

**Prachi Bhuptani, Ph.D. - 2023 Awardee**

*Department of Adult Psychiatry  
Rhode Island Hospital*

“The Impact of Shame on Clinical Outcomes among Sexual Violence Survivors Who Use Opioids”

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Opioid use is a growing public health concern and has high morbidity and mortality. Sexual violence (SV) and opioid use co-occur at high rates. Among individuals who use opioids, SV is associated with a severe clinical course (e.g., increased opioid use). Despite clear clinical relevance of the role of SV in opioid use, no studies have explicated mechanisms that contribute to the worsening of outcomes among opioid users with a history of SV. Shame, a universal emotion with extensive roots in trauma and substance use, is pronounced among individuals who use opioids as well as those who have a history of SV. Shame is cyclical in nature and fluctuates daily in response to internal and environmental cues. However, no study has evaluated the role of shame in relation to proximal opioid outcomes (cravings, use, motivation for changing opioid use, self-efficacy for changing opioid use, engagement in opioid use treatment) for individuals who use opioids and have a history of SV. The specific aims are 1) Use community-based participatory research methods to deepen partnerships with stakeholders through capacity-building and knowledge sharing, 2) Gain an in-depth understanding of the experience and impact of shame among people who use opioids and have a history of SV (n=24) using semi-structured interviews, and 3) Develop, pilot, and refine a 30-day ecological momentary assessment (EMA) protocol (n=24) to assess EMA acceptability/feasibility for assessing shame and opioid use outcomes in this population. Successful completion of the research and training detailed in this proposal will prepare the PI to develop a research program focused on identifying mechanisms that impact clinical and treatment outcomes among individuals who use opioids and have a history of SV. Identifying event-level associations between shame and clinical opioid outcomes also represents the first step in the development of just-in-time interventions to improve such outcomes.

**Phillip Chan, MB.ChB., Ph.D** - 2023 Awardee

*Department of Neurology  
Yale University*

“Impact of Vascular Risk Factors on Synaptic Density in People Living with HIV on Stable Treatment”

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Despite advances in antiretroviral therapy (ART), people living with HIV (PLWH) on ART continue to suffer from the residual effects of the infection and persistent immune activation, resulting in a higher risk of developing non-communicable diseases as compared to HIV-uninfected populations. Specifically, HIV-associated neurocognitive disorder (HAND) remains prevalent in PLWH on ART, with 18-40% meeting HAND criteria. Understanding the underlying mechanisms of HAND persistence is crucial as cognitive function affects not only quality of life but also treatment adherence. Years of research suggest that PLWH on ART are at-risk for vascular brain injuries (VBI). First, they have higher rates of hypertension, diabetes mellitus and hyperlipidaemia due to HIV-related mechanisms, possible side-effects of ART and lifestyle tendencies, leading to VBI and cognitive impairment through macrovascular and small vessel diseases. Second, closer inspection of the residual effects of HIV infection, namely, persistent immune cell activation, increased microbial translocation in the gut and persistent low-level HIV protein transcription, reveals consistent associations with atherosclerosis and endothelial injury. This proposal aims to determine associations between vascular risk factors and vascular biomarkers on neurological integrity using novel [11C]UCB-J positron emission tomography (PET). In our pilot study, [11C]UCB-J PET identified reduced synaptic density (SD) in PLWH compared to uninfected populations as reported in pathological studies. Further, the SD measurement in [11C]UCB-J PET associated with cognitive performance in our study and studies focused on other neurodegenerative diseases. The novel investigation of vascular mechanism of synaptic injury in HIV in this proposal will offer new insights into HAND persistence in the ART era. The investigator is a neurologist by training and has completed a PhD focusing on the neurological presentation and longitudinal outcomes of acute HIV infection followed by immediate ART. His goal is to become an independent investigator studying the neurological and cognitive sequelae of HIV infection.

**Christina Cho, Ph.D.** - 2023 Awardee

*Department of Immunobiology  
Yale University*

“Investigation of cancer-associated fibroblast-derived factors in CD8+T cell exclusion and identification of novel predictive biomarkers for cancer immunotherapy in non-small cell lung cancer.”

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Non-small cell lung cancer (NSCLC) is the most fatal type of cancer in the world. Traditional chemotherapies and radiation therapy is not effective against NSCLC and patients who undergo curative surgery generally experience recurrence. Immune checkpoint inhibitors (ICIs) have dramatically altered the way we treat advanced NSCLC. Compared to traditional chemotherapies, ICIs significantly improve overall survival in advanced NSCLC patients. Unfortunately, only a minority of patients benefit from ICIs. Most patients are non-responders, and the molecular drivers of non-response are still unclear. The efficacy of ICIs depends on the availability of functional CD8+T cells (CTLs) in the tumor microenvironment (TME). Tumors that are non-responsive to ICIs are characterized by CTL exclusion, and the mechanisms underlying CTL exclusion are poorly defined. Cancer-associated fibroblasts (CAFs) are the predominant cell type in the solid tumor microenvironment (TME) and CAFs have been shown to promote the formation of CTL- exclusive TMEs. Unfortunately, attempts at targeting CAFs have largely failed in the clinic, indicating that depletion of CAFs is not a feasible treatment strategy. Instead, targeting CAF-derived molecules that drive CTL exclusion may be a more practical approach. Preliminary studies using digital spatial profiling have identified 441 differentially expressed genes (DEGs) in CAFs residing in CTL-exclusive tumors. This project aims to determine which of these DEGs inhibit CTL inclusion—either by (1) prohibiting T cell migration, or (2) inhibiting T cell activation and subsequent survival in the TME. By identifying these T cell inhibitory molecules, we will uncover novel targets for therapy. Furthermore, these molecules could be used as new predictive biomarkers for ICI-based immunotherapies. Ultimately, this study will improve our understanding of the molecular mechanisms underlying CTL exclusion—a major obstacle for ICI efficacy—and provide new biomarkers that will enhance our ability to identify patients who are likely to respond to ICI therapy.

