Clinical & Translational Science Institute

PRIME

Cohort 2

DIRECTED BY

Tuhina Neogi, MD, PhD   **Richard Wainford, PhD**

Michael Alosco, Ph.D. – Description of Research

Repetitive head impacts (RHI) are associated with the neurodegenerative disease, chronic traumatic encephalopathy (CTE). According to research diagnostic criteria for CTE, known as Traumatic Encephalopathy Syndrome (TES), CTE presents with behavior, mood, and/or cognitive symptoms. There is diversity in the presence of symptoms due to differences in pathology and brain regions affected, and mechanisms of the later-life clinical deficits from RHI are ill-defined. As a result, long-term neurological diseases from RHI (e.g., CTE) cannot be detected at this time. White matter signal abnormalities (WMSA) are non-specific magnetic resonance imaging (MRI) markers of pathologies that may be associated with RHI and affect the clinical presentation of CTE. WMSA predict increased risk for Alzheimer's disease (AD) and pathological correlates of WMSA are common in CTE. Our published data linked T1 WMSA with RHI and executive deficits in former National Football League (NFL) players, independent of vascular status. However, multi-modal neuroimaging studies with control and comparison (e.g., AD) groups are needed to clarify the presence, nature, and effects of WMSA in former NFL players. This K23 will use fluid attenuated inversion recovery (FLAIR) and diffusion MRI to examine WMSA as a long-term consequence of RHI that are distinct from AD and affect later-life clinical function. A team of transdisciplinary scientists from Boston University (BU) will address Dr. Alosco's knowledge gaps in areas key for the study of CTE (exposure science, neuroimaging, neuropathology), leading to an R01 to launch his own research program. The K23 will include 30 male symptomatic former NFL players (45-74 years), 30 same-age and vascular risk-matched male normal controls (NC), and 30 same-age and vascular-risk matched males with AD. NC and AD subjects will be without head trauma history. Former NFL players and NC will be from Dr. Stern's (primary mentor) NINDS U01 examining CTE biomarkers. AD subjects will be from the BU AD and CTE Center (ADCTEC) Registry. The ADCTEC outreach core will ensure inclusion of young AD males (45-55 years). All subjects complete medical, cognitive, behavior/mood, neuroimaging evaluations (T1, FLAIR, diffusion, PET), and lumbar puncture, and blood draw. FreeSurfer and Tracts Constrained by UnderLying Anatomy will assess lobar volumes and fiber paths. WMSA will be estimated via a Bayesian probability structure. We will test if former NFL players have a distinct pattern of lobar and fiber path WMSA relative to NC and AD, and if regional WMSA predict cognitive, behavior, and mood function. We will examine whether RHI predicts WMSA and fiber path dysintegrity. In the former NFL players, we will test whether WMSA correspond to lobar volume loss and fiber path dysintegrity, and explore if WMSA are related to fluid and PET markers of tau. Millions of Americans are exposed to RHI and this study will have a major public health impact by improving knowledge on the neurological sequelae of RHI, which is imperative to facilitate research on the diagnosis, treatment, and prevention of brain diseases, like CTE.

Stacy Andersen, Ph.D.- Description of Research

The goal of the proposed project is to investigate the association of digitally captured neuropsychological test performance with traditional test measures, dementia status, and neuroimaging markers in a healthy aging cohort to establish digital metrics as a sensitive measure of cognitive change in individuals with and without dementia leading to earlier detection and therefore earlier treatment of underlying brain pathology

