Charles H. Hood Foundation
Child Health Research Awards Program
July 2015 Award Recipients

- **Sudha Arunachalam, Ph.D.**
  Assistant Professor
  Department of Speech, Language and Hearing Sciences
  Boston University

  "Improving Child-Caregiver Interactions for Young Children with Autism"

  Key Words: Autism Spectrum Disorder, Language Learning

The goal of this project is to improve the language skills of young children with autism spectrum disorder by helping their caregivers speak to them in a way that increases their comprehension and their learning. Caregivers play a critical role in interventions for preschoolers with autism, but currently little is known about how caregivers should speak to children to best support their language development. The current project aims to increase our understanding of what features of caregiver speech children with autism understand best in order to inform such interventions.

We use an innovative new experimental paradigm in which the caregiver and child play a game together on a tablet. We use an eye-tracker to measure the child's eye gaze as he or she listens to the caregiver's speech. This paradigm allows us, for the first time, to see how children with autism understand their own caregiver's speech in real-time. We use the results of this investigation to determine positive features of the caregiver's speech, and to help caregivers use more of these positive features when speaking to their child.

- **Marcelo Dietrich, M.D.**
  Assistant Professor
  Department of Comparative Medicine and Neurobiology
  Yale School of Medicine

"Hypothalamic Circuits Underlying Brain Development during Childhood"

Key Words: Hypothalamus, energy balance, brain development, behavior, AGRP neurons, mouse models

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Development of the nervous system is critical for a healthy life and proper insertion of the individual in society. Many disorders, including metabolic (e.g., obesity) and neuropsychiatric (e.g., depression, autism) diseases appear to have neurodevelopmental components involved in their etiology. The mechanisms that impact brain development during childhood are unknown and discoveries in the field have the potential to change our view on these medical conditions. We hypothesize that brain development is determined by the metabolic state of the animals.

Based on our previous findings, we postulate that during childhood, hunger-promoting hypothalamic neurons (named Agrp) that integrate information about the metabolic state of the animal control the development and maturation of other brain regions. To test these assumptions, we will investigate the following aims: (1) Test whether manipulation of Agrp neuronal activity during "childhood" influences brain development and behavior; (2) determine the role of the mediators of Agrp neuronal function, GABA, Agrp and NPY, on brain development outcomes. Here, we will use mice as a model organism to test these aims. The development and elucidation of the above aims will shed new light on the role of energy balance regulating hypothalamic circuits on brain development and behavior.

This is a new and innovative line of research that we have pioneered and will open a new dimension to the understanding of brain development in response to environmental changes. These basic experimental studies have the potential to guide the development of new therapeutic approaches to diseases that result of a previously unappreciated change in brain development during childhood.

- **Hiroyuki Inuzuka, Ph.D.**
  Assistant Professor of Pathology, Harvard Medical School
  Beth Israel Deaconess Medical Center

"Targeting Fbw7 for the Treatment of Pediatric T-cell Acute Lymphoblastic Leukemia (T-ALL)"

Key Words: T-cell Acute Lymphoblastic Leukemia (T-ALL), Fbw7, Tumor Suppressor, Acetylation, Ubiquitination, Mediator Complex (MED)

The long-term goals of this research proposal are to uncover the molecular mechanisms by which the SCF(Fbw7) E3 ubiquitin ligase complex is implicated in pathogenesis of the most common pediatric cancer, T-cell acute lymphoblastic leukemia (T-ALL) and to develop a new therapeutic intervention for this disease. Critically important to the translational impact of our proposed studies, tumor suppressor Fbw7 is deleted or mutated with high frequency in human T-ALL, approximately 30% of T-ALL patients. Fbw7 is a substrate recognition subunit of SCF(Fbw7) E3 ubiquitin ligase complex that is involved in numerous cellular processes by promoting the degradation of critical oncogenic proteins.

Our group has made significant contributions to the understanding of the critical role of Fbw7 in T-ALL development and progression by defining Mcl-1 as a downstream substrate of Fbw7. Although deficient Fbw7 function has been implicated in T-ALL, the exact molecular mechanisms underlying the anti-cancer activity of Fbw7 and upstream signaling pathways that control Fbw7 stability and activity have not been fully elucidated. Therefore, in this proposal, we plan to 1) Examine the regulation of Fbw7 function by reversible acetylation during T-ALL development: 2) Investigate the molecular mechanisms by which Fbw7 regulates the stability of components of the Mediator complex to influence T-ALL development. The major goal of this proposal is to explore how Fbw7 signaling pathway is regulated by acetylation-dependent mechanisms (Aim 1), how Fbw7 exerts its anti-cancer functions through regulating downstream pathways including the Mediator complex protein MED15 (Aim 2). Results derived from Aim 1 and 2 will provide the rational for the utilization of deacetylase inhibitors to promote stabilization of Fbw7 in T-ALL cells, or the utilization of TGF beta specific inhibitors in T-ALL that carry mutated or deleted Fbw7, which would overexpress MED15 due to loss of Fbw7 activity, leading to increased TGF beta signaling activity.