**Katherine Cox-Flaherty, M.D. - 2023 Awardee**

*Division of Pulmonary and Critical Care, Department of Medicine  
Brown University*

**“Dehydroepiandrosterone, Sexual Dimorphism and Endothelial Cell Phenotypes in Pulmonary Arterial Hypertension”**

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Pulmonary arterial hypertension (PAH) is a fatal disease with a strong female predilection in which pulmonary artery endothelial cell (PAEC) dysfunction leads to increased vascular resistance and right heart failure. The median survival from diagnosis is six years and therapeutic options are limited. There is an urgent need to identify mechanistically distinct therapeutic options. Both chromosomal sex and sex hormones play an important role in PAH pathogenesis, but have not been well studied in human PAECs (HPAECs). The goal of this research is twofold: 1) to understand the mechanism by which the sex hormone dehydroepiandrosterone (DHEA) may be protective at the cellular level in HPAECs 2) to characterize clinical features of individuals who respond in vitro to help unravel clinical sexual dimorphism in PAH in a step towards precision-based therapy. To achieve these goals, we propose a translational study using a unique biorepository of HPAECs acquired from living patients with PAH. In Aim 1, we will assess whether exogenous exposure to DHEA impacts the in vitro phenotypic behavior of HPAECs derived from patients with PAH as compared to age and sex matched controls. In Aim 2, we will examine how DHEA alters intracellular signaling in response to inflammatory stimuli in PAH PAECs versus age and sex matched controls. In Aim 3, we will study changes in inflammatory pathways of diseased PAH PAECs before and after DHEA exposure. Throughout all aims, we will pay close attention to stratification by cellular sex and will examine clinical features of patients with differential responses to DHEA. We hypothesize that PAH HPAECs will disproportionately respond to DHEA based on sex. These studies will help clarify the role of sex and DHEA on PAEC function. This is an essential step to harness sex hormones as a therapeutic target in PAH and towards precision-based therapy in PAH.

**Katherine Darling, Ph.D.** - 2023 Awardee

*Weight Control & Diabetes Research Center; Department of Psychiatry and Human Behavior  
The Miriam Hospital*

“Improving Weight-Related Conversations in Adolescent Primary Care: Communication Enhancement Intervention for Pediatricians”

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Adolescent obesity is a significant public health concern associated with negative physical and psychosocial outcomes. Primary care pediatricians are instrumental in prevention and treatment of adolescent obesity. However, despite intentions of healthcare providers to provide high-quality care for patients, weight stigma and bias are widespread in healthcare settings. Adolescents’ experience of weight bias in the medical setting can impede healthy weight management, increase distress about body shape and weight, and perpetuate healthcare avoidance.

Weight bias from medical providers is especially detrimental during adolescence, given self-identity formation during this period and the long-term effects of weight stigma on youth. A shift in pediatricians’ training and intervention strategies is needed to overcome weight stigma experienced by adolescents with obesity during primary care visits, as well as to empower pediatricians to improve the health behaviors of the adolescents they treat.

The present study will address this gap by employing a patient-centered approach to improve weight-related conversations between adolescents and pediatricians. Specifically, a communication enhancement intervention for pediatricians will be developed to improve adolescent-pediatrician communication.

Phase 1 of the study will include qualitative data collection with adolescents (ages 13-17) with obesity, their caregivers, and pediatricians that treat adolescents in a primary care setting. This phase is designed to develop semi-structured prompts and brief weight bias training (5 session intervention) for pediatricians to use when addressing weight and weight-related behaviors with adolescents. Phase 2 will include pilot testing of this communication enhancement intervention with six pediatricians in a primary care clinic and measuring adolescent outcomes (n=10/provider; N=60 adolescents total). Results from this pilot trial are designed to provide initial effect size estimates for a fully powered trial to evaluate the impact of a weight-related communication enhancement intervention on adolescent health behaviors.

**Amy Hunter, Ph.D.** - 2023 Awardee

*Public Health Sciences*

*University of Connecticut Health Center*

“Improving Identification of Pediatric Patients at Risk of Child Physical Abuse”

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Child maltreatment is a significant public health problem associated with adverse health outcomes across the lifespan, including premature death. Early detection is imperative to protecting child health, however maltreatment is challenging to detect. Many victims experience multiple interactions with healthcare providers before their abuse is diagnosed. This is in-part attributed to provider bias, a known barrier to child maltreatment screening. Identifying these biases is a first step to developing methods to motivate uniform screening behaviors. Recent changes to the International Classification of Diseases, Clinical Modification classifications allows child maltreatment to be distinguished by level of certainty (confirmed or suspected) in addition to by maltreatment type (e.g., physical, sexual, emotional). Comparing the characteristics of confirmed and suspected maltreatment may reveal biased diagnostic behaviors at the patient, provider, and encounter levels that can be used to facilitate screening improvements. The objective of the proposed study is to identify biases in child physical abuse screenings among Connecticut children aged 0-10 years in the period 2017-2021. We will achieve the study objective using the following specific aims:

Aim 1. Build and tune a child physical abuse algorithm. We will develop an algorithm for predicting child physical abuse outcomes based on patient and provider information from previous encounters and identify important risk factors. Data will consist of electronic health records from pediatric patients treated in 8 hospital settings: Connecticut Children’s Medical Center and seven hospitals affiliated with Hartford HealthCare.

Aim 2. Apply and test the algorithm. We will test the predictive accuracy of the algorithm in visits coded for confirmed and suspected child physical abuse using independent samples.

Aim 3. Distinguish risk algorithm characteristics of child physical abuse by level of diagnostic certainty. Biases will be assessed by comparing patient, provider, and visit- level characteristics of healthcare encounters for confirmed and suspected child physical abuse.

**Jessica Stempel, M.D. - 2023 Awardee**

*Department of Internal Medicine, Division of Hematology/Oncology  
Yale-New Haven Hospital*

“Treatment patterns and outcomes of patients with acquired aplastic anemia in the United States”

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Acquired aplastic anemia (AA) is a bone marrow failure disorder characterized by increased risk of bleeding, infections, and death. The goal of treatment is to suppress the immune system with immunosuppressive therapy (IST) and stimulate stem-cell production with the addition of Eltrombopag (EPAG). Allogeneic stem cell transplant (HCT) is an option for patients  $\leq 40$  years and have a matched sibling donor. However, approximately 60% of patients rely on IST-based approaches or supportive care strategies for management.

EPAG was initially approved for second-line treatment of AA in the United States in 2014 and has influenced the treatment landscape. Institutional, personal, and financial limitations, as well as access to care, often dictate the implementation of EPAG and IST strategies and questions remain on how these factors impact the selection of front-line treatment regimens, and how to approach relapsed/refractory disease, duration of treatment and the risk for clonal evolution and development of myeloid neoplasms (MN).