Louis Awad, PT, Ph.D. – Description of Research

Stroke survivors often regain the ability to walk; however, compared to healthy individuals, it takes longer to travel a particular distance and requires more than double the energy. Importantly, reduced speed and poor walking economy are independent predictors of walking-related disability and future mobility decline. The slow and metabolically-expensive gait of individuals poststroke is the result of inadequate compensations for the weakness and impaired control of the paretic muscles. Interventions that facilitate walking recovery via paretic limb functional restoration, and not compensation, are desperately needed to improve long-term outcomes. An impaired ability to generate propulsion via the paretic limb (paretic propulsion) is a major contributor to walking dysfunction. This project aims to develop wearable sensor technology that is able to accurately estimate propulsion in clinic and home environments. Measuring propulsion is important for the translation of interventions targeting this salient gait parameter. Indeed, for his doctoral studies, Dr. Awad demonstrated that a hypothesis-driven, propulsion-targeting, intervention (FastFES) centered on electrically-stimulated activation of the ankle muscles during fast locomotor training was exceptionally effective at improving walking function in a particular subset identified based on measurements of propulsion. Unfortunately, the tools required to evaluate propulsion (i.e., instrumented treadmills and force plates) are not accessible to most clinicians. This is a major barrier to the translation of the FastFES training program and other therapies targeting this key gait parameter, like the exosuit technology developed and tested by Dr. Awad at the Wyss Institute at Harvard University to help individuals with stroke walk faster and with less effort. Informed by our preliminary work, the goal of this project is thus to identify clinically-accessible measures of paretic propulsion that can serve as prognostic indicators of a therapeutic response to FastFES targeted training and for use in controllers for exosuits and other wearable systems. Informed by a retrospective analysis of an existing dataset and laboratory-based motion capture, this effort will be centered on using low-cost, bodyworn sensors to measure the most salient aspects of propulsion. Ultimately, this project will enable identification of homogenous subgroups of individuals poststroke who respond similarly to targeted interventions, and thus more informed delivery of targeted therapies in future clinical trials.

Sabrina Assoumou, M.D., MPH – Description of Research

Recent human immunodeficiency virus (HIV) and hepatitis C virus (HCV) outbreaks around the United States (U.S.) illustrate that these infections should be addressed simultaneously to improve outcomes. In the U.S. most of the new HCV infections are among young people who inject drugs (PWIDs). Studies at detoxification centers have shown that linkage to care is problematic. Social services support such as case management has the potential to improve linkage to care; however, little is known about its potential influence on the care of young PWIDs. We will use in-depth, qualitative interviews to identify facilitators and barriers to linkage and retention in HIV, HCV and substance use care among young PWIDs. These data will inform the adaptation of strengths-based case management (SBCM), an evidence-based linkage to care intervention, to address the specific needs of youth with a history of injection drug use.

Tehnaz Boyle, M.D., Ph.D. – Description of Research

Dr. Boyle's research focuses on testing patient-centered interventions that will improve outcomes of critically ill and injured children requiring emergency care. This proposal focuses on telemedicine as a novel intervention to improve prehospital treatment of children with acute respiratory emergencies and facilitate transitions of care to emergency departments in urban environments.

Dr. Boyle's career development plan includes: systematic education and mentoring related to clinical trial design and analysis; the use of simulation as a research tool for pilot trials of intervention efficacy; and training in the ethics of emergency care research, including emergency exceptions to informed consent and protection of children as human subjects. Her training plan includes a combination of formal coursework and workshops, scientific seminars and meetings, and a focused research ethics internship. These will be paired with mentored research studies where she will test the central hypothesis that prehospital telemedicine improves the quality of care delivered by paramedics in pediatric emergencies by enhancing medical direction. Dr. Boyle has partnered with Boston Emergency Medical Services, the largest urban advanced life support provider for the City of Boston, to perform pilot trials to test this intervention in simulated and real pediatric respiratory emergencies.

