2018 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 2018 Marshall Klaus Neonatal-Perinatal Research Award! The Research Committee received 39 very strong applications and all applicants deserve recognition for their already strong bios, outstanding mentors, and exciting projects. Thanks to our sponsors, this year we are able to fund the top 10 ranked fellows with the $5,000 research award. The money will be used towards supplies etc. to support the proposed research project.

Klaus Bench or Clinical Research Awardees

Melissa H. Althouse, MD - Baylor College of Medicine

Title: Role of Gut Microbiota in Neonatal Lung Injury: Implications for Bronchopulmonary Dysplasia

Mentor: Bhagavatula Moorthy, PhD

Personal Statement: I am currently training as a Neonatal-Perinatal Medicine Fellow at Baylor College of Medicine and Texas Children's Hospital. From a young age I aspired to be a pediatrician. My interest in neonatology began in medical school in Norfolk, VA and was solidified with my residency experience at the University of South Florida. It was in residency that my research interest in neonatal gastrointestinal disease started when I was part of a team treating a patient with a devastating case of necrotizing enterocolitis. Around that time, I had begun working on NEC research in a basic science laboratory under the guidance of a physician-scientist. Investigating the molecular mechanisms behind necrotizing enterocolitis in the lab enabled me to have a greater understanding of the clinical disease and management when caring for patients in the NICU. My career path then led me to Houston, Texas for
neonatology fellowship and to work under the mentorship of Dr. Moorthy, a leading expert in the field of hyperoxic lung injury and cytochrome P450. Building upon my background in neonatal intestinal disease, I developed my fellowship project to study the gut-lung axis. My long-term goal is to investigate the mechanisms by which the neonatal microbiome affects chronic lung disease. Ultimately, I hope this research will lead to novel treatment or management strategies for bronchopulmonary dysplasia. The Marshall Klaus Award will allow me to further my research and assist me to begin a career as a physician-scientist.

Abstract: Under the guidance of my mentors Dr. Moorthy and Dr. Lingappan, I am currently investigating the relationship between gut dysbiosis and chronic lung disease in a murine model. We are creating dysbiosis, or an altered gut microbiome, by exposing mouse pups to antibiotics both prenatally and postnatally. The pups are then exposed to hyperoxia for several days after delivery to induce lung injury which will mimic bronchopulmonary dysplasia development in neonates. Our hypothesis is that alteration of the intestinal microbiome will worsen lung injury after hyperoxia exposure in a neonatal murine model. If we discover a connection between the microbiome and lung injury, we plan to attempt to attenuate the disease process using fecal transplantation.
research will explore the exciting field of microchimerism and the role of these cells in neonatal development.

**Abstract:** Bidirectional transplacental exchange of cells between mother and fetus ubiquitously occurs during mammalian pregnancy. The long-term persistence of these genetically foreign cells results in microchimerism in both individuals. Roles beyond reproductive fitness for these cells are unclear. Given the rapid physiological changes that occur in the perinatal period, microchimeric have the potential to alter development and maturation of the offspring. The neonatal immune system is particularly immature and neonates are at high risk of developing sepsis or other serious infections. Given that a large fraction of maternal microchimeric cells derive from the immune system, these cells could potentially provide protection against infection in offspring or aid in immune development. Currently, the transfer of cellular immunity remains poorly described. My proposal will test the hypothesis that maternal microchimeric cells provide a means of vertically transferring cellular adaptive immunity from mother to offspring. I will utilize Listeria monocytogenes as a model organism and track epitope-specific T cell responses in infected neonatal mice. The results of these studies will highlight the possibility of preconceptual vaccination as a means to protect offspring when they are the most vulnerable. Additionally, these studies could demonstrate another crucial role for breastfeeding, namely transfer of protective cellular immunity.

