



**Charles H. Hood Foundation Child Health Research Awards Program  
January 2018 Award Recipients**

• **Kira Bona, M.D., M.P.H.**

Instructor in Pediatrics, Harvard Medical School  
Department of Pediatric Oncology  
*Dana-Farber Cancer Institute*

“PediCARE: Feasibility of Novel Poverty-Targeted Intervention to Reduce Childhood Cancer Disparities”

Key Words: Pediatric Oncology, Disparities, Poverty, Household Material Hardship, Food Insecurity, Transportation Insecurity, Intervention

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Cancer remains the leading non-accidental cause of childhood death in the U.S., and novel efforts to address residual drivers of mortality in pediatric cancer are essential. One in five children with cancer lives in poverty; and poor children experience higher risks of relapse and decreased survival. Despite these disparities, poverty as a contributor to disease outcome has never been targeted in a systematic fashion in childhood cancer care. We hypothesize that interventions targeting remediable domains of poverty during cancer therapy will reduce disparities in childhood cancer relapse and survival.

Household material hardship (HMH)—a concrete measure of poverty defined as unmet basic needs including food, heat, housing or transportation—represents an ideal focus for poverty-targeted intervention. HMH is both associated with inferior child health outcomes and remediable with interventions. Prior work by our group has identified HMH in 30% of pediatric cancer families. Randomized trials in primary care have demonstrated that systematic screening for HMH and referral to existing resources (e.g. food stamps) both reduce HMH and improve health outcomes. We hypothesize that the time-sensitive and life-threatening nature of childhood cancer disparities require more immediately impactful HMH interventions that build upon systematic screening and referral.

We propose to refine and pilot the Pediatric Cancer Resource Equity (PediCARE) intervention, composed of scalable components targeting food and transportation insecurity including (1) provision of monthly grocery delivery in a dollar amount equal to the USDA thrifty-cost food plan (via AmazonFresh); (2) provision of weekly transportation from home to hospital/clinic (via Uber/Lyft). In Aim 1, we will pre-test and refine PediCARE based on qualitative family interviews. In Aim 2, we will pilot the refined intervention to assess preliminary change in family HMH. Data from this pilot will support a subsequent multi-center trial of PediCARE aimed at reducing disparities in childhood cancer relapse and survival.

- **Andrew Kodani, Ph.D.**

Instructor in Pediatrics

Department of Pediatrics

*Boston Children's Hospital*

“Zika Virus Alters Centrosome Architecture to Abrogate Developmental Signaling in the Brain”

Key Words: Zika, Innate Immunity, Brain Development, Centrosome

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Zika virus (ZIKV) is an arbovirus transmitted by mosquitos and causes neurodevelopmental disorders such as microcephaly in infants. Recent pandemic infections in South and Central America have led to increased cases of microcephaly, a developmental disorder that disrupts brain size, causing cognitive and motor defects. Studies have revealed that ZIKV specifically infects neural stem cells to abrogate neurogenesis in humans and mice. However, the mechanism by which ZIKV disrupts neurogenesis remains unclear.

We have found that ZIKV disrupts centrosome organization, a phenotype associated with inherited forms of microcephaly (MCPH). ZIKV infection causes the formation of aberrant Centrin foci that accumulate the MCPH-associated protein CEP63 and its interacting partner MIB1. The K63-ubiquitin ligase, MIB1 activates the NOTCH signaling and innate immunity pathways that regulate neurodevelopment. As misactivation of either signaling pathway can disrupt neurogenesis, we propose that ZIKV-induced centrosomal disorganization misactivates MIB1 causing aberrant NOTCH signaling and innate immunity preventing timely neuronal differentiation and cortical expansion.

To determine how ZIKV associated centrosome disorganization causes microcephaly, we will investigate how ZIKV disrupts NOTCH signaling, how MIB1 is activated upon ZIKV infection, and how ZIKV activates the innate immunity pathway to alter developmental signaling required for brain development. These studies will provide functional insight into the pathogenesis of ZIKV-associated microcephaly and shed light on the contribution of centrosomes during neurogenesis.

- **Richard Pierce, M.D., M.S.**

Instructor of Pediatrics

Department of Pediatrics

*Yale University*

“Assessment and Mechanisms of Blood Vessel Dysfunction in Critically Ill Children”

Key Words: Capillary Leak, Endothelial Dysfunction, Single Cell RNA Sequencing, Translational Research

