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2017 Marshall Klaus Neonatal-Perinatal Research Awardees

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, Johnson and Johnson Pediatric Institute, Mead Johnson, and the AAP, we would like to congratulate the recipients of the 2017 Marshall Klaus Neonatal-Perinatal Research Award! The Research Committee received over 30 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 7 ranked fellows with the \$5,000 research award. In addition, we would like to congratulate the recipient of the 2017 Marshall Klaus Newborn Medicine Education Award, sponsored by Brodsky & Martin at Beth Israel Deaconess Neonatology Foundation, Inc. The money will be used to support the proposed research projects and towards advancing the academic careers of our neonatology fellows.

In the written award notifications, Klaus awardees are expected to submit a report on their funded project by June 30 of the following year and to submit an abstract to the AAP National Conference & Exhibition (NCE, SoNPM meeting) within the next two years to present their research. Awardees are also instructed to list the AAP Marshall Klaus Award in the acknowledgement sections of their project-related publications.

Marko Culjat, MD, PhD - MedStar Georgetown University Hospital



Title: *Effects of Brivaracetam, a Novel Anticonvulsant Drug, on Cell Apoptosis in the Developing Rodent Brain*

Mentor: Patrick Forcelli, PhD

Personal Statement: Prior to starting pediatric residency, I had extensive experience in basic science research focusing on the normal human brain development, analyzing fetal and neonatal brain tissue with histology, immunohistochemistry and post-mortem magnetic resonance imaging. Our research team's focus expanded to clinical research, which involved a multidisciplinary team of neonatologists, neuroradiologists and neuroscientists. My research was further expanded to include

analysis of rodent brain development using electron microscopy when our team wanted to clarify the underlying morphological changes of the corpus callosum during the phase of its exuberance during the early postnatal period.

Transitioning into clinical practice as a pediatrician, and now a neonatology fellow, my scientific interests have shifted from analyzing solely normal developmental patterns of the human brain in the perinatal period to how our clinical interventions could influence brain maturation on morphological and functional levels. The intriguing aspect of this project for me is the potential of affecting future therapeutic choices in treatment of neonatal seizures.

Abstract: Use of antiepileptic drugs (AED) in the neonatal period is often necessary despite the fact that there is little data supporting their comparative safety for this age group. Phenobarbital, phenytoin and, lately, levetiracetam are being used as first line treatment choices for neonatal seizures, and this practice varies between institutions. The AEDs that are used in the newborn period have gone largely unscreened in terms of

their effect on the maturation pattern of the neonatal central nervous system, prior to their wide-spread clinical application. Recent animal studies on effects of AEDs on the developing brain have shown that phenobarbital and phenytoin in therapeutic doses increase the rate of neuronal apoptosis in the telencephalic gray matter, while levetiracetam does not. A novel AED brivaracetam, a highly potent levetiracetam analogue, is currently marketed as an adjunct therapy for partial-onset seizures in ages 16 years and older. Given its pharmacodynamic profile, it has a potential of being an effective AED for treatment of neonatal seizures. We hypothesize that brivaracetam, at doses that suppress seizures, does not induce aberrant neuronal apoptosis in the grey and white matter of the developing rodent brain. We aim to provide the preclinical profile during brain development for this drug prior to its potential clinical use in neonates. Using the methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM) neonatal rat seizure model we will establish the dosing range for effective seizure control, then use that dosing range to determine the degree of neuronal apoptosis within the white and gray matter of the central nervous system in healthy rat pups.

Kendell R. German, MD - University of Washington



Title: *Urine Hepcidin as a Measure of Iron Regulation in Preterm Infants*

Mentor: Sandra (Sunny) Juul, MD, PhD

Personal Statement: I developed an interest in working with children with special developmental needs through my former position as a therapist for children with Autism, and my research with Dr. Elizabeth Rogers, at UCSF, examining neurodevelopmental outcomes of former preterm infants. This interest brought me to the University of Washington where I am pursuing fellowship training in Neonatology and clinical research training under the mentorship of Dr. Sandra Juul.

My current research focuses on iron sufficiency in neonates. Iron sufficiency is essential for neurodevelopment and despite national iron supplementation guidelines published by the AAP, premature infants remain at-risk for iron deficiency. With support from the Marshall Klaus Award, we aim to improve our understanding of iron regulation in neonates and in so doing guide optimal iron supplementation. I hope to improve the neurodevelopmental outcomes of neonates through translational research during my career in academic Neonatology.