**Cicely W. Fadel, MD, PhD - Boston Children’s Hospital**

**Title:** Microfluidic Modeling to Study Interactions of the Premature Microbiome with Intestinal Epithelial Cells

**Mentor:** Don Ingber, MD, PhD

**Personal Statement:** My desire to use emerging technologies to better understand and more effectively treat human disease has been the driving force behind my many career stages from bench to bedside. I have used a wide range of experimental techniques to investigate a variety of disease processes, from hereditary hemochromatosis to breast cancer and neural tissue injury. While technical expertise is undoubtedly a necessary component of a research career, I have always been the “MacGyver” in the room. Although I do not have a mullet, I do have a passion for creative problem solving, tinkering, and seeing connections between seemingly disparate ideas and disciplines. With guidance from some of the greatest minds in science and medicine, I have fine-tuned the application of my skills to directed scientific problem solving at the laboratory bench and in the clinic.

For my postdoctoral and neonatology fellowship training, I would like to apply my knowledge, skills, and extensive training to understanding the factors that affect neonatal gut health. There is ample evidence that early gut health, via the microbiome, affects susceptibility to disease in both the neonatal and adult periods. Premature neonates are a particularly vulnerable population whose altered microbiomes may promote susceptibility to infectious and inflammatory diseases. My mentor Dr. Don Ingber, the director of the Wyss Institute for Biologically Inspired Engineering, has developed a unique human gut-on-a-chip microfluidic platform that utilizes continuous fluid-flow and peristalsis-like mechanical deformations to recapitulate the villous epithelium of the human intestine. Through key institutional collaborations we will apply clinical human intestinal biopsy specimens and gut bacteria from premature neonates to
the platform to better understand how the premature microbiome affects basic intestinal biology. The Marshall Klaus Award will facilitate not only this innovative research project, but also the final stages of my development into an independent physician scientist.

Abstract: The early microbiome is notably aberrant in premature neonates, where baseline gut immaturity is coupled with environmental exposure to hospitalization, antibiotic administration, artificial feeding and delayed initiation of feeds. This dysbiosis is associated with increased susceptibility to infectious, inflammatory and metabolic disorders from the newborn period and into adulthood. The goal of this project is to develop an in vitro model to study the effect of the abnormal premature neonatal microbiome on intestinal epithelial cell biology. Our established organs-on-a-chip platform presents a unique opportunity to utilize mechanics to create stable cultures of human bacteria with intestinal epithelial cells in a biomimetic environment that supports villus structure formation, intestinal barrier formation, mucus production and digestive capacity. Our central hypothesis is that the premature neonatal microbiome directly contributes to the vulnerability of the premature gut to illness and injury by compromising intestinal function. To explore this hypothesis primary human small intestine epithelial cells isolated from the crypts of pediatric biopsy specimens will be exposed to peristaltic-like deformations and continuous flow with media containing individual fecal samples from extremely premature infants (<28 weeks) or moderately premature infants (33 weeks) in anaerobic growth conditions. Understanding how the premature microbiome directly affects intestinal function particularly in a platform that is optimized for therapeutic testing will provide important insight into additional opportunities for therapeutic intervention and may put infants on the right track to life-long health.

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Scott M. Gordon, MD, PhD – The Children's Hospital of Philadelphia

Title: Role of Interleukin-15 in Driving the Phenotype and Function of Novel CD122+ Macrophages