Sanjib Chowdhury, Ph.D., MS – Description of Research

Brief summary of research projects A. Cohesin biology My primary research interest is to study the role of cohesins in colorectal cancer. In our recent report published in Neoplasia 2018 (role: co-corresponding author), we used patient samples to identify loss of cohesin stromal antigen 1 (SA-1) in colorectal cancer. Next, we used bioinformatics and SNP arrays to identify potential causal SNPs that are associated with SA-1 loss and risk of colorectal cancer. Using CRISPR/Cas9 gene editing, we performed knock-in to alter the SNPs of interest and identified the mechanisms of SA-1 loss through microRNA association and mRNA degradation. Currently, we are studying in-depth the biology of SA-1 that includes chemoresistance, metabolic alterations, stemness and interaction with PD-L1 through nutrient competition. B. CDK5 biology and targeting I have been actively interested in cyclin dependent kinase 5 (CDK5), an atypical CDK and recently co-authored an original research article in Oncotarget 2018 where we generated CDK5/CDK2 inhibitors and tested them in animal models. Currently, in collaboration with a medicinal chemist from the University of Nebraska Medical Center, I am studying the biology of CDK5 and using PROTAC strategy (an area of active interest within NIH to target undruggable targets) to generate CDK5 degraders. C. Akt2/ MTSS1 biology We have reported the role of Akt2 and metastasis suppressor 1 (MTSS1) in colorectal cancer metastasis in Oncogene 2017 (role: corresponding author). Currently, we are studying the mechanisms associated with MTSS1 loss downstream of Akt2 activation in colorectal cancer using cell culture, two animal models (MTSS1 KO mice and APC del14 mice) and human patient samples. D. Exercise myokines and cancer We have developed an in vitro cell culture platform for exercise using mouse muscle cells and have generated copious amounts of preliminary data indicating strong anti-cancer and anti-NAFLD effects of myokines. Currently, we are working to identify individual myokines that could be leveraged for therapy either as single agent or in combination with chemotherapeutic agents. Another area of emerging interest is using exercise myokine for treatment of cancer cachexia.

Gemme Fix, Ph.D.- Research Description

As a leader in healthcare, the Department of Veteran Affairs (VA) is transforming to a patient-centered model where care is personalized, proactive and patient-driven; health and wellbeing are situated within patients' context; patients are at the center of care. Complex patients, such as those with HIV, may benefit in particular from a transformation to patient-centered, contextually sensitive model of care. HIV has been transformed into a chronic condition. Veterans with HIV are living longer. Consequently, comorbidities are often of greater importance to their overall health than HIV status alone and a major concern of providers. Further complicating disease management, patients with HIV have less education, high unemployment, and are more likely to live in poverty or experience homelessness. Yet, HIV providers may not be attuned to patient contexts and, as specialists, may not be comfortable managing other comorbidities. Patient-centered management of HIV requires patient-provider communication that entails providers asking about patient context, engaging them about daily activities, priorities, and then tailoring recommendations accordingly.

OBJECTIVES: 1) Understand how Veterans with HIV engage in health behaviors in the context of their daily lives. 2) Explore how HIV providers consider the role of patient context and comorbidities when providing care. 3) Examine communication between HIV providers and their aging patients to understand how they attend to context and comorbidities.

Cassidy Gutner, Ph.D. – Description of Research

Cassidy A. Gutner, Ph.D, is an Assistant Professor of Psychiatry at Boston University School of Medicine and a researcher at the National Center for Posttraumatic Stress Disorder (PTSD) at VA Boston Healthcare System. Dr. Gutner received her PhD in clinical psychology from Boston University. She completed her clinical internship at the University of California, San Diego/VA San Diego Healthcare System and an NIMH T32 postdoctoral fellowship at Boston University School of Medicine and the National Center for PTSD. Dr. Gutner has a National Institute of Mental Health K23 award that utilizes a hybrid effectiveness/pre-implementation design to examine the Unified Protocol for the Transdiagnostic Treatments of Emotional Disorders within routine care with trauma exposed Veterans. More broadly, her research focuses on bridging the gap between research and practice by identifying effective treatments that meet the needs and fit the context of the practice setting, as well as testing the best methods for effective implementation in trauma exposed populations. She recently began working with collaborators in Bogota, Colombia on implementing evidence-based treatments for victims of the Colombian Conflict.

