Congratulations to the 2019 SPIRiT Awardees

The SPIRiT (Sharing Partnership for Innovative Research in Translation) consortium is a partnership between Clinical and Translational Science Award (CTSA) sites including: Johns Hopkins University, University of Chicago, University of Pennsylvania, University of Pittsburgh, Washington University in St. Louis, and Yale University. SPIRiT awardees must submit projects where they collaborate with an investigator from a participating CTSA institution. The program awarded four projects in 2019, two of which had investigators from Washington University.

Longitudinal Lysosome and Complement Expression in Bacterial Sepsis Outcomes

Lead PI: Charles S. Dela Cruz, MD, PhD (Yale University)
PI: Hrishikesh Kulkarni, MD, MSCI (Washington University)

Abstract:
Sepsis is a complex clinical syndrome with high mortality; however, the pathophysiology of sepsis remains incompletely understood. Understanding the mechanisms driving the pathophysiology of sepsis is likely to yield better biomarkers and newer therapeutic targets. Here, we investigate two evolutionarily conserved pathways (lysosomal pathway and the complement system) which are interrelated and ordinarily protect the host from infection, but in the setting of a dysregulated inflammatory response (sepsis), may contribute to worse outcomes. Our hypothesis is that non-survivors of sepsis have increased complement activation and an upregulation of certain lysosomal pathways which results in uncontrolled inflammation, multorgan dysfunction and death. This proposal focuses on establishing a collaboration between Yale and Washington University to understand how a dysregulated immune response affects the clinical course of sepsis by: (1) validating if lysosomal gene expression pathways associate with mortality, and (2) evaluating whether locally active complement in the lung associates with worse outcomes.

This project is funded in part by WU Institute of Clinical and Translational Sciences.

ENGAGE: Promoting Participation for People with Stroke-Related Disability and Low Income

Lead PI: Elizabeth R. Skidmore, PhD, OTR/L (University of Pittsburgh)
PI: M. Carolyn Baum, PhD, OTR/L (Washington University)

Abstract:
Advancements in medical management have transitioned stroke from an acute condition with a high prevalence of mortality to a chronic condition with high prevalence of morbidity. This morbidity is manifested in low levels of participation in education; paid and volunteer work; civic, social, and religious activities; and leisure. These low levels of community participation contribute to significant health declines and secondary stroke. These consequences are even more prevalent among people with low income. Our new collaboration combines expertise among investigators at Washington University, the University of Pittsburgh, and community partners at each site to examine the feasibility, safety, and acceptability of a community-based intervention to promote self-management and community participation after stroke, with a particular focus on the needs of people with low income. We will also characterize variance in intervention response. These findings will provide the last remaining pilot data needed to inform a multi-site randomized controlled clinical trial.

This project is funded in part by WU Institute of Clinical and Translational Sciences.
Implementation of HPV Vaccine for Mid-Adult Women

*Lead PI:* Sangini Sheth, MD, MPH (Yale University)
*PI:* Jenell Coleman, MD, MPH (Johns Hopkins University)

**Abstract:**
In 2012, there were 249,512 U.S. women with cervical cancer and 4,092 deaths. Human papillomavirus (HPV), the most common sexually transmitted infection, causes 91% of cervical cancers. For over 10 years, we have had the opportunity to prevent oncogenic HPV infection with a safe and highly effective vaccine. However, uptake in the U.S. is poor: only 43% of adolescents are fully immunized. Even among poor women or racial/ethnic minorities, who have disproportionately high rates of cervical cancer, immunization rates are low. In 2018, the FDA expanded the approved age range for a 9-valent HPV vaccine to mid-adult women (27-45 years old). Novel strategies for catch-up immunization are critical to protect adults against HPV. The objective of this pilot study is to identify facilitators and barriers to vaccination and characterize the immune response among mid-adult women. Data will inform a larger implementation science proposal to increase vaccination using a multi-level intervention.

Microbime and Cerebral Cavernous Malformation

*Lead PI:* Assam Iwad, MD (University of Chicago)
*PI:* Mark Kahn, MD (University of Pennsylvania)

**Abstract:**
Cerebral cavernous malformation (CCM) is characterized by formation of dilated microvessels, primarily in the brain. Despite identifying three CCM causing genes, gene mutations cannot completely explain the variation of clinical course in CCM patients. We found that gut microbiome, specifically Gram-negative bacteria, and its product, lipopolysaccharide (LPS) impact CCM disease in mice. Furthermore, polymorphisms of the LPS receptors TLR4 and CD14 associate with different CCM lesion load in patients. These data suggest that the microbiome may participate in CCM disease. Our preliminary human microbiome study supports this hypothesis. We now aim to test this hypothesis by 1) determining microbiome compositions in CCM patient groups with different clinical parameters, 2) analyzing functional differences of microbiota associated with CCM patient groups. The proposed studies will help us to determine if the microbiome could be used as a biomarker for CCM disease severity, and identify causative pathogenic microbiome that influences CCM disease course/severity.