Abstract: Iron sufficiency is critical for optimal neurodevelopment. Better understanding of the regulation of iron absorption in extremely low gestational age newborns (ELGANs) is needed to guide iron supplementation in order to optimize neurodevelopmental outcomes while limiting any risk for toxicity. In this analysis of urine samples from ELGAN's, we aim to investigate iron regulation in ELGAN infants by the peptide hepcidin, the prime regulator of iron absorption and availability in children and adults. To assess its role in iron regulation in the ELGAN population, we will correlate urine hepcidin concentrations with measures of iron status. We hypothesize that hepcidin concentration will reflect iron status, indicating the ability of ELGAN's to regulate their iron absorption. We anticipate this may provide a non-invasive biomarker of iron homeostasis. The association between hepcidin levels and pro-inflammatory complications of prematurity as well as erythropoietin will also be assessed given the influence of the inflammatory cascade and erythropoiesis on iron status.

Ellen Coley Ingolfsland, MD - University of Minnesota



Title: *Role of Anemia in Pathogenesis of Retinopathy of Prematurity: Evaluation of Mechanism through Multi-point Transcriptome Pathway Analysis in a Rat Model*

Mentor: Michael Georgieff, MD

Personal Statement: I am a neonatal-perinatal fellow at the University of Minnesota. I have a passion for research in retinopathy of prematurity (ROP), with the overall goal of improving understanding of this devastating disease in order to develop targeted preventative and therapeutic approaches. In the lab of my mentor, Dr. Michael Georgieff, I have collaborated with a multidisciplinary team to develop

this proposed project to investigate the impact of anemia on ROP and determine its molecular mechanism of action on a transcriptomic level. With a background in clinical research, I have previously developed approaches to investigate outcome-driven questions and explore causative factors of disease. My interest in the molecular mechanism of ROP and my desire to delineate causative clinical factors promoting this disease, however, led me to basic science research. The Marshall Klaus Neonatal-Perinatal Research Award will be instrumental in starting my career with a firm understanding of the molecular mechanisms of ROP, serving as the springboard towards my goal of becoming an independent physician-scientist in the field of ROP.

Abstract: The goals of my project are to investigate the independent role of anemia in the pathogenesis of retinopathy of prematurity (ROP) and identify the changes in transcriptome regulation underlying this pathologic process. ROP remains a devastating retinal disease of prematurity worldwide, whose prevalence in the United States is the same today as it was 30 years ago. This project, through the use of a unique preclinical model of anemia and RNA sequencing with pathway analysis, will address critical knowledge gaps which should allow for directed interventions in prevention and treatment of this disease, including management of anemia in preterm infants.

Viral Jain, MD - Cincinnati Children's Hospital



Title: *Role of Progesterone in Suppressing Fetal Membrane Inflammation*

Mentor: Louis Muglia, MD, PhD

Personal Statement: I am a first year neonatology fellow at Cincinnati Children's, and have research interest in genomics of preterm birth, newborn genital development and evidence-based medicine. I started my research career early in medical school in India to understand the role of endocrine disruptors in newborn genital development. During residency, I continued this work by serving as the Resident PI to investigate the role of steroid hormones in newborn

infants. I simultaneously worked on investigating the mechanism of fetal membrane rupture as a cause of preterm birth. To further advance my understanding of placental inflammation and preterm birth, I moved to Cincinnati to work under Dr. Louis Muglia. Using my background knowledge of studying steroid hormones, I want to study the role of progesterone and its analogues in suppressing inflammation in human fetal membranes. This project will lay a solid foundation for my future career as a physician-scientist.

Abstract: Intrauterine inflammation (IUI) is a leading cause of preterm birth (PTB). Progesterone is widely used to prevent PTB. Given the strong association between IUI and PTB, it is likely that progesterone exerts its protective effect, at least in part, through its anti-inflammatory action. However, the mechanism of action of progestogens in suppressing IUI and reducing resultant PTB remains a fundamental knowledge gap. We have identified a novel target IL-1 receptor-associated kinase 1 (IRAK1) that hold substantial promise in fetal membrane inflammation. Based on our preliminary data and current literature, we hypothesize that progesterone and its analogues suppress inflammation in human fetal membranes via inhibition of IRAK1. In

Aim 1, we plan to further improve our established ex-vivo human placental explant model to understand the role of IRAK1 in mediating human fetal membrane inflammation. While Aim 2 will test the hypothesis that progesterone prevents inflammation in fetal membrane via suppression of IRAK1. Progesterone, Medroxyprogesterone acetate and 17- α -OH-progesterone will be used to inactivate IRAK1 in the fetal membrane explants. Results of this study will provide critical information on the roles of IRAK1 in human fetal membrane inflammation and the role of progestogens in preventing PTB.