My program of research has included translational research from basic science to implementation of treatment in routine care. I am a clinical psychologist and implementation scientist with expertise and research experience in cognitive behavioral therapy (CBT), randomized controlled trial methodology, augmentation of CBT through cognitive enhancers, effectiveness trials, and implementation science. My current NIMH K23 Award focuses on how treatment protocols address comorbidity, how these symptoms impact psychosocial treatments, and whether a transdiagnostic treatment could address an unmet need of patients in routine care.

More broadly, my program of research is routed in implementation science and aims to study the effectiveness and implementation of evidence based psychosocial treatments in routine care, primarily with trauma-exposed populations presenting to routine care. My work aims to bridge the gap between research and practice by identifying effective treatments that meet the needs and fit the context of the practice settings and testing the best methods for effective implementation in trauma exposed populations.

Shakun Karki, Ph.D. – Description of Research

Obesity is associated with ectopic fat accumulation, lipotoxicity, adipose tissue dysfunction, and inflammation that have been implicated in mechanisms of insulin resistance and endothelial dysfunction, which drive cardiovascular disease, however pathological mechanisms are incompletely understood. The endothelium plays a critical role in vascular homeostasis and many of its functions are governed by the basal and stimulated release of anti-atherogenic endothelium-derived nitric oxide (NO) that maintains arterial tone, inhibits inflammation, promotes fibrinolysis, and modulates reparative angiogenesis. Thus, signaling pathways that regulate endothelial function are pivotal for atherosclerosis initiation and progression. Animal and clinical studies show that insulin resistance not only perturbs pathways in organs such as liver, fat, and muscle, but also negatively influences the vasculature. Insulin regulates blood flow through activation of endothelial NO synthase (eNOS) by binding to its IRS-1-linked receptor with subsequent phosphorylation and activation of eNOS via PI3-K/Akt. Defective insulin signaling promotes vascular inflammation, vasoconstriction, plaque progression and ischemia, and endothelium-specific deletion of the insulin receptor in animals causes atherosclerosis. The current proposal focuses on the role of FSP27 in the regulation of vascular biology.

FSP27 is a lipid droplet associated protein that regulates lipolysis in adipocytes. Experimental models show that FSP27 deletion augments basal lipolysis and leads to insulin-resistance under high-fat diet conditions. Human genetic FSP27 mutations are associated with lipodystrophy, hypertriglyceridemia, and insulin-resistance. While metabolic regulation of FSP27 has been essentially characterized exclusively in adipocytes, my preliminary data shows, to my knowledge for the first time, that it is highly expressed in vascular endothelial cells and is down regulated particularly in association with visceral/central obesity. Perturbations in FSP27 may promote conditions that elevate free fatty acids (FFA), which have been implicated in insulin resistance and endothelial dysfunction. However, lipid storage/breakdown is generally not viewed as a primary function of vascular endothelial cells, thus FSP27 may govern cell autonomous functions by yet undiscovered mechanisms beyond regulation of lipid metabolism, for which I have pilot data and will investigate further in this proposal. My compelling preliminary data shows that FSP27 may serve as a previously unrecognized, but critical regulator of arteriolar vasodilation and angiogenesis, which are pivotal in mechanisms of atherosclerosis and ischemic cardiovascular disease. My proposal also touches upon the broad hypothesis that cardiovascular disease may be the consequence of adipose tissue dysfunction and pro-atherogenic mediators released from fat that promote pathogenic vascular changes that we can already detect in the adipose vasculature.

Moreover, at the local adipose tissue level, capillary rarefaction and impaired perfusion and angiogenesis have been linked to adipose tissue pseudohypoxia and metabolic dysregulation.