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The objectives of this proposal are to develop better assessments and understanding of blood vessel function in critically ill children. Blood vessels are continuously lined by endothelial cells that regulate intravascular volume and nutrient exchange to organs. Most important is the capillary blood vessel segment, due to its large cumulative surface area. In critical illness, the capillary barrier becomes disrupted and intravascular fluid leaks into the extravascular space, contributing to shock, organ dysfunction and if not addressed, death. Currently, there is no way to assess leak to help clinicians to identify patients at risk or to evaluate treatment regimens, complicating care in the sickest children. Furthermore, a better understanding of EC changes that induce capillary leak can aid in developing new therapies. To improve the care of critically ill children, I aim to develop a bedside assessment of capillary leak using retinal fluorescein angiography and analyze the EC transcriptome by single cell RNAseq of ECs isolated from discarded guide wires removed from critically ill compared to non-critically ill children and normal surgical specimens to identify significantly different gene products that can be evaluated for causality by electrical cell-substrate impedance sensing in an established in vitro model of human capillary barrier function. My research will take place in my laboratory within the Yale Vascular Biology and Therapeutics Program and in conjunction with my position at Yale-New Haven Children's Hospital. This environment features researchers and mentors in pediatric critical care medicine and in vascular biology and immunology. Yale's infrastructure and supportive environment can facilitate the successful completion of this project. Through this proposal, I hope to make discoveries that will immediately direct treatment decisions in critically ill children and ultimately discover new therapies for vascular leak.

- **Aaron Remenschneider, M.D., M.P.H.**  
Assistant Professor of Otolaryngology  
*University of Massachusetts Medical School*  
Investigator, Department of Otolaryngology  
*Massachusetts Eye and Ear Infirmary*

“Advancing Pediatric Tympanoplasty with 3-Dimensionally Printed Eardrums”

Key Words: Eardrum, Tympanoplasty, Chronic otitis media, Hearing loss, Mechanics of hearing

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Perforations of the eardrum occur as a result of chronic ear infections, trauma or blast injury and annually affect millions of pediatric and adult patients worldwide. Patients suffer from ear pain, hearing loss, speech and language delay as well as decreased quality of life. The repair of the eardrum (tympanoplasty) is a common surgical procedure that typically utilizes harvested (autologous) tissue from the patient to heal the perforation; however, graft failure and persistent conductive hearing loss are frequent surgical outcomes, especially in children. Systematic reviews find failure rates using autologous grafts in 15–20% in children. Given limitations of current graft materials there is a need to modify tympanoplasty grafts to improve post-operative TM perforation closure and hearing outcomes. Advances in the field of 3D printing may provide solutions to persistent healing and hearing challenges in tympanoplasty. Specifically, advanced 3D printing techniques now permit creation of bioabsorbable grafts to recapitulate a ‘biomimetic’ eardrum. We hypothesize that 3D printed grafts will 1) integrate with the remnant TM to consistently close chronic perforations, and 2) establish ‘biomimetic’ architecture that transmits sound energy similar to the normal eardrum.

The aims of this study are to: 1) determine efficacy of 3D printed grafts to heal chronic TM perforations and 2) determine bioacoustics properties of 3D printed TM in vivo. An assessment of perforation closure using a chronic TM perforation animal model will describe the efficacy of 3D printed grafts in TM repair. The primary outcomes of AIM 1 are the rate of perforation closure and histologically assessed graft integration. While perforation closure is critical, restoration of conductive hearing is of equal importance. Experiments in AIM 2 measure hearing following tympanoplasty with 3D printed graft materials. The primary outcomes of AIM 2 are auditory brainstem response, and acousto-mechanical measurements of reconstructed TMs.

- **Sichen Shao, Ph.D.**

Assistant Professor

Department of Cell Biology

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“Activation of Nonsense-mediated Decay in Genetic Diseases and Childhood Development”

Key Words: Gene regulation, Gene expression, Premature termination codon, Genetic diseases, Development, mRNA degradation

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Mutations that introduce a premature termination codon (PTC) into protein-coding transcripts cause over 10% of congenital diseases. Nonsense-mediated decay (NMD) is a dedicated cellular pathway that degrades these mRNAs to prevent the production of toxic truncated proteins. NMD also regulates the expression of normal transcripts during numerous physiological processes including blood, muscle, and neuronal cell differentiation. The importance of NMD in childhood health is underscored not only by the prevalence of PTCs in genetic diseases, but also by NMD misregulation in various cancers and neurodevelopmental disorders. Modulating NMD activity is an attractive target for treating these diseases. However, rational design of such therapeutics is limited by the lack of molecular understanding of NMD mechanisms.

NMD initiates when ribosomes synthesizing new proteins encounter a PTC. How NMD selectively activates at PTCs while avoiding normal termination codons remains a fundamental question. We hypothesize that differences in the affinities and conformations of specific interactions made by ribosomes terminating in various contexts directly alter translation termination and NMD activation efficiencies.

To test this, we will biochemically reconstitute NMD activation in a cell-free system for mechanistic and structural dissection. I previously reconstituted and captured structural snapshots of the normal translation termination pathway using electron cryomicroscopy (cryo-EM). We will build onto this experimental system to quantitatively assay NMD activation (Aim 1), reconstitute PTC recognition (Aim 2), and determine cryo-EM structures of functional intermediates of NMD activation (Aim 3). This will allow us to systematically break down this complex biological pathway into individual steps to uncover molecular insights that are intractable in the complex environments of cultured cells and model organisms. In the long term, these studies will pave the way towards developing precise tools to investigate and manipulate this complex physiologic process in vivo in order to identify new therapeutics to regulate NMD.