Mentor: Edward M. Behrens, MD

Personal Statement: Despite our best clinical care in the NICU and beyond, infants affected by intrauterine growth restriction (IUGR) face dismal short- and long-term outcomes. With our current knowledge of IUGR, we can neither detect nor reverse growth restriction of the fetus to prevent such outcomes. As a fellow in neonatal and perinatal medicine with a background in basic cellular immunology, I am fascinated by the notion that the placenta and the maternal immune system communicate with each other to ensure adequate growth of the fetus. Specifically, I study how macrophages are called upon to during pregnancy to support proper development of the placenta. As a physician-scientist and graduate of the American Board of Pediatrics Accelerated Research Pathway for residency, I hope to lead a basic and translational research group that advances understanding of the immune mechanisms underlying placental insufficiency and IUGR.
Abstract: Growth of the fetus is linked with the quality of placentation, or development of the placenta. If placentation is impaired, the fetus is starved of essential oxygen and nutrients and becomes growth-restricted. Abnormal inflammation in and around the placenta has been associated with IUGR. Macrophages are abundant at the maternal-fetal interface from the earliest phases of placentation, but we do not yet understand how macrophages function to support the placenta and drive fetal growth. I have found a novel subset of macrophages unique to the maternal-fetal interface in mice and humans. With support from the Marshall Klaus Neonatal-Perinatal Research Award, I am more deeply investigating how these new macrophages develop and function in the context of placentation.

Ravikiran M. Raju, MD, PhD - Picower Institute of Learning and Memory, MIT

Title: Structural and Epigenetic Effects of Early Life Adversity and Resource Deprivation on Neurodevelopment

Mentor: Li-Huei Tsai, PhD

Personal Statement: Throughout my career, it is a deep sense of social justice that has led me to pursue research and advocacy aimed at reducing gross disparities that exist in disadvantaged communities. Up until residency, my career had focused on the problems that disproportionately affect the poor, such as tuberculosis and high maternal mortality. I saw poverty as a collection of different pathologies that, if addressed individually, would lead to better outcomes. However, as a physician caring for children and getting to intimately know families in the most neglected areas of Boston, my understanding of poverty began to evolve. Whether it was the higher frequency of asthma attacks or behavioral problems in school, I found myself caring for the same underserved children over and over again. Turning to the literature, I found a rich body of evidence confirming my suspicions; that even when controlling for access to medical care, poor children had worse overall health and cognitive outcomes than their more well-off counterparts. As a result, I came to view poverty itself as the root cause of poor outcomes. With a desire to understand the physiological derangements that occur when children are exposed to this early adversity, I began to explore potential research opportunities and had the fortune of meeting Professor Li-Huei Tsai. Though conversations with her, I began to see the field of neuroepigenetics as setting a precedent for elucidating how experience affects biology. With Professor Tsai’s support, I decided to join the lab during my final year of residency and have started to use epigenetic tools to identify molecular markers of resource deprivation.
Abstract: Nearly 50% of all US children live in poverty, and epidemiological studies indicate that exposure to early life adversity, including poverty, has profound, long-term consequences for health and cognitive development. While countless studies have shown the strong association between exposure to poverty and poor health and cognitive outcomes, the mechanism through which poverty exerts this influence remains unknown. The main goal of this project is to establish a mouse model of resource deprivation that enables us to study the mechanisms through which poverty causes cognitive deficits and poor health outcomes. Using a novel mouse model of resource deprivation, along with advanced imaging and epigenomic sequencing techniques, we aim to determine how neural and immune systems are affected by exposure to such stress. Elucidating the molecular networks that mediate how social stress causes derangements in normal physiology will aid in the development of revolutionary therapies that protect a child’s developmental trajectory and ensure resiliency, even in the face of significant adversity.

Elizabeth S. Taglauer, MD, PhD - Boston Children’s Hospital

Title: Mesenchymal Stromal Cell-Derived Exosome Therapy for the Prevention of Fetal Growth Restriction and Improvement of Neonatal Lung Disease

Mentor: Stella Kourembanas, MD

Personal Statement: As a neonatology fellow with an extensive background in placental immunology, I joined the Kourembanas lab to investigate placental-based diagnostics and therapeutics that can help ameliorate fetal lung disease. I have studied both human and rodent placental biology for over 10 years and have developed a unique niche in examining how this vital organ dictates neonatal health. I am currently exploring a mechanistic connection between the maternal pre-eclamptic environment and neonatal lung disease and whether mesenchymal stem cell-derived therapies can improve the intrauterine environment to facilitate improved fetal lung development.