Clinical data from weight loss studies demonstrate that bariatric surgery is the most durable and effective method for sustained weight reduction. Despite much publicity about dietary weight reduction strategies, bariatric surgery has emerged as a most effective treatment for obesity and its cardiometabolic co-morbidities, as it improves cardiac risk factors, remits diabetes, and to date represents surprisingly the only clinical weight-loss intervention shown to improve long-term total and cardiovascular mortality. Mechanisms for risk reduction are unclear but point to reversal of insulin resistance and endothelial dysfunction as clinically important targets. Thus, unraveling molecular mechanisms that govern vascular function and the effects of weight loss are immensely important for moving the field forward.

In this proposal, I will utilize novel proteomics analyses to generate mechanistic frameworks that may lead to identification of new pathways in obesity-related vascular disease. Moreover, I will examine these relationships before and after bariatric surgical weight loss, where to my knowledge little information exists. While bariatric surgery saves lives, it is obviously not for everyone and only ≤1% of eligible individuals undergoes this procedure. However, by studying how the human vasculature favorably remodels following surgery, I will be well-positioned to gain crucial information, and potentially identify new signaling pathways and pharmacological targets that have the potential to have a significant impact on ~2 billion overweight/obese people worldwide at cardiovascular risk.

Michelle Long, MD. – Description of Research

Michelle T. Long, MD, is a faculty member of the Boston Medical Center, Division of Gastroenterology and an Assistant Professor at the Boston University (BU) School of Medicine. Dr. Long has a background in epidemiology, patient-oriented research, gastroenterology, and hepatology. Her research has focused on non-alcoholic fatty liver disease (NAFLD) as measured by computed tomography scan in the Framingham Heart Study (FHS). In her prior work, she has evaluated the association between NAFLD and physical activity and NAFLD and sub-clinical measures of cardiovascular disease (CVD) in the FHS cohort. Her work in these areas has resulted in 4 first author publications including the development and validation of a simple clinical diagnostic score for hepatic steatosis called the Framingham Steatosis Index. In addition, her recent study utilizing blood-based non-invasive hepatic fibrosis markers in the FHS determined that the available fibrosis markers give widely disparate predictions of the risk for significant hepatic fibrosis when applied to this community-based cohort. NAFLD associated hepatic fibrosis is an important public health problem. More than 15 million Americans are estimated to suffer from hepatic fibrosis from NAFLD which worsens metabolic disease and increases the risk of liver- related and CVD-related death. Studies to date examining NAFLD in community-based cohorts in the United States have relied on imaging modalities that are insensitive to hepatic fibrosis. Dr. Long's proposal will focus on testing three hypotheses; 1) FHS participants with hepatic fibrosis, as measured by vibration-controlled transient elastography (VCTE), have a more adverse CVD risk factor profile compared to those with no fibrosis, 2) Genetic determinants for the risk of hepatic fibrosis are identifiable by genome wide association studies and 3) A diagnostic model based on clinical and genetic traits distinguishes NAFLD patients with and without fibrosis as defined by VCTE and the model performs well when applied to an external validation cohort. The study of the clinical and genetic traits associated with hepatic fibrosis in the community will lead to insights into disease mechanisms, biomarker development, and novel therapeutic targets, which has the potential to improve public health

outcomes. This study will be performed as an ancillary study of approximately 3,500 FHS Third Generation and OMNI 2 cohort participants who are undergoing evaluation for hepatic fibrosis using VCTE. Dr. Long's ultimate career goal is to use epidemiological insights for two purposes: a) identify potential novel drug targets; and b) develop tools to identify high risk NAFLD patients to prevent disease progression. To complete this proposal and progress towards these goals, Dr. Long has developed a five year mentored career development program that incorporates both didactic and formal research training guided by two well established investigators with expertise in clinical and translational research in CVD and NAFLD. She will receive formal didactic training in epidemiology, advanced biostatistics, predictive modeling, and implementation science through the BU School of Public Health. With this additional education and guidance, as well as the supportive environment provided by BU, Dr. Long will be well positioned to complete this proposal and develop

