Charles H. Hood Foundation Child Health Research Awards Program
July 2017 Award Recipients

- **Todd Anthony, Ph.D.**
  Assistant Professor of Psychiatry and Neurology
  Boston Children's Hospital

"Neural Circuit-Level Mechanisms that Control Persistent Consequences of Early Life Stress"

Key Words: Adverse childhood experiences, ACE, Vasopressin, CRH, CRF, CRFR2, AVP, Lateral septum, Medial amygdala, Bed nucleus of the stria terminalis, Imaging, Calcium. Photometry

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Adverse childhood experiences such as neglect and emotional or physical abuse are associated with significantly increased risk of multiple health issues later in life, including depression, drug addiction, and antisocial behavior. The higher incidence of such disorders in individuals subjected to stress during early life (SEL) is thought to involve stress-induced functional changes that persist into adulthood in neural pathways that control reward, social behaviors, and responses to threat. However, the identities of the neuronal populations affected and manner in which they are chronically perturbed by SEL to increase morbidity of mental illness remain largely undefined. The lateral septum (LS) is a subcortical structure known to exhibit behaviorally relevant neurochemical abnormalities following SEL, but is a large, understudied, and poorly understood region comprised of numerous distinct cell types distributed across multiple connectionally and functionally discrete subdomains. This project's broad, long-term objectives are to identify the specific LS neural circuits that control the persistent behavioral consequences of SEL, and determine how stress-induced changes in neural activity and gene expression patterns in these circuits mediate particular affective, social, and/or motivational components of SEL-induced phenotypes.

In this proposal, we plan to test a working model for how interactions between a critical stress circuit within and key neuromodulatory inputs to the LS regulate social and defensive behaviors, and how SEL-induced perturbations of these interactions might lead to elevated anxiety and passive coping responses to threat, and to decreased sociability. To achieve these objectives, we will employ techniques for in vivo imaging of neural activity with high temporal resolution from molecularly defined neuronal populations and long-range projections in freely behaving mice in order to define the neural circuit-level mechanisms by which SEL produces persistent changes in mood and social behaviors.

- **Mehdi Hedjazi Moghari, Ph.D.**
  Assistant Professor in Pediatrics
  Boston Children's Hospital

"Improved 3D Cine Cardiovascular Magnetic Resonance Imaging for Children"

Key Words: Congenital heart disease, Cardiovascular magnetic resonance imaging, Respiratory motion, Compressed sensing, Hemodynamics.

Congenital heart disease affects approximately 1.2% of children and is the leading cause of birth defect-related deaths. Single ventricle heart disease is a severe form of congenital heart disease, with high morbidity and mortality. These patients require multiple palliative surgeries, culminating with a total cavopulmonary anastomosis (Fontan operation). Despite considerable improvements in the survival of patients with single ventricle heart disease, there is an increasing morbidity and mortality over time. It remains unclear why some single ventricle heart disease patients fail their surgical repairs while others remain relatively well. Clinicians often rely on 2-dimensional images acquired from echocardiograms, catheterizations, or cardiovascular magnetic resonance imaging exams to assess single ventricle heart disease patients. The 2-dimensional images often lead to a suboptimal understanding of the complex 3-dimensional spatial relationships and hemodynamics, and limit efficient decision making. Moreover, catheterization is invasive and associated with x-ray radiation exposure. Lengthy cardiovascular magnetic resonance imaging exams in young children require anesthesia which is associated with neurological development impairments.

To address these deficiencies, we will develop a 3-dimensional cine cardiovascular magnetic resonance imaging technique that reduces examination time to <20 minutes compared with the 60-90 minute conventional exams, and, consequently, reduces the risk associated with general anesthesia. It will also enable the noninvasive measurement of other imaging biomarkers, such as pressure differences in the heart and great vessels, which will improve the risk assessment of patients at high risk of heart failure after the Fontan procedure.

- **Danielle Levac, P.T., Ph.D.**
  Assistant Professor of Physical Therapy, Movement and Rehabilitation Sciences
  Northeastern University

"From Virtual Reality to Real Life Skill: Enhancing the potential of Virtual Environments for Rehabilitation in children with Cerebral Palsy"

Key Words: Cerebral Palsy, Virtual reality, Active video games, Motor learning, Transfer, Rehabilitation, Physical Therapy

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Cerebral palsy (CP), the most common cause of pediatric disability, limits functional independence and requires long-term participation in rehabilitation. Therapists require interventions that engage children in the repetitive practice required to learn new motor skills and that promote transfer of learning from therapy to real-life contexts. Children with CP demonstrate slow, error-prone learning. As such, therapists use motion-controlled virtual reality games because their engaging, feedback-rich virtual environments may motivate children to practice frequently. Practice in a virtual environment can improve motor skills to a greater extent than a comparable amount of conventional practice. Yet a major limitation preventing optimal benefit from this approach is the lack of evidence for transfer of performance improvements to the real world. Identifying the mechanisms underlying transfer from virtual environments to real-life skills is therefore critical.

