Advancing Child Health through Translational Research Funded Projects

The Harvard Catalyst Child Health Initiative sponsored this Pilot Grant opportunity in order to generate new insights about conditions and diseases affecting children and their long-term consequences for adult health.

This 2012 RFA sought innovative applications that addressed one or more of three main themes:

1. Innovative Technologies to Advance Child Health

2. Health Systems and the Community

3. Life-course, Development, and Transitions

This funding opportunity was open to any faculty member holding a Harvard University faculty appointment. A collaborative team was required and inter-disciplinary and inter-institutional collaborations were encouraged. Seven Pilot Grants were awarded in amounts of up to $50,000 for each one-year project.

Funding decisions for the Child Health Pilot Grants were announced in early April 2012.

For more information about these awards, see the following news article.

Transcription Profiles of Severe Pediatric and Persistent Adult Asthma Phenotypes

Principal Investigator: Joel Hirschhorn, MD, PhD, Boston Children's Hospital

Co-Investigators: David Kantor, MD, PhD, Boston Children's Hospital
                      Benjamin Raby, MD, MPH, Brigham and Women's Hospital

Asthma originates from a combination of genetic and environmental interactions that occur in early childhood. Among children with asthma, some will undergo remission by adolescence, others will have a remitting and relapsing course into adulthood, while still others will have lifelong, active symptoms and progressive loss of lung function. These variable temporal phenotypes likely result from different underlying pathogenic mechanisms. Longitudinal studies have identified risk factors such as early allergen sensitization, age of onset, and disease severity that predict persistent asthma. However, the genetic and genomic factors that distinguish the child who will enter remission from the one who will have disease that persists into adulthood are entirely unknown.

Building on our experience with gene expression profiling, we will adopt a two-tiered approach to examine the genomic distinctions between remitting and persistent asthma phenotypes. In the first tier, we will investigate the gene expression profiles of young adult subjects followed in the Childhood Asthma Management Program (CAMP), now an observational study of mild to moderate asthmatics. The temporal patterns of asthma symptoms in this cohort have been followed for as long as 10 years, allowing comparisons of transcriptional signatures between well characterized subjects who have either remitting and persistent phenotypes. In the second tier, we will compare gene expression profiles, at the time of asthma exacerbation, between cohorts of pediatric asthmatics that are predicted to develop either remitting or persistent phenotypes.

Cardiac Remodeling in Adolescents with Metabolic Syndrome Using Cardiac MRI

Principal Investigator: Michael Jerosch, PhD, Brigham and Women's Hospital

Co-Investigators: Oscar Benavidez, MD, Massachusetts General Hospital
                      Paul Boepple, MD, Massachusetts General Hospital
                      Alison Hoppin, MD, Massachusetts General Hospital
                      Raymond Kwong, MD, MPH, Brigham and Women's Hospital
                      Lynne Levitsky, MD, Massachusetts General Hospital
                      Ravi Shah, MD, Massachusetts General Hospital
                      Avram Traum, MD, Massachusetts General Hospital

Early identification of metabolic and structural changes in the adolescent heart before the onset of clinical cardiovascular disease in the obese adult is critical to understanding the pathophysiology of cardiac remodeling in the adolescent obese. We have developed techniques to assess tissue architecture (e.g., diffuse myocardial fibrosis) using cardiovascular magnetic resonance (CMR), and have validated these measures against histologic fibrosis in mouse models of cardiac disease, as well as in adults with diabetes and obesity. We plan to provide a full phenotype characterization of early myocardial remodeling in obese adolescents, including diastolic function, ventricular morphology, metabolism, and diffuse myocardial fibrosis in one CMR exam. We aim: (1) to identify/quantify diffuse fibrosis in adolescents with obesity, relative to normal-weight young adults free of cardiometabolic disease; (2) to study the mechanism of obesity cardiomyopathy in the young by clarifying the impact of myocardial lipid content and

peripheral endothelial function (by CMR) on fibrosis and diastolic dysfunction. We hypothesize that adolescents with obesity/metabolic syndrome will have more fibrosis, which will be associated with a higher myocardial lipid content, a stiffer peripheral vasculature, and ultimately with subclinical diastolic dysfunction identified by CMR. In addition, we will obtain serum biomarkers to establish the relationship between early remodeling by CMR and easily assessed (and widely portable) serum biomarkers of cardiac remodeling. Ultimately, this proposal will lead to an understanding of the cardiac implications of obesity in the young, and a collaborative research program to further investigate this important condition.