Yael Nillni, Ph.D. – Description of Research

My research program focuses on the intersection between psychopathology and women's health with the ultimate goal of improving intervention efforts for women. Specifically, I am interested in: 1) women's reproductive mental health - understanding psychological and neurobiological risk factors involved in the etiology and maintenance of psychological and physical health problems during hormonal transitions (e.g., anxiety and depression during the pregnancy and postpartum period, premenstrual dysphoric disorder), and 2) identifying sex-specific transdiagnostic vulnerability-stress pathways involved in the onset and maintenance of PTSD and comorbid disorders in women. I am a translational scientist and my research has been informed by my training and experience in both experimental psychopathology and treatment outcome research. Specifically, I seek to: a) understand mechanisms that contribute to psychopathology, particularly during times of hormonal flux, b) use this information to inform assessment and intervention efforts for women, and 3) implement these assessment and interventions within an existing medical care system. My research program uniquely incorporates a wide range of assessment strategies (e.g., daily diary and laboratory paradigms) and methods (e.g., psychophysiology and hormonal measures) to refine our understanding of complex processes and to better inform targeted intervention efforts.

Astha Singhal, BDS, MPH, Ph.D. – Description of Research

Sarah Valentine, Ph.D. – Description of Research

Sarah Valentine is an Assistant Professor in Psychiatry at BUSM and Psychologist at BMC. She received her PhD in Clinical Psychology from Suffolk University, and completed her predoctoral internship and postdoctoral research fellowship in the Department of Psychiatry at Massachusetts General Hospital/Harvard Medical School. Dr. Valentine's research focuses on the implementation of evidence-based treatments for posttraumatic stress disorder (PTSD) and co-occurring disorders among underserved populations, including racial and ethnic minorities, immigrants and refugees, sexual orientation and gender minority populations, and criminal justice involved youth. Her clinical research projects focus on reducing health disparities through the development, implementation, and dissemination of treatments that dually address minority stress factors (e.g., discrimination, stigma, and access barriers) and mental health symptoms. Dr. Valentine recently received an NIMH-funded K23 grant that aims to optimize a brief cognitive behavioral therapy for PTSD for use in primary care.

Duo Zhang, Ph.D.– Description of Research

Gram-negative (G-) bacteria frequently induce an overwhelming inflammatory responses in hosts. Despite years of research, the regulation of the inflammatory responses after G- bacterial-infection remains unclear, thus impeding the development of novel therapeutic/diagnostic strategies. Mammalian genomes encode thousands of long non-coding RNAs (lncRNAs). LncRNAs are extensively expressed in various immune cells including the monocytes, and macrophages. The lncRNAs have been reported to be involved in diverse biological processes, including the regulation of the expression of genes, the dosage compensation and genomics imprinting, but as yet very less research has been carried out to explore how they alter cell differentiation/function during host-pathogens interactions. We found that Lincenc1 is strikingly induced in the lungs obtained from the mice infected with G- bacteria or after exposure to LPS, an abundant glycolipid of the outer membrane of G- bacteria. Furthermore, our in vitro data suggest that Lincenc1 is induced in macrophages but not in other cells, such as the epithelial cells and neutrophils. Functionally, Lincenc1 promotes the classical activation of macrophages and the secretion of inflammatory cytokines. Here we propose that lncRNA Lincenc1 promotes G-bacteria/LPS induced lung inflammation via activating alveolar macrophages. To test this hypothesis, we propose the following two specific aims: Specific Aim I: To investigate the role of Lincenc1 in macrophage activation in vitro. Specific Aim 2: To investigate the role of Lincenc1 in lung inflammation in vivo. Successful completion of the proposed aims will uncover the role of Lincenc1 in G-bacterial infections. This study potentially will help to identify novel mechanisms and/or therapeutic strategies for lung inflammation and injury.