- **Kristin Moffitt, M.D.**
  Assistant Professor of Pediatrics, Harvard Medical School
  Division of Infectious Diseases
  Boston Children's Hospital

"Host and Bacterial Factors in Staphylococcus aureus Skin Infections in Autosomal dDminant-Hyper IgE Syndrome"

Key Words: Staphylococcus aureus, STAT3, hyper IgE Syndrome, Job's syndrome, IL-17A, TH17 cells, staphylococcal skin infection

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Staphylococcus aureus is one of the most frequent causes of bacterial infection in children and lack of understanding of critical protective immune responses hinders staphylococcal vaccine development. Patients with autosomal dominant Hyper IgE Syndrome (AD-HIES), also known as Job's syndrome, suffer recurrent S. aureus skin and soft tissue infections (SSSTI). The genetic basis of this primary immunodeficiency includes mutations within stat3, the gene encoding Signal Transducer and Activator of Transcription 3 (STAT3). Differentiation of TH17 cells is STAT3-dependent, and affected patients lack TH17 cells. AD-HIES patients also have defective memory antibody responses. The relative contribution of TH17 cells and memory antibody responses to immunity to SSSTI remains unclear. Furthermore, the interplay between defective STAT3-dependent adaptive immune responses and bacterial virulence factors that facilitate SSSTI in AD-HIES is not well defined.

Using a mouse model of AD-HIES, we will evaluate both host and bacterial gene expression during SSSTI. Using RNA extracted from staphylococcal abscesses in WT and AD-HIES mice, we will evaluate the transcriptome of the host immune response during SSSTI to better elucidate the effector immune responses that are defective in AD-HIES animals during infection. We will also use mice with the same stat3 mutation isolated to either the B-cell or T-cell lineage to evaluate the respective roles of humoral and cellular adaptive immune responses in SSSTI. Also from abscess RNA, we will evaluate the staphylococcal transcriptome to identify bacterial factors that are differentially expressed under varying host immune pressures. Identification of staphylococcal genes whose expression is significantly increased during infection in AD-HIES mice compared to WT mice may inform a deeper understanding of staphylococcal factors that are critical to establish infection. Finally, comparison of the staphylococcal expression profiles in this work with those from abscesses of healthy pediatric patients will inform efforts in staphylococcal vaccine development.

- **Benjamin Shore, M.D., M.P.H.**
  Assistant Professor of Orthopaedic Surgery, Harvard Medical School
  Department of Orthopaedic Surgery
  Boston Children's Hospital

"Responsiveness of the Pediatric Evaluation of Disability Inventory Computer Adaptive Test in Children with Cerebral Palsy"

Key Words: Cerebral palsy, PEDI-CAT, Computer adaptive testing

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Cerebral palsy (CP) is the most common cause of chronic childhood disability in the United States. The Pediatric Evaluation Disability Inventory- Computer Adaptive Test (PEDI-CAT) is a new clinical assessment for children and youth (0-20 years) with functional disability, including those with limitations in mobility requiring walking aids or wheelchairs. The PEDI-CAT using a computer adaptive platform, exhibits a simple form of artificial intelligence, which selects questions that are directly tailored to an individual, thus shortening the test to achieve desired precision.

This prospective study will focus on children with CP undergoing orthopedic and neurosurgical surgery. We will compare the responsiveness of the PEDI-CAT to standard legacy outcome measures. Specifically we will estimate the minimal detectable change (MDC) and identify what the minimum clinically important difference (MCID) is for each domain of the PEDI-CAT. Finally we will identify which children according to the Gross Motor Function Classification Level (GMFCS) experience the greatest benefit in functional mobility from orthopedic/neurosurgical surgery.

The "holy-grail" of outcomes-based research in CP is to develop a common comprehensive functional outcome instrument that is quick to administer, precise, and user friendly with the potential to enable clinicians to serially monitor the impact of medical, surgical and rehabilitation interventions over a range of cognitive and functional disability level. The validation of the responsiveness of the PEDI-CAT has the opportunity to change the way we measure and interpret functional changes after orthopedic surgery in children with CP.