Novel Autoantigen Discovery with a Synthetic Human Peptidome in Juvenile Idiopathic Arthritis

Principal Investigator: Robert Plenge, MD, PhD, Brigham and Women's Hospital

Co-Investigators: Daniel Brown, MD, PhD, Harvard Medical School
                       Stephen Elledge, PhD, Harvard Medical School
                       Peter Nigrovic, MD, Brigham and Women's Hospital

Juvenile Idiopathic Arthritis (JIA) is a chronic autoimmune disease causing erosive joint damage in children. Autoantibodies present in JIA patients have the potential to be useful markers to aid in the diagnosis and treatment of this heterogeneous condition. Presently, the known autoantibodies observed in JIA patients were originally described in other adult autoimmune diseases, and have only limited clinical utility. Recent technological advances make possible the rapid detection of autoantibodies from patient serum by screening libraries of human proteins expressed in bacteriophage. While this technology has been employed successfully in many adult autoimmune diseases, it has yet to be applied to study pediatric autoimmunity. We propose to use a recently described innovative phage library expressing a synthetic representation of the entire human proteome to identify autoantibodies from our unique cohort of newly diagnosed JIA patients. This will allow the discovery and validation of novel JIA specific autoantibodies and their cognate autoantigens. Such antibodies could serve as useful candidate biomarkers for the management of JIA, and understanding of the autoantigens unique to JIA will permit future avenues of research into the pathogenesis ultimately resulting in novel therapeutic strategies.

Physiological Interventions and Biormrkers for Enhancing Neonatal Health

Principal Investigator: Vincent Smith, MD, MPH, Beth Israel Deaconess Medical Center

Co-Investigator: John Osborne, MS, Harvard Medical School

Objective: This research study aims to evaluate the effect of stochastic mechanosensory stimulation on Apnea of Prematurity (AOP) and identify candidate biomarkers to aid in prediction and prompt treatment of this condition.

Background: AOP involves a cessation of breathing that lasts for more than 20 seconds and may be accompanied by oxygen desaturation and/or a decrease in heart rate and is almost universal in infants with a birth weight of <1000g. Stochastic resonance is the introduction of noise into a system to alter the system's behavior. Prior research suggests that this technology has the potential of reducing the incidence of apnea in preterm neonates.

Methods: Eligible subjects will be inpatient preterm infants in the neonatal intensive care unit who have demonstrated AOP. The intervention in this study is the stochastic resonance stimulation via the apnea mattress. The study is designed as an experimental protocol, with the subjects serving as their own control, receiving alternating intervals of intervention and no intervention. During each study session, cardio-pulmonary, temperature, audiometry and photometry data will be collected using a novel data acquisition system. This custom-built system provides streamlined data acquisition by extracting data from the monitor used for clinical care already in the infant's room, eliminating the need of placing additional sensors on the infant. This system also allows the data from the different sources to be aggregated and time-synchronized. We expect to analyze a variety of data points and variables. Data will be analyzed using an intention-to-treat approach.

Innovative Clinical-community Partnerships to Reduce Disparities in Childhood Obesity: Exploring Positive Deviance and the Role of Neighborhood Context

Principal Investigator: Elsie Taveras, MD, MPH, Harvard Pilgrim Health Care/DPM

Co-Investigators: Roberta Goldman, PhD, Harvard School of Public Health
                     Richard Marshall, MD, Harvard Pilgrim Health Care
                     Steven Melly, MS, Harvard School of Public Health
                     Thomas Sequist, MD, MPH, Brigham and Women's Hospital
                     Mahnoosh Sharifi, MD, Boston Children's Hospital