To address these gaps in knowledge, we will leverage a large, population-based resource which captures the healthcare claims of nearly 1/3 of Americans, Blue Cross Blue Shield Axis, to examine treatment patterns and outcomes of adult patients with AA before and after the approval of EPAG from 2016 through 2022. Specifically, we will assess the utilization of HCT and IST agents as front-line therapy, as well as the use of supportive care measures and the temporal trend of EPAG use during the study period. In addition, we will evaluate the clinical outcomes of patients with AA including the incidence of infections and bleeding complications, development of MN, and hospitalization characteristics. Furthermore, we will identify patient- and system-level factors associated with inferior outcomes in this population. Findings from our study can help inform interventions to improve the clinical care and outcomes of AA patients, who are understudied and underserved.

**Stephanie Wemm, Ph.D.** - 2023 Awardee

*Department of Psychiatry  
Yale University*

“Investigating Real-world Stress-related Mechanisms In Heavy Cannabis Users”

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As recreational use of cannabis has become more widespread, the number of individuals who use cannabis daily has also grown. There has been a concomitant increase in the rates of Cannabis Use Disorder (CUD), yet the mechanisms that lead to the transition from light, recreational use to heavy cannabis use is not well-understood. Studies on other drugs of abuse have shown that chronic, heavy use of drugs and alcohol dysregulates stress and motivational pathways, yet this has remained unstudied in cannabis. Identifying stress-related targets that predict heavier cannabis use could provide targeted interventions that could divert the course of CUD.

We propose to use a novel, multi-domain approach to target real-world cannabis and motivational responses in non-treatment-seeking individuals who regularly use cannabis. We will examine if heavy, chronic use of cannabis alters an individual’s biological response to stressors and cannabis-related contexts in their day-to-day lives (Aim 1). We will investigate if heavy, chronic use of cannabis alters the subjective response to cannabis-related cues and real-world stressors (Aim 2). Finally, we will examine if sex is a predictor and moderator of the associations between craving, stress, and cannabis use (Exploratory Aim). We will recruit 60 individuals who use cannabis at least once weekly. Individuals will complete four weeks of surveys delivered via smartphones daily in the morning, evening, and at three random times during the day. In addition to these four weeks, participants will complete two 3-day intensive monitoring periods consisting of subjective (i.e., craving, negative affect), neuroendocrine (i.e., cortisol), and autonomic variables (i.e., heart rate variability [HRV], salivary alpha amylase). If successful, the findings from this project will have high clinical and societal impact by prospectively identifying adaptations in stress pathophysiology that result from heavy cannabis use as they naturally occur and provide key targets for a future intervention.



**Sanjay Aneja, M.D.** - 2022 Awardee  
William O. Seery Foundation  
*Department of Therapeutic Radiology*  
*Yale University*

“Deriving Imaging Based Biomarkers for Non-Small Lung Cancer Using Deep Learning”

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Despite recent therapeutic advances, non-small lung cancer (NSCLC) represents a significant public health concern with 5-year overall survival ranging from 50-60% for early stage disease and 15-20% for locally advanced disease respectively. The traditional methods for risk stratification have relied on the TNM staging system, but there exist wide variations in outcomes among patients with similar stages of disease. There is a need for tools which can individualize patient risk and guide personalized therapy. Although molecular and laboratory biomarkers display promise, they often require additional testing and specialized equipment which may not be scalable in all clinical settings. Quantitative imaging-based biomarkers represent a potential accurate low-cost alternative to traditional laboratory biomarkers. In this career enhancement program proposal, we aim to investigate the utility of imaging-based biomarkers for locally advanced NSCLC outcomes derived using deep-learning image analysis. Our laboratory is especially well suited for this study because we have previously developed a novel deep learning imaging platform which generates imaging-based cancer biomarkers using pre-treatment CT imaging and radiation dosimetry data. We propose to take advantage of this technology to investigate the following specific aims:

AIM 1: To investigate the efficacy of imaging-based biomarkers for locally advanced NSCLC, we will employ our deep learning platform to derive imaging-based biomarkers on an institutional dataset of 873 locally advanced NSCLC patients treated with definitive chemoradiation.

AIM 2: To examine the generalizability of imaging-based biomarkers across different NSCLC patients, we will validate our imaging-based biomarkers on a multi-institutional dataset of NSCLC patients from three other geographically distinct comprehensive cancer centers

Upon successful completion of this proposed grant, we will identify imaging-based biomarkers for locally advanced NSCLC and possess a diverse multi-institutional clinical and imaging linked dataset of approximately 817 early stage and 2,500 locally advanced NSCLC patients that can be used for further research.

**Robert Becher, M.D., M.S. - 2022 Awardee**

*Department of Surgery, Division of General Surgery, Trauma, and Surgical Critical Care  
Yale University*

“Improving Hospital-Level Mortality Performance for Major Surgery in Older Adults: A Mixed Methods Study”

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Major surgery is a common event in the lives of older Americans. The 5-year cumulative risk of major surgery is 14%, equal to 1 in 7 Medicare beneficiaries and representing nearly 5 million unique older persons. Major surgery occurs regularly in high-risk vulnerable subgroups such as the oldest-old ( $\geq 85$  years), those with frailty or dementia, and those undergoing non-elective surgery. Fully 40% of all major surgeries in older persons are unplanned operations.

As the geriatric population ( $\geq 65$  years) grows in size, the number of older persons who will require major surgical intervention will increase substantially. And yet, despite the importance of major surgery as a defining health issue for older Americans and despite decades of efforts to improve care for patients undergoing major surgery, we know little about what distinguishes poor-performing, high-mortality hospitals from exceptional-performing, low-mortality hospitals for geriatric surgery. This lack of evidence is a critical gap in our current knowledge.

We will employ a rigorous set of innovative quantitative and qualitative analyses assessing geriatric surgery at the hospital-level to: (1) define how mortality performance – as measured by standardized mortality ratio and cluster analysis – differs across hospitals in the United States; (2) compare how patient-, operation-, and hospital-level characteristics inform the differences in hospital mortality performance; and (3) develop the methods and processes for how to best make hospital site visits to assess hospital-specific efforts which may inform the differences in mortality performance.

By taking a mixed methods approach, this project will provide information that is essential to understanding geriatric surgical outcomes. Our long-term objective is to improve the quality and safety of major surgery for older persons, and the proposed project will lay the groundwork for future, larger-scale investigators to define, test, disseminate, and implement evidence-based efforts to improve outcomes for older persons having major surgery.