Carmen T. Monthe-Dreze, MD - Boston Children's Hospital



Title: *Maternal Obesity-associated Inflammation and Oxidative Stress: Impact on Offspring Neurodevelopmental Outcomes*

Mentor: Sarbattama (Rimi) Sen, MD

Personal Statement: I am a second year fellow in the Harvard Program in Neonatal-Perinatal Medicine. I aspire to be a neonatal physician-scientist with a focus on neurodevelopmental outcomes of children of obese mothers. Maternal obesity, which affects one in three women of childbearing age, is associated with profound impact on the child's health throughout the lifespan. Given that obesity is a growing public health issue with increasing incidence worldwide, an understanding of the relationship between maternal obesity and infants' health outcomes is becoming urgent. These infants are at higher risk than the general population for neurodevelopmental disability and delay, and based on animal data, exposure to chronic inflammation and oxidative stress during in utero development may play a key role in this association. My overall objective is to elucidate underlying mechanisms of the neurodevelopmental effects of maternal obesity on offspring, and to contribute to the development of the tools needed to assess neurodevelopmental outcomes (NDO) in infants born to obese mothers. My focus is on the impact of obesity-related inflammation and oxidative stress on offspring's NDO. My long-term goal is to devise and evaluate clinical interventions targeted at these mechanisms, in order to improve NDO. The receipt of this award would allow me to develop specific skills that will augment my expertise in the performance and interpretation of neuroelectrophysiological and neuropsychological assessments.

Abstract: Under the mentorship of Dr. Sarbattama Sen, my work under the Klaus Award will be truly translational, and will allow me to examine the associations between maternal markers of inflammation and oxidative stress during pregnancy and novel electrophysiological studies in a subset of infants born to participants in an ongoing randomized control trial, the "BMI-Based Prenatal Vitamins to Ameliorate Oxidative Stress in Obese Pregnancy." It is expected that this work will shed light on the mechanisms and impact of maternal obesity-associated inflammation and oxidative stress on infant development, and could offer evidence of atypical neural processes influenced by the maternal metabolic environment, before the emergence of overt developmental deficits.

Julie Margaret Noguee, MD - Washington University



Title: *Oligogenic Variants in Familial Atrioventricular Septal Defect*

Mentor: Patrick Jay, MD, PhD

Personal Statement: I am a second year Neonatal-Perinatal Medicine fellow at Washington University in St. Louis and St. Louis Children's Hospital. I have a background in basic science research in cardiovascular proteomics and neonatal brain injury. As a clinician, I have always had a special interest in children who have congenital diseases with genetic origins. Under the mentorship of Dr. Patrick Jay, I am currently exploring the

oligogenic nature of congenital heart disease. We hypothesize that a few genes may interact to result in the development of a heart defect, and use genetically engineered mouse models to explore these interactions. My current project involves using CRISPR-Cas9 mice to investigate oligogenic variants identified in a human family. I have a long-term goal of investigating the oligogenic interactions in the genome that may have both protective and deleterious effects on the development of birth defects. Ultimately, I hope that this work may provide a mechanism to pursue genome-based strategies for the prevention and treatment of severe congenital diseases, and provide a foundation for a career as an academic physician-scientist.

Abstract: Congenital heart disease is the most common birth defect, and at the current pace of discovery all the monogenic causes of congenital heart disease will soon be known. Monogenic etiologies, those that result from a single genetic insult, currently account for only one-third of congenital heart disease. Large studies consistently demonstrate that an increased familial risk for congenital heart disease does not fit a single genetic hit model, indicating more complex genetics may explain the remaining two-thirds. My proposal takes steps to bridge this gap. We performed whole-exome sequencing of members of a family in which two brothers have atrioventricular septal defects. No candidate variantbrittanys were identified that fit a Mendelian pattern of inheritance, but several rare, missense variants, predicted to be deleterious are present in cardiac developmental genes in the family. We hypothesize that a combination of the variants in these cardiac developmental genes may contribute to the development of atrioventricular septal defects in the family. Using CRISPR-Cas9 technology we have engineered several candidate variants into mice. We will first consider if any of the variants are causative of disease and investigate the individual variants in both the homozygous and heterozygous state. Our second aim involves looking at the variants in combination to test the hypothesis that a few deleterious variants in combination may contribute to the development of a heart defect. The goal is to offer the first, specific validation of the oligogenic basis of human congenital heart disease.