A native of the southern United States, my training in medicine and research has taken me across the globe, including fellowships at the Lawrence Berkeley National laboratory in Berkeley CA and the Marie Curie Institute in Paris, France. I joined the Harvard Perinatal-Neonatal Fellowship program in 2016 and will continue my clinical career as neonatal physician-scientist with ongoing exploration of the placenta to understand and improve neonatal disease. I am so grateful to have continued opportunities such as the Klaus award to encourage my professional trajectory and to support our ongoing pursuit of placentally-derived diagnostics and therapeutics to ameliorate neonatal health.
Abstract: The goal of our project is to investigate the therapeutic properties of mesenchymal stromal cell (MSC)-derived exosomes for treatment of fetal growth restriction and neonatal lung injury. Our research focuses on the role of preeclampsia in fetal lung injury. In preeclamptic pregnancies, alterations in the uterine immune environment lead to abnormal placentation, intrauterine inflammation and fetal growth restriction, which may cause a primary insult in the developing fetal lung, predisposing it to further post-natal damage. Preeclamptic disease and its complications in the fetus/neonate remain highly difficult to treat despite a variety of attempted interventions. Thus the utility of cell-based treatments has become an emerging area of research for therapeutic intervention.

MSC are well-characterized for their ability to ameliorate a variety of disease processes with pluripotent capabilities. Of particular interest are MSC-derived exosomes, a subset of secreted membrane-bound extracellular vesicles. MSC-derived exosomes (MEX) have anti-inflammatory and immunomodulatory capabilities but low immunogenic potential, making them a particularly interesting therapy for immune-mediated diseases such as preeclampsia and its sequelae. We hypothesize that preeclampsia-associated placental insufficiency and inflammation cause a harmful environment for the developing lung. MEX can ameliorate the intrauterine environment during pregnancy through immunomodulatory pathways, thereby preventing growth restriction and fetal lung injury.

To address this hypothesis, we have established a pre-clinical model of fetal growth restriction using the heme oxygenase-1 (HO-1) knockout mouse. HO-1 is an enzyme involved in heme degradation with well-characterized concomitant immunoregulatory functions, particularly for macrophages. In pregnancy, HO-1 null (HO-1⁻/⁻) female mice exhibit fetal loss as well as maternal preeclamptic-like features. Our preliminary data show that the HO-1⁻/⁻ pregnancies are associated with fetal growth restriction and have increased infiltration of intrauterine macrophages with a pro-inflammatory phenotype. In ongoing studies, we are examining the effects of this preeclamptic maternal environment on neonatal lung disease using an established hyperoxia model of BPD. Further, we are evaluating the effects of maternally administered antenatal MEx therapy on fetal growth and intrauterine immune homeostasis with long-term evaluation of downstream effects on neonatal lung disease. Overall, these studies are addressing important questions on the placental origins of neonatal lung disease and exploring the highly innovative potential of a maternally-delivered stem cell-based therapy to ameliorate the intrauterine environment for improvement of fetal health.
Kent A. Willis, MD - The University of Tennessee, Health Science Center

**Title:** The Intestinal Microbiome Influence on Bronchopulmonary Dysplasia

**Mentor:** Joseph Pierre, PhD

**Personal Statement:** As a second-year neonatology fellow at the University of Tennessee Health Science Center my research interests include a passion for understanding the etiology of bronchopulmonary dysplasia (BPD), especially in relation to emerging developments in mucosal immunology. With a mixed background in basic and clinical research, I have assembled a team of outstanding mentors to pursue a translational approach to host-microbe interactions in BPD. Building on expertise in the neonatal respiratory immune system from the Cormier laboratory, extensive experience in host-microbiome interactions from the Pierre laboratory, and clinical trials and neonatal immunology expertise from Dr. Talati, this cross-disciplinary research platform allows me to thoroughly explore the role of the gut-lung axis in BPD. In addition to directly understanding the pathology of BPD and to hopefully translating to clinical interventions, my research is also designed to foster foundational skills in planning, conducting, and publishing translational research with multi-pronged approaches. Support from the Marshall Klaus Award enables me to dedicate more time to mature as a translational researcher. Utilizing the collective research skills fostered through this and related projects, my goal is to pursue a career in academic neonatology focusing on respiratory mucosal immunology.