**Catherine Buck, M.D. - 2022 Awardee**

*Department of Pediatrics, Division of Neonatal Perinatal Medicine  
Yale University*

“Biomarkers of adiposity development in preterm infants of mothers with obesity and diabetes”

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The goal of this project is to understand how perinatal exposure to energy metabolism hormones influences early growth in preterm infants. Moderate preterm birth, between 32- and 36-weeks gestational age accounts for the majority of all preterm births, or 300,000 children born in the US each year. This group has 20% higher odds of obesity and cardiometabolic disease in adulthood compared with those born at term. Factors that may contribute to obesity risk in preterm infants include developmental re-programming due to perinatal exposure to maternal obesity and diabetes, conditions which are associated with metabolic disease in offspring. Other factors include exposure to energy metabolism hormones, such as leptin and adiponectin, which are associated with infant body composition and later cardiometabolic outcomes in children. The optimal pattern of fat development which is associated with outcomes in preterm infants is largely unknown. Developing preventative interventions to the reduce risk of adverse growth and cardiometabolic outcomes in preterm infants is not possible without first understanding the mechanism of how perinatal metabolic exposures contribute to the developmental re-programming of preterm infant growth and adiposity development.

To fill this critical gap, this project will advance foundational knowledge of the role of energy metabolism hormones in the programming of adiposity development in moderate preterm infants of mothers with diabetes and obesity. Aim 1 will examine patterns of leptin, adiponectin, and insulin concentrations and how they relate to fat development in the newborn period. Aim 2 will explore the influence of human milk bioactive substances on the relationship of obesity and diabetes in pregnancy with newborn adiposity in preterm infants. Completion of these aims will identify potential mechanisms of developmental re-programming of adiposity in moderate preterm infants and determine the feasibility of using metabolic hormone biomarkers as predictors of growth trajectory in the newborn period.

**Eileen Carter, Ph.D., R.N.** - 2022 Awardee

*School of Nursing  
University of Connecticut*

“Reported Penicillin Allergies in Children: Quantification of Impact and Promotion of Parent Involvement in Management Decisions”

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More than 5 million children have a reported allergy to penicillin, yet 95% of these children can safely take penicillin. Most reported penicillin allergies are diagnosed exclusively by parents without a medical evaluation. The impact of reported penicillin allergies in children is unknown and likely substantial. Indeed, adults with reported penicillin allergies receive less-effective, broad-spectrum antibiotics, resulting in increased healthcare utilization, costs, and antibiotic-resistant infections compared to adults without penicillin allergies. Penicillin allergy testing is recommended to safely identify patients with inaccurate reports of penicillin allergy. Yet, referral for penicillin allergy is rare and even after formal allergy testing results in the removal of inaccurate penicillin allergy labels from medical records, the re-reporting of these allergies by parents is common.

In the proposed study, “Reported Penicillin Allergies in Children: Quantification of Impact and Promotion of Parent Involvement in Management Decisions,” I will analyze 5-years of patient-level data from a comprehensive health information exchange and use logistic regression and Poisson regression to determine whether children with reported penicillin allergies have higher rates of broad-spectrum antibiotic use, healthcare utilization, and antibiotic resistant infections relative to children without a reported penicillin allergy. Then, using user-centered design principles, I will develop a theory-informed, interactive parent decision support tool i.e., Parent Engagement in the Management of reported Penicillin Allergies “PEM-PAL” in which I will target parents’ capability, opportunity, and motivation to engage in discussions with their child’s prescriber regarding penicillin allergy testing. The mentors guiding my career development are exceptional, consisting of researchers with expertise in health outcomes research (Dr. Aseltine) and patient-facing behavioral interventions (Dr. Pagoto). Results from this study will lay the foundation for my submission of a R01 efficacy trial to test the usability and feasibility of PEM-PAL.

**Patrick Cudahy, M.D. - 2022 Awardee**

*Department of Medicine, Section of Infectious Diseases  
Yale University*

“Host transcriptomic markers of TB treatment response and recurrence”

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Individuals with multidrug-resistant tuberculosis (MDR-TB) and HIV co-infection are at especially high risk of death during TB treatment. Approximately one in four people coinfecting with MDR-TB/HIV die during the first three months of therapy. We are currently recruiting participants from South Africa with MDR-TB and HIV to prospectively evaluate novel biomarkers to rapidly identify treatment failure. This proposal focuses on signatures of host RNA expression (transcriptome). We will also follow participants after treatment completion when they remain at elevated risk of recurrent TB from relapse or reinfection. We will utilize the same biomarkers to predict recurrent tuberculosis. Our group’s models show that targeting this group for screening could significantly decrease the community burden of tuberculosis.

Specific aim 1) To evaluate changes in host blood transcriptome of people living with HIV as biomarkers of

early MDR-TB treatment response

Specific Aim 2) To evaluate changes in the host blood transcriptome of people living with HIV who have

recently completed treatment for tuberculosis as biomarkers of recurrent tuberculosis.

We will utilize nested case-control studies to evaluate these aims within our larger prospective cohort study of people living with MDR-TB and HIV. The biomarkers identified in this project will lead to changes in treatment guidelines and interventions that 1) save lives, 2) prevent the selection of additional resistance, and 3) reduce tuberculosis transmission. They also have the advantages of not requiring sputum and are able to run on point-of-care platforms that are widely deployed in high tuberculosis prevalence settings, such as the Cepheid GeneXpert.

Better TB treatment monitoring tools will allow clinicians to triage the patients at highest risk of treatment failure and better allocate resources, especially in the resource-limited settings where TB is endemic.

**Marcello DiStasio, M.D., Ph.D. - 2022 Awardee**

*Pathology*  
*Yale University*

“Mechanisms of Proinflammatory Microglial Activation in Degenerative Diseases of the Central Nervous System”

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My goal is to perform research focused on the molecular mechanisms underlying dysregulation in immune interactions associated with neurodegenerative and neuropsychiatric disease. The current proposal, which is the first step towards this overall objective, concentrates on dysregulation in key immune checkpoints that regulate microglial activation, including TREM2-TYROBP-APOE signaling, and how this contributes to progression of neurodegeneration. Assaying transcriptional states in disease-associated microglia within lesions of the brain and retina at single cell resolution across multiple diseases including age-related macular degeneration, Alzheimer disease, and multiple sclerosis will provide a new paradigm to understand the role of the immune system in central nervous system degeneration and probe the largely unaddressed question of the role of microglia in AMD pathogenesis directly using human samples. It will also set the stage for further study of neuroinflammatory biology using AMD as a paradigm to discover principles with application to other degenerative diseases including dementia, demyelinating disease, and motor system degenerative diseases. I hypothesize that proinflammatory microglia contribute to neurodegeneration similarly across diseases. To test this, I will first perform massively parallel single-nucleus transcriptional profiling of brain and retinal microglia from individuals with varying stages of AMD, AD, and MS pathology and use new machine-learning algorithms for analysis of disease state progression at the single-cell level. I will then investigate how microglial states define interactions in the tissue microenvironment to contribute to neurodegenerative pathology by performing multiplexed in-situ RNA sequencing and multiplex immunofluorescence on brain and retinal tissue. Finally, I will use CRISPR-Cas9 knockout of key immune checkpoints in human retinal microglia to identify potential targets of novel therapeutics.