While childhood obesity rates may have plateaued in some US population subgroups such as whites and those of higher socioeconomic status, overall rates remain stubbornly high and racial/ethnic and socioeconomic disparities appear to be widening. Our long-term goal is to develop unique, sustainable models of clinical and community partnerships to reduce disparities in childhood obesity. The proposed research is critical to this goal. We will work with 14 pediatric practices of Harvard Vanguard Medical Associates (HVMA), a large multi-site group practice in MA. Using residential addresses from the HVMA electronic health record, we will use novel geospatial methods to characterize the built and socio-environmental context of the communities in which children live. Next, using longitudinal data of over 100,000 children, we will examine the relationships between neighborhood socioeconomic characteristics, the built environment, and changes in child BMI. Finally, we will identify children who have reduced and / or maintained their BMI over a 2-year period and conduct focus groups with these "positive deviant" parents and children who have successfully changed their behaviors and have developed resilience in the context of adverse environments. We will leverage this information to ultimately inform the design of a scalable, obesity risk reduction program within HVMA that uses "guided health coaches" trained to use clinical, public health, population, and positive deviance data to best support families in achieving a healthy weight.

Shortening the Behavioral Diagnosis of Autism through Artificial Intelligence and Mobile Health Technology

Principal Investigator: Dennis Wall, PhD, Harvard Medical School

Co-Investigators: William Barbaresi, MD, Boston Children's Hospital
                     Elizabeth Harstad, MD, MPH, Boston Children's Hospital

Autism rates continue to rise with more and more children being referred for autism screening every day. Behavioral exams currently used for diagnosis tend to be long and the diagnosis

process as a whole is cumbersome for families. In addition, clinical professionals capable of administering the exams tend to be too few and well above capacity. The average time between initial evaluation and diagnosis for a child living in a large metropolitan area is greater than one year and approaches 5 years for families living in more remote areas. The delay in diagnosis is not only frustrating for families, but prevents many children from receiving medical attention until they are beyond developmental time periods when targeted behavioral therapy would have had maximal impact.

To combat this significant public health challenge, the goal of this research plan is to develop algorithms and associated deployment mechanisms to diagnose autism rapidly and with accuracy equal to or greater than the best approaches in use today. The intent is to build machine learning algorithms that will work within a mobile architecture, combining a small set of questions and a short home video of the subject, to enable rapid online assessments. We anticipate this technology to reduce the time for autism diagnosis by nearly 95%, from hours to minutes, to be easily integrated into routine child screening practices, and to enable a dramatic increase in reach to the population at risk. To test these potentials we will validate the system at the Developmental Medicine Center through a collaboration with co-investigators Barbaresi and Harstad on a minimum of 200 children who will also undergo a standard clinical workup. The research will provide critical information needed to secure further funding of multi-site testing and development.

Diabetes Social Networking for Safe Healthcare Transitions into College

Principal Investigator: Elissa Weitzman, MSc, ScD, Boston Children's Hospital

Co-Investigators: Kenneth Mandl, MD, MPH, Boston Children's Hospital
                    Karen Olson, PhD, Boston Children's Hospital
                    Howard Wolpert, MBBCh, Joslin Diabetes Center

Our goal is to improve the health of adolescents with diabetes who are leaving home for college and undertaking social, educational and healthcare transitions. These transitions will have enormous and long lasting impacts on the lives of chronically ill youth in the US, underscoring the importance of understanding them. Currently, no system exists to support chronically ill adolescents in staying connected to their pediatric specialty care team when they leave home for college. Moreover, information is lacking about risk and protective factors that support stable engagement of this group with their health, disease management and healthcare over transitions. We test a model for supporting youth with diabetes who are making the transition to college. We will engage a cohort of 60 adolescents with type 1 diabetes in using a novel social networking software application that supports bidirectional communication with their specialty care team, peer-based communication, online group discussion and social networking. We will evaluate uptake and use of the application over the first college semester. We hypothesize that use of the application will positively impact cohort retention, engagement and health during a vulnerable period when loss to follow-up and non-adherence are common, considering also the influence of prospectively measured levels of psychosocial well-being and health on outcomes. Results will support improved transition preparation and targeted psycho-educational interventions for transitioning youth, and provide preliminary data for ongoing cohort investigation of chronically ill youth making major transitions and rigorous trial evaluation of the social networking support model.