We hypothesize that transfer from virtual environments is enhanced when therapeutic practice conditions are task-specific, i.e., similar to performance conditions in real life. We will compare how children with CP learn the same new task in 3 environments with differing task-specificity: a physical environment, a two-dimensional (2D; flat screen display) virtual environment, and a 3D virtual environment (head mounted display). We will measure how their movements change as they acquire the skill, because we hypothesize that the amount of movement variability during learning differs in each environment, and that environments eliciting more functional variability enhance transfer. We will then measure how well children's learning transfers from each environment to a new, unpracticed real-life task. This research is significant because it will provide proof of principle for modifiable mechanistic targets to enhance how established (2D) and emerging (3D) virtual environments improve functional outcomes for children with CP. This will inform a long-term research program to develop and test task-specific virtual environments designed to enhance functional variability and promote real-life skill.

- **Carrie Lucas, Ph.D.**
  Assistant Professor of Immunobiology
  Yale School of Medicine

"Mechanisms of Disease in Pediatric Lymphocyte Disorders Caused by PI3K Gene Mutations"

Key Words: Pediatric, Phosphoinositide 3-kinase (PI3K), Genomics, Immunodeficiency, Lymphopenia, Lymphoproliferation, Homeostasis

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Primary immunodeficiency diseases (PIDs) affect approximately 10 million people worldwide and most commonly present in childhood as severe susceptibility to infections. The broad objective of this study is to expand on our discoveries of phosphoinositide 3-kinase (PI3K) gene mutations in pediatric immunodeficiencies to better understand the mechanistic basis of disease. We and others have described a novel PID caused by heterozygous, gain-of-function mutations in either the catalytic (*PIK3CD*) or the regulatory (*PIK3R1*) subunit of the leukocyte-restricted PI3Kδ complex. This disorder has been called PASLI disease (for PI3Kδ-Activating mutation causing Senescent T cells, Lymphadenopathy, and Immunodeficiency), or Activated PI3Kδ Syndrome (APDS) for short. These mostly pediatric patients exhibit recurrent sinopulmonary infections, susceptibility to herpesviruses and lymphoma, as well as lymphadenopathy/splenomegaly. We will pursue two specific aims to achieve our broad objective.

In Aim 1, we will study the mechanistic basis of CD4 T cell lymphopenia in APDS patients by examining patient samples to investigate readouts of T cell development/production, responses to growth cytokines, as well as cell death. Since CD4 T cells are "helper cells" that orchestrate the adaptive immune response, a clearer understanding of CD4 T cell pathology in this disorder could elucidate the defects in other lymphocyte subsets (namely, CD8 T cells and B cells).

In Aim 2, we will further investigate the role for PI3K and related genes in pediatric immune disorders by performing whole-exome sequencing and genomic analysis of undiagnosed PID patients. We have succeeded in identifying novel PI3K gene defects in a proof-of-concept study and aim to expand this approach and couple with rigorous mechanistic studies. These efforts will provide fundamental insights that inform precision therapies targeting PI3K or related pathways that may be applied not only to these rare disorders but also more broadly in common childhood diseases of immunity or autoimmunity.

- **Andrea Reboldi, Ph.D.**
  Assistant Professor of Pathology
  University of Massachusetts Medical School

"Microbial and Dietary Reprogramming of Intestinal Immune Memory"

Key Words: Memory B Cells, Intestinal Commensals, Oral Vaccines, Diet

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Enteric pathogens cause millions of cases of hospitalizations and deaths among children, especially in low-income countries, but effective vaccines are not available.

Memory B cells are essential for an effective vaccine: their ability to quickly give rise to antibody-producing cells upon re-exposure assure long-term protection of the host. However, the study of intestinal memory B cells has been difficult due to the chronic stimulation on the immune system driven by the diverse members of the intestinal microbiome. Cellular and molecular requirements for intestinal memory B cell generation and maintenance have not yet been elucidated.

We recently established a platform to generate and track memory B cell specific for commensal bacteria in vivo. In Aim 1 we propose to elucidate how commensal bacteria generate intestinal memory B cells at a single cell level. Understanding at high molecular resolution how the mucosal immune system gives rise to an efficient protection against bacteria present in the intestine will help shed a light on the mechanism behind the generation, or lack thereof, of memory B cells upon oral vaccination.

The intestinal immune system not only integrates signals from immune cells and commensal bacteria, but it also responds to absorbed dietary nutrients: we recently showed that oxidized forms of cholesterol control several aspects of the immune response. Intestinal memory B cells specifically express a receptor that recognizes cholesterol-derived lipids: in Aim 2 we will characterize how dietary cholesterol shapes intestinal memory B cell generation and maintenance.

The long-term goal of this work is to facilitate the development of strategy to reprogram intestinal memory B cells response against enteric pathogen by targeting intestinal microbiome and selected metabolic pathways.