**Samir Gautam, M.D., Ph.D.** - 2022 Awardee

*Department of Internal Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine  
Yale University*

“Pathogenic Chi3L1/CRTH2 signaling in patients with neutrophilic asthma”

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Neutrophilic asthma is a subtype of disease associated with severe lung impairment and unresponsiveness to steroid therapy. Significant efforts have been made to develop treatments that target the underlying pathogenic neutrophil responses, but none have yet been approved. Our prior work in murine models of lung inflammation has shown that the immune protein, Chi3L1, elicits a dysfunctional neutrophil phenotype marked by defective apoptosis and excessive release of neutrophil extracellular traps (NETs). This neutrophil phenotype, referred to here as ‘proNET-antiApop’, is associated with exaggerated lung injury and mortality in mice. Our work has also implicated CRTH2 as the receptor for Chi3L1 on neutrophils. Here, we seek to assess whether this novel Chi3L1/CRTH2 neutrophil signaling axis plays a pathologic role in asthma. Consistent with this hypothesis, we have shown that Chi3L1 levels in sputum samples from asthmatic patients correlate closely with neutrophilic inflammation and disease severity. To clarify the mechanistic basis of these findings, we propose to test whether Chi3L1/CRTH2 signaling directly promotes pathologic NETosis and suppresses apoptosis in human samples. To this end, we will expose human neutrophils to Chi3L1 and measure its effects on apoptosis and NETosis using our established in vitro assays. We will elucidate the role of CRTH2 using small molecule CRTH2 antagonists. We will also evaluate the pathogenicity of Chi3L1/CRTH2 signaling in sputum samples from patients with neutrophilic asthma by assessing for correlations between elevated Chi3L1 levels, increased NETs, and decreased neutrophil apoptosis. Finally, we will test whether inhibition of Chi3L1 and CRTH2 abrogates the proNET-antiApop effects of Chi3L1-rich supernatant from asthmatic sputum. Successful completion of this research will help to (i) establish the Chi3L1/CRTH2 axis as a novel regulator of neutrophil cell death, (ii) reveal new therapeutic strategies against neutrophilic asthma, and (iii) help to establish the applicant as an independent translational investigator in respiratory disease.

**Nahed Jalloul, Ph.D.** - 2022 Awardee

*Department of Pathology and Laboratory Medicine  
Rutgers University*

“Bioinformatics Methods for Serial Circulating Tumor (ct)DNA Analysis to Inform Precision Oncology”

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Clinical sequencing of tumor biopsies has become a routine process for individualized patient care by identifying diagnostic and prognostic biomarkers. Continuous molecular characterization of tumors can predict the selection of cancer-cell subpopulations with greater fitness under therapy and inform on markers of response and relapse. However, serial tissue biopsy is an invasive procedure; it also does not accurately capture tumors' spatial and temporal genomic landscape due to existing heterogeneity between different regions of the same tumor as well as dynamic changes of cancer cell populations in response to treatment. Therefore, profiling cancer cell-derived genetic material circulating in the blood –circular tumor (ct)DNA– has emerged as a novel alternative approach for monitoring tumor evolution. ctDNA sequencing has a high degree of concordance with tissue biopsy data and allows repeatable assessment throughout treatment. Recent studies demonstrated that ctDNA profiles represent true tumor molecular profiles and can identify emerging, therapy-resistant, actionable alterations missed by tissue sampling prior to clinical progression. Despite ctDNA profiling's potential for identification of diagnostic, prognostic, and predisposition biomarkers, limitations in presenting longitudinal sequencing data and complexities in interpreting clonal relationships between detecting variants has hindered its implementation into routine clinical practice. This project builds on my recent work in analyzing tumor sequencing data to develop and integrate scalable bioinformatics tools to incorporate ctDNA analysis into the precision oncology setting. Aims include 1) developing a robust workflow for analysis and clinician-oriented presentation of ctDNA data; 2) designing integrated tools for phylogenetic analyses of serial ctDNA data in the context of estimated circulating tumor DNA abundance. These tools will be continually refined against clinical data generated for and discussed in a molecular tumor board (>30 expected cases /year). This proposal has the potential for high impact by providing objective, reproducible support for practicing clinicians and medical trainees to guide personalized treatments.



**Oh Sung Kwon, Ph.D.** - 2022 Awardee

*Department of Kinesiology, College of Agriculture, Health and Natural Resources  
University of Connecticut*

“The Mito-Frail Trial: Effects of MitoQ on Vasodilation, Mobility and Cognitive Performance in Frail Older Adults”

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Chronic diseases and associated declines in physical and cognitive performance contribute greatly to lost independence with aging. In addition to a lack of effective interventions other than exercise to address either problem, few studies have examined strategies for targeting both conditions in frail individuals who experience difficulties with both walking and memory. Use of geroscience-guided therapies permits us to target mechanisms shared by aging with multiple chronic conditions for which aging represents a major risk factor.

In the Mito-Frail study we wish to improve peripheral and cerebral blood flow, as well as physical and cognitive performance in frail older adults by using MitoQ, a mitochondria-targeted antioxidant, to overcome declines in mitochondrial function and endothelium-derived nitric oxide (NO) seen with aging, frailty, and associated declines in physical and cognitive performance.

Our preliminary data shows that MitoQ restores impaired flow-mediated vasodilation in frail older adults, enhancing gait speed and quadriceps muscle strength. MitoQ is known to modify the function of the vascular endothelium and enhance NO bioavailability.