**Abstract:** During a critical period in early life, the intestinal microbiome may influence development of the newborn lung. A better understanding of the gut-lung axis and the role of the intestinal microbiome in neonatal pulmonary disease is needed to protect newborns from effects of microbiome alteration that may influence health throughout life. We therefore sought to characterize the role of the intestinal microbiome in development of bronchopulmonary dysplasia (BPD). In these studies, we first aim to characterize the association of an altered microbiome with an increased risk of BPD or death in a prospective nested cohort of very low birthweight neonates, and second, to explore the underlying mechanisms using a hyperoxia model in neonatal mice. Because antibiotic exposure most directly alters the intestinal microbiome and may increase the risk for BPD, we hypothesize that maternal peripartum antibiotic exposure-driven perturbations in the neonatal intestinal microbiota increase susceptibility to BPD. We anticipate this project may help in limit antibiotic use and lay ground work for microbial ecology-restoring therapeutics. The role of the intestinal microbiome on the systemic inflammatory cascade will also be explored given the importance of inflammation in the development of BPD.
Title: Improving Resident Delivery Room Resuscitation with Just-In-Time Training

Mentor: Tina Leone, MD

Personal Statement: I am a second-year neonatal-perinatal medicine fellow at New York Presbyterian Columbia University Medical Center, with research interests in neonatal resuscitation and medical education. I believe that the importance of effective and efficient education of medical providers is paramount to maintain and improve patient outcomes. I have had the benefit of working with gifted teachers, but I have also experienced some of the challenges in modern medical education, including reduced opportunities for hands-on learning due to reduced work hours and increased competing demands on trainees’ time. My clinical and research experience as a resident and fellow at Columbia University Medical Center provided me a unique perspective to design an intervention to improve our neonatal resuscitation education for pediatric residents with a goal to eventually improve training for all neonatal providers. As a fellow, I have gained valuable clinical experience in the resuscitation of newborns and have planned for a career that focuses on providing excellent neonatal care, educating providers of all levels, and investigating new ways of using simulation and other teaching methods to improve the care we provide to newborns.

Abstract: Proficiency in the skills required to resuscitate newborns is essential for pediatric trainees. Residents and program directors report a lack of confidence and competence in these skills at graduation. Additionally, changes in practice have led to decreased frequency of invasive procedures such as intubation, which in turn have led to less opportunities for trainees to practice such skills. In the current training environment, a more effective method to provide experience to these neonatal resuscitation providers in an efficient manner is needed. Studies have demonstrated that simulation-based training is an effective tool for teaching the steps of the Neonatal Resuscitation Program (NRP). Just-in-time and in-situ simulation are techniques that bring the simulation experience closer in time and space to the real-life event they are replicating. My project will study the use of these methods of simulation to enhance resident education. We hypothesize that using content from the day’s obstetric census for the simulation and performing the simulation on the day and in the location where the resident could potentially use the NRP skills in practice will improve their learning, increase their participation in deliveries and increase their confidence with neonatal resuscitation. The overall goal of this project is to study whether just-in-time, in-situ simulation-based training sessions can improve trainee performance of neonatal resuscitation.
Title: Characterization of Stress in Immigrant Families in the Neonatal Intensive Care Unit