Laurie Gorham Sherlock, MD - University of Colorado



Title: *Impact of SOD3 on Neonatal Lung and Vascular Development*

Mentor: Eva Grayck, MD

Personal Statement: I am a second year NICU fellow with research interests in pulmonary developmental biology and the pathophysiology of bronchopulmonary dysplasia and pulmonary hypertension. I am studying the role of redox state and signaling within the developing lung. BPD and PH are diseases we see and treat daily at the bedside, but lack effective prevention or treatment strategies. My time in lab is fueled by this clinical link caring for sick infants and their parents. It is invigorating that through research, we can aim to improve patient outcomes by developing a deeper understanding of the mechanisms contributing to a clinical problem.

Abstract: My time thus far in the Grayck lab has been focused on understanding how extracellular superoxide dismutase (SOD3 or EC-SOD) regulates normal lung development and response to injury. SOD3 is the only known extracellular antioxidant defense for superoxide and is highly expressed in the lung and vascular extracellular space. Currently, we are investigating how the precise location of SOD3 can modulate or mitigate injury. We are using a novel knock-in model with a naturally occurring SOD3 SNP (the R213G SNP) that alters SOD3 tissue binding properties without changing enzyme activity. In humans and adult mice, the R213G SNP is associated with decreased risk of lung injury, but paradoxically an increased risk of cardiovascular disease and pulmonary hypertension. The R213G SNP provides an interesting dichotomy, as it appears that the site of active SOD3 due to its matrix binding affinity impacts disease outcomes depending on the site of oxidative stress, with bound SOD3 protecting against vascular disease and unbound SOD3 protecting against alveolar injury driving COPD. We are now studying this SNP in normal pulmonary developmental and with experimental neonatal lung injury. Our unique preliminary findings suggest that the R213G SNP leads to impaired vascular development under control conditions, but no worsening after bleomycin induced lung injury. Through this

project, I am furthering my understanding of where as well as how SOD3 is protective, with the goal of developing more specifically targeted antioxidant therapies for the prevention and treatment of BPD and PH.

Brittany Schwarz, MD - University Hospitals Rainbow Babies and Children's Hospital



Title: *Flash Cards in the NICU: A Novel Approach to Resident Education*

Mentor: Mary Elaine Patrinos, MD

Personal Statement: For as long as I can remember, I wanted to be a teacher. My interest in science led me to pursue a career in medicine, but I was concerned that I would be giving up my passion for teaching. I am very grateful to Dr. Kermis, my Pre-Med Advisor, who opened my eyes to the many teaching opportunities within the field of medicine and convinced me that my passion for teaching would only enhance

my career as a physician. After completing my pediatric residency at Rainbow Babies and Children's Hospital, part of my decision to stay at Rainbow for fellowship was a desire to improve the educational experience for other trainees. Ongoing restrictions to resident work hours along with fewer NICU rotations during residency limit the amount of time residents are involved in the care of high risk newborns. Innovative strategies that provide effective and efficient resident education are needed. My experiences in the NICU as a resident gave me great insight into how the Neonatology Division could improve resident education. My goals for this project are to improve the educational experience for residents and fellows in the NICU, and to gain experience in curriculum development and education research.

Abstract: The work pace and work flow of the NICU is highly efficient to address the needs of an often fragile patient population. It is within this environment that resident didactic education occurs, albeit with the competing demands of patient care, documentation, work hour restrictions, etc. This project will assess resident satisfaction of their educational experience before and after instituting short, daily learning sessions prior to bedside rounds. These sessions will be led by the on-service fellows and attending physicians. To assist the educators, I will create a set of Flash Cards to use as an educational tool. Subject matter will be derived from the current NICU curriculum, along with the newborn content specifications according to the American Board of Pediatrics. Each flash card will contain a sample patient case on one side with key teaching points and question prompts on the reverse side. We hypothesize that this project will improve resident satisfaction with their NICU rotation, as well as increase neonatology fellow and attending physician participation in education. Additionally, this project serves to meet The American College of Graduate Medical Education requirement that fellowship programs provide their trainees with opportunities to enhance their teaching skills.

The Section for Neonatal-Perinatal Medicine Research Committee:

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