Therefore, Aim 1 will assess peripheral and cerebral NO bioavailability and mtROS levels in older adults older adults who are healthy, frail with slow walking speed and those who meet criteria for MCI. Aim 2 will determine whether MitoQ supplementation can enhance NO bioavailability and improve declines in flow-mediated vasodilation seen in these groups. Thus, the overall goal of the proposed studies is to better understand the role of vascular endothelium in aging and determine if cerebral and peripheral endothelial function and NO bioavailability are viable therapeutic targets to limit this debilitating age-related disease. Moreover, in addition to addressing the question of whether the use of MitoQ results in circulatory improvements, this study will also generate physical performance and cognitive data needed to design and power a future clinical trial focused on these functional outcomes.

**Erin Longbrake, M.D., Ph.D. - 2022 Awardee**

*Department of Neurology, Division of Neuroimmunology  
Yale University*

**“Optimizing COVID-19 Vaccination Strategies for B-Cell Depleted Patients”**

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The COVID-19 pandemic is the greatest threat to human health and safety in generations. Vaccination has emerged as our strongest weapon against the virus, but not all individuals can achieve protective immunity after vaccination. Specifically, immunocompromised patients have an attenuated immune response to vaccination, which not only puts them at high personal risk for infection but also establishes them as reservoirs for a mutating virus. The recent wave of hospitalizations and deaths attributed to the highly infectious delta variant highlights the population-level danger that can result from emergence of new viral variants. It is imperative to identify how immunocompromised people can best be protected from COVID-19 infection and determine what adjustments to standard vaccination protocols may enable them to build protective immunity.

B-cell depleting immunotherapies are widely used for autoimmune diseases. These anti-CD-20 antibodies are administered every 6 months and lyse circulating B-cells within days. Although B-cell precursors, mature plasma cells and some tissue-resident B-cells are not impacted, circulating B-cells are usually undetectable for ~6 months. Treatment is associated with an attenuated response to infections and vaccination. B-cell depleted patients have increased morbidity/mortality from COVID-19 and require prolonged time to clear the virus 1, 2. Emerging data confirm an attenuated or absent humoral response to both infection and vaccination 3-6.

We will use our large cohort of patients with autoimmune disease on B cell depletion to examine the dynamics of the immune response to standard and booster SARS-CoV-2 vaccinations in B cell depleted individuals and establish which clinical and serologic variables are most strongly associated with seroconversion and strong humoral response. This information can be leveraged to design rational approaches that improve vaccine strategies for this vulnerable population.

**Ankit Shah, M.D. - 2022 Awardee**

*Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition  
Rutgers University Robert Wood Johnson Medical School*

“Substrate Preference for Gluconeogenesis”

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Type 2 diabetes mellitus (T2DM) affects over 30 million American adults. Despite current treatments, hyperglycemia remains a persistent and progressive problem for patients and is driven in part by increased hepatic gluconeogenesis as the liver combines smaller non-carbohydrate substrates to form a six-carbon glucose molecule. Many consider lactate, which comes from muscle cells, the predominant carbon contributor to gluconeogenesis. However, prior human studies have not directly compared lactate and glycerol, which comes from adipose cells, making each substrate's relative role in GNG unclear. We have shown that glycerol is the preferred substrate for gluconeogenesis in mice and induces enzymatic changes in the liver that promotes glycerol's own conversion to glucose. The objective of this proposal is to use labeled isotope tracers and metabolic flux analysis to study de novo glucose production in humans with and without T2DM. We hypothesize that glycerol is preferred over lactate for gluconeogenesis in humans and subjects with T2DM are more proficient at generating glucose from glycerol. Specifically we will 1) Compare the human body's preference to synthesize new glucose from either glycerol or lactate when given both substrates simultaneously; 2) Assess for differences in glycerol and lactate utilization among subjects with and without T2DM. To accomplish these aims, we will enroll metabolically healthy subjects and subjects with T2DM to complete a crossover study with two study visits. One visit involves administering an oral bolus of labeled glycerol and unlabeled lactate at equimolar amounts followed by serial blood draws. The other visit is similar but involves an oral bolus of equimolar labeled lactate and unlabeled glycerol. Blood specimens will undergo liquid chromatography-mass spectrometry analysis. These results will lead to a better understanding of the determinants of T2DM hyperglycemia and could identify glycerol's conversion to glucose as a novel therapeutic target for T2DM.

**Aaron Slusher, Ph.D.** - 2022 Awardee

*Department of Pediatrics - Endocrinology  
John B. Pierce Laboratory, Inc., Yale University*

“Mechanisms of Adipose Tissue Insulin Resistance in Obese Adolescents”

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Adolescent obesity has increased alarmingly in the United States, and in parallel, contributes to the increased prevalence of insulin resistance (IR) and nonalcoholic fatty liver disease (NAFLD). Although obesity during childhood is associated with premature death from more progressive chronic liver diseases and liver cancers during adulthood, research focusing on the molecular mechanisms responsible for IR and NAFLD among obese adolescents is extremely limited.

Our group (Yale University) has identified that the thinning of the subcutaneous adipose tissue (SAT) depot and expansion of the visceral adipose tissue (VAT) depot represents a distinct phenotype in obese adolescents that robustly predicts IR and NAFLD. Utilizing SAT biopsies, we have further shown that obese adolescents with high compared to low ratios of VAT relative to total abdominal fat (VAT+SAT) have smaller adipocytes that are less responsive to insulin-mediated suppression of lipolysis (fat breakdown into glycerol and free fatty acids [FFA]). This impaired capacity of SAT to expand and store lipids in response to insulin results in excess fat accumulation within the liver.

Building upon these results, I propose two aims involving SAT biopsies obtained before and after 30 minutes of insulin infusion to identify the potential molecular mechanisms by which obese adolescents with high compared to low ratios of VAT/(VAT+SAT) develop IR and NAFLD.

**Aim 1:** Examine the molecular mechanisms of impaired insulin-mediated suppression of adipose tissue lipolysis (decreased Akt phosphorylation; increased PLIN1, CGI-58, ATGL, and HSL phosphorylation) and receptor signaling (increased plasma membrane sn-1,2-DAG and n-PKC $\epsilon$ ) in obese adolescents with high vs. low VAT/(VAT+SAT) ratios.

**Aim 2:** Examine the role of the aberrant adipose tissue to liver crosstalk (elevated plasma FFA concentrations and increased glycerol, glucose, and  $\beta$ -OHB stable isotope turnover rates) as a mechanism contributing to NAFLD in obese adolescents with high vs. low VAT/(VAT+SAT) ratios.