Mentor: Charles A. Nelson, PhD

Personal Statement:
As a neonatology fellow at the Harvard Neonatal-Perinatal Medicine Program, I have been increasingly passionate about understanding disparities and the social determinants of newborn health and outcomes. My career goal is to become an academic neonatologist and health services researcher focused on the effects of early psychosocial adversity on brain and behavioral development, particularly the immediate and long-term impact of stress in immigrant families. My own experience as a clinician and immigrant in the U.S. has enabled me to understand the issues faced by immigrant families of infants in the NICU in a unique way. With the guidance of my mentor Dr. Charles Nelson (expert on stress and early life adversity) and with the support of the AAP Marshall Klaus Award we will perform an exploratory sequential mixed methods study to explore the effects of immigration experience and stress in the NICU context. In addition, I have been accepted into the Harvard-wide Pediatric Health Services Research Fellowship with additional mentorship and support to successfully conduct my study. Characterizing stress in immigrant families will provide the foundation for further research to improve the quality, delivery of care, and outcomes in this highly understudied and underserved group.

Abstract:
It is known that families of infants hospitalized in NICUs, experience high levels of both psychological and biological/medical stress. Parental stress has adverse effects on children, and adverse early life experiences and excessive or prolonged stress can negatively impact short- and long-term health. Many NICU families are immigrants or foreign-born, a socio-demographic risk factor that has been independently identified as contributing to poor health; however, the effects of foreign-born status have not been well studied in the NICU context. We hypothesize that immigrant and foreign-born families experience an increased prevalence of immigration-related concerns, and that these in turn are associated with increased levels of stress in the NICU.
Vidya V. Pai, MD - Stanford University

Title: The Referral and Follow-up Patterns of High-Risk Infants

Mentor: Susan Hintz, MD, MS Epi

Personal Statement: My research interests are in neonatal epidemiology, specifically understanding risk factors and characteristics that contribute to disparities in the outcomes and follow-up care of high-risk neonates. After completing residency at the Children’s Hospital of Philadelphia, I chose the neonatal fellowship program at Stanford University because of the opportunities available for population-based research and the ability to work with mentors, such as Drs. Susan Hintz and Henry Lee who are leaders in the field of perinatal and neonatal epidemiology. I am currently a second-year fellow and am also pursuing a Master’s Degree in Epidemiology and Clinical Research at Stanford University. The Marshall Klaus Health Services Research Award and this proposed research will help to build my content knowledge in neonatal epidemiology and develop my skills to contribute to the understudied field of disparities in neonatal follow-up care. The overall goal of my current research is to improve our understanding of disparities in the patterns of referral of high-risk infants with the hope of identifying potentially modifiable factors that can improve outcomes for this population of infants.

Abstract: High-risk infant follow-up (HRIF) programs are critically important in following high-risk infants after discharge from the neonatal intensive care unit (NICU), evaluating the functional and developmental outcomes of these infants, and identifying those requiring referral to medical and supportive services. Infants with very-low birthweight (VLBW) and term infants with moderate-severe hypoxic ischemic encephalopathy (HIE) are two groups that have been the focus of neonatal follow-up investigations due to their significant risk of neurodevelopmental, functional, and medical sequelae. Ensuring referral to HRIF at the time of NICU discharge is the first step in ensuring follow-up, but barriers to referral and to follow-up exist. Prior research in California has demonstrated significant variations in referral rates of VLBW infants to HRIF associated with patient sociodemographic characteristics, and NICU and regional factors. A targeted quality improvement (QI) initiative was implemented in 2013 to improve HRIF referral at NICU discharge. Our objective is to identify patterns of referral to HRIF for VLBW and HIE infants and whether they changed since implementation of this QI initiative in 2013. We will also identify changes in patient-level, NICU and regional factors associated with failure to refer. We will use a large, population-based dataset that includes maternal, neonatal and follow-up data and encompasses >95% of all VLBW infants and infants with HIE in California born from 2010-2016. Our results will demonstrate the effects of targeted QI initiatives on improving follow-up care that can potentially be replicated in other states and frameworks. This project will advance our knowledge of facilitators and barriers to neonatal follow-up and health services access, and present opportunities for future QI and collaborative research to enhance NICU-to-home transition with an ultimate goal of improving long-term outcomes for high risk infants and their families.