quality improvement project to create a curriculum on joint perinatal counseling. The goal of the project is to educate the maternal-fetal medicine and NPM fellows and then implement joint counseling into daily practice for periviable and high-risk deliveries. To improve the project and advance my quality improvement skills, I participated in a Quality Education Series through UPMC and took a palliative care course through Columbia University. My project has allowed me to combine my interest in medical education, quality improvement, and palliative care into one. I am grateful to the support of the Marshall Klaus Award to continue my work.

Abstract: Maternal Fetal Medicine (MFM) and Neonatal-Perinatal Medicine (NPM) fellows rarely perform joint inpatient perinatal counseling for pregnant people with serious fetal or maternal issues at University of Pittsburgh Medical Center (UPMC) Magee-Womens Hospital (MWH) despite the best practice recommendation. An initial needs assessment showed 79% of the fellows had never had a joint perinatal counseling session and 100% felt a formal curriculum would be beneficial. Baseline chart review solidified the need for education by showing that only 6.4% of high-risk deliveries were counseled jointly. Our project aims to build a perinatal counseling curriculum for MFM and NPM fellows modeling collaborative perinatal counseling, teaching and practicing critical communication skills, and ensuring topic specific medical knowledge. Each educational experience includes communication skills based on Vitaltalk^Ó methods and medical content presented in pre-learning and didactic session. Simulation through peer discussion, peer to peer practice and standardized patient encounters help to solidify this information. I predict this will increase participant comfort level and knowledge related to joint perinatal counseling, as well as the occurrence of joint perinatal counseling consults. The learning experiences are evaluated using pre and post surveys. Likert scale questions with ordinal data are analyzed



via descriptive statistics. Preliminary data shows an increase in self-reported comfort and knowledge. Since beginning education, clinical chart review has shown an increase in occurrence of inpatient MFM and NPM joint perinatal counseling consults to 26.9%. After each session, the fellows have requested to have more practice. With the help of the Marshall Klaus Award this project will be able to have patient actor simulation to allow for a realistic and safe environment to improve joint perinatal counseling skills.