**Garrett Ash, Ph.D.** - 2021 Awardee

*Center for Medical Informatics  
Yale University*

“Electronic Exercise Support for Type 1 Diabetes”

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Approximately 1 million American adults have type 1 diabetes (T1D). Interventions for T1D address glycemic control but not the multitude of modifiable risk factors prevalent in T1D (e.g., hypertension, obesity). Exercise interventions could provide a novel solution if they could innovatively address the diabetes management and psychosocial challenges around exercise posed by T1D. Our preliminary work among inadequately active adults with T1D found that health feedback from continuous glucose monitoring overlaid with exercise biosensor feedback (HF) increased confidence to exercise while avoiding safety hazards. Yet, they stated it was inadequate to motivate sustained behavior change because it lacked defined goals for when and how to exercise. This gap could be addressed short-term by brief human-delivered motivational enhancement therapy (ME), and long-term by automated context-aware coaching regarding when and how to exercise. In accord with NIH Model Stages #0-#1 of intervention development (basic science, creation, and preliminary testing), it is warranted to add an immediately available refinement (ME) and conduct a larger feasibility study, while also collecting longitudinal data to develop more advanced refinements (context-aware coaching). This larger feasibility study will follow a single group of inadequately active adults with T1D (N=28) who receive a mobile intervention that incorporates HF and ME, for 10 weeks to evaluate intervention acceptability and preliminary efficacy upon exercise behavior, related health outcomes, and common barriers for exercise. Furthermore, the resulting longitudinal data will be assessed for potential informants of automated feedback: a) day- and participant-level determinants of exercise behavior that could indicate opportune time windows to encourage exercise, and b) causal impact of exercise upon blood glucose that could inform tailoring exercise frequency, intensity, and type to maximize health benefit by learning from prior results. The results will guide a future more advanced intervention combining the acceptable components from this pilot trial with automated feedback.

**Benjamin Bates, M.D. - 2021 Awardee**

*Rutgers Center for Pharmacoepidemiology and Treatment Science  
Rutgers University Robert Wood Johnson Medical School*

“Immune Checkpoint Inhibitor Use and Adverse Events Among Individuals with Melanoma and Non-Small Cell Lung Cancer”

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Immune checkpoint inhibitors (ICI) are a novel class of targeted antibody therapies used to treat cancer by influencing the immune system to recognize cancer cells. Immune-related adverse events (irAEs) are the most prominent reported adverse events of ICI, potentially lethal, and have been reported to occur in up to 90% of users. Due to the potential severity of irAEs and concern immunosuppressive medications may hinder ICI effectiveness, patients with autoimmune disorders have been excluded from ICI clinical trials. Important knowledge gaps exist concerning the effects of immunosuppressants and adverse outcomes in patients with autoimmune disorders.

The incidence of immune-related cardiovascular events (irCVE) appears to be more common than initially found in trials. The initial underappreciation may be multifaceted, including relatively healthier individuals and exclusion of preexisting autoimmune disorders in trials. Publication bias may also be contributing to the dissemination of more severe events while overall cardiac events may actually be underrecognized. No large cohort studies have evaluated the potential multifaceted presentation of irCVE or assessed the association with preexisting cardiovascular comorbidities, autoimmune disorders, or concomitant use of chemotherapy.

We will use SEER-Medicare to conduct cohort studies of nationally representative Medicare patients with melanoma and non-small cell lung cancer who receive ICI. The study population will be described, Cox proportional hazards regression models will be used to estimate the time to risk of primary and secondary outcomes, and propensity score-based methods will be used to adjust for potential confounding variables. The results will fill important knowledge gaps concerning use of ICI and immunosuppressants among patients with history of autoimmune disorders, the influence on irAEs, and the risk factors, incidence and treatment of CVE following initiation of ICI. The results will inform clinicians about the current practice of ICI use and incidence of rare and deadly cardiovascular events in real world patients.

**William Damsky, M.D., Ph.D.** - 2021 Awardee

*Department of Dermatology  
Yale University*

“Evaluating the Role of Janus Kinase Inhibition in the Treatment of Sarcoidosis: Focus on Disease Heterogeneity and T Cell Responses”

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Sarcoidosis is an idiopathic inflammatory disorder characterized by the formation of granulomas in affected tissues including the lungs, the heart, and skin, among others. Sarcoidosis is a T cell dependent auto-immune disease that disproportionately affects African Americans in the United States and current treatment approaches are inadequate; either they are ineffective, or their side effects are problematic. We have discovered that Janus kinase (JAK) inhibitors appear to be a promising molecularly targeted treatment approach for sarcoidosis, likely through inhibiting the activity of pathogenic cytokines that drive this disease including IFN-gamma, IL-6, and GM-CSF. We are currently performing an open-label clinical trial to further evaluate the activity of tofacitinib in sarcoidosis and have created an associated biorepository.

Although efficacy evaluation in our trial is still underway, presently it appears that patients with sarcoidosis tend to have either a complete response to therapy (no significant disease remaining on treatment) or partial response (improvement, but still active disease). In this proposal, we will combine this annotated clinical response information with analysis of the biorepository. In Aim 1, we will evaluate immunologic heterogeneity of sarcoidosis as it relates to response tofacitinib using RNA sequencing and cytokine profiling of peripheral blood samples. In Aim 2, we will examine the effect of treatment on the diversity and frequency of pathogenic T cells in both lesional tissue (skin) and in circulation in order to better understand the effect of tofacitinib on the natural history of this disease.

These analyses will give us a better understanding of why responses to JAK inhibition are somewhat heterogeneous and design strategies to further refine our approach moving forward. This work has the potential to revolutionize the treatment of a potentially devastating disease for which there is a significant unmet need for more effective, safer therapies.

**Margaret Davis, Ph.D.** - 2021 Awardee

*Department of Psychiatry  
Yale School of Medicine*

“Dysregulation in KOR as a Marker of BPD and Suicide Related Endophenotypes”

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The goal of this study is to investigate the role of the kappa opioid receptor (KOR) in borderline personality disorder (BPD), a condition associated with alarmingly elevated risk for self-injury (SIB; 80%), suicide attempt (SA; 75%) and death by suicide (10%). Despite increased risk, most available treatments are not capable of addressing overall BPD symptom severity or rapidly reducing suicide risk. Investigation of molecular mechanisms responsible for BPD symptoms, and suicide risk specifically is an essential next step to both promote development of novel treatments and facilitate risk prevention in BPD. Emerging evidence implicates KOR in BPD and suicidal behavior. KOR plays critical roles in emotion regulation, social functioning, and pain perception – all of which are central to BPD and related to suicide risk. Postmortem studies have shown an association between KOR and death by suicide. Further, KOR antagonists can produce antidepressant, anxiolytic, and even anti-suicidal effects. Importantly, KOR agents’ effect on dopamine is modest relative to drugs of abuse, reducing concerns about abuse potential. Here, we propose a novel investigation of KOR availability of in individuals with BPD using positron emission tomography (PET), a brain imaging technique, and radioligand [11C]EKP which binds selectively to KOR in the brain (Aim 1). Given the high prevalence of suicide-related behavior in BPD, we will also evaluate the association between KOR availability, SA and SIB (Aim 2). Lastly, we will evaluate the association between pain tolerance, and executive dysfunction– key endophenotypes of BPD associated with suicide risk – and KOR availability (Aim 3). Results of this study will provide potentially critical insight into the relationship between this novel molecular target, BPD symptom presentation, and suicidal behavior. Based on findings we will pursue funding for a larger PET study to test potential non-addictive KOR targeted medications in BPD.



**Anna Eisenstein, M.D., Ph.D.** - 2021 Awardee

*Department of Dermatology  
Yale School of Medicine*

“Exploring the Role of Environmental Xenobiotics in the Development of Food Allergy”

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Atopic disease, including asthma, food allergies and atopic dermatitis, are on the rise for unclear reasons. It is clear, however, that these are diseases of modernity and urbanization, but what specific factors in the modern environment are contributing to disease pathogenesis are poorly understood. The prevalence of manmade xenobiotics, including medications and chemical additives, are closely linked to modernization. The use of non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX) enzymes and have been associated with worse allergic diseases, now total 30 billion American doses yearly. We thus hypothesize that NSAIDs possess adjuvant properties and are sufficient to induce allergic sensitization, and thus may partially explain the exponential increase in the prevalence of allergic diseases. In preliminary studies, we sensitized mice with intraperitoneal injections of the model antigen ovalbumin (ova) with commonly utilized NSAIDs. Preliminary results suggest that certain NSAIDs, irrespective of COX specificity are sufficient to generate immunologic memory to ova with induction of ova-specific IgE and IgG1, and with anaphylaxis upon ova challenge. Our initial studies implicate the xenobiotic sensor, nuclear factor erythroid 2- related factor 2 (Nrf2), as necessary for this response. Our proposal will address three specific aims. First, we will determine the extent to which NSAIDs promote immunologic memory to food antigen. Second, we will explore the mechanism underlying the ability of NSAIDs to act as adjuvants in allergic disease and whether other environmental xenobiotics may act similarly. Third, we will determine the extent to which the use of NSAIDs and other xenobiotics in infants is associated with atopic conditions. This project has the potential for significant public health impact as well as important developments in our understanding of allergic sensitization.

**Lama Ghazi, M.D., Ph.D. - 2021 Awardee**

*Department of Internal Medicine, Section of Nephrology  
Yale School of Medicine*

**“Risk Factors for and Outcomes of Severe Inpatient Hypertension”**

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Acute severe hypertension (hypertensive emergency) accounts for 5% of adult emergency room visits. Hypertensive emergency and outpatient severe hypertension episodes are associated with higher risk of cardiovascular events and mortality. However, more common are severe blood pressure elevations that occur during hospitalization for other causes. There are currently no guidelines on how to assess or manage inpatient hypertension or if treatment improves patient outcomes. In an effort to narrow this gap, we aim to use the electronic health record database of patients admitted to the Yale New Haven Health System (6 hospitals). We will evaluate the overall prevalence of inpatient hypertension and identify risk factors that contribute to the blood pressure elevation. We will evaluate treatment options currently used and their blood pressure lowering effect. We will further assess whether inpatient hypertension is associated with clinical outcomes, such as acute kidney injury, mortality, and 30 day hospital readmission. We hypothesize that this association will differ based on whether inpatient elevation of blood pressure was treated or not. This study will have important clinical implications, we hypothesize that inpatient hypertension is a common complication that will be treated with various medications and clinical outcomes will vary based on treatment management. As a future direction, we plan to randomize patients who develop inpatient hypertension to various treatment regimens. We will leverage electronic health record data to identify patients eligible for the study and to assign different treatments.

**Yuan Huang, Ph.D.** - 2021 Awardee

*Department of Biostatistics  
Yale School of Medicine*

“Regularized Learning and Subgroup Analysis for Cognitive Declines, with Applications to Improve Clinical Trial Design for Huntington’s Disease”

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Huntington’s Disease (HD) is a devastating neurodegenerative disease that typically strikes in middle age and spans a long disease course with development of uncontrolled movement disorder and cognitive impairment leading to dementia. HD is caused by an elongated cytosine-adenine-guanine (CAG) repeat (40 repeats or more) in the Huntingtin gene, with a longer CAG repeats associated with an earlier motor onset. Motor onset is a landmark event for HD, but the decline of cognitive functions happens much earlier than the motor diagnosis, starting subtly and accelerating as the disease progresses. However, it is not clear about the time at which these changes begin to occur and how the accelerated decline is related to the length of CAG repeat. This information, however, is very important for guiding clinical care and making timely treatment decision. This study targets to fill this knowledge gap.

Using longitudinal observations from ENROLL-HD, the largest prospective HD cohort data, the proposed study develops novel statistical methodologies to characterize the pattern of accelerated cognitive decline along the course of HD and explore its relationship with the length of CAG repeat. In Aim 1, for each CAG repeat length, we formulate longitudinal cognitive measures into a high-dimensional framework and identify the changes in cognitive decline with regularization methods. This approach allows for simultaneously estimating the timing window and the rate of accelerated cognitive decline in a complete data-driven manner. In Aim 2, we further hypothesize that the pattern of cognitive decline shows some similarity for adjacent CAG repeat lengths at certain age ranges. An integrative analysis is conducted to jointly model the pattern of cognitive decline across all CAG repeat lengths with accounting for neighboring similarity. In Aim 3, we apply our findings to improve clinical trial design by conducting simulation-based power analysis.

**Stephanie Kerrigan, Ph.D.** - 2021 Awardee

*Psychiatry*  
*Yale School of Medicine*

“Optimizing Low-intensity Interventions for Promoting Physical Activity among Individuals at High Risk for Diabetes”

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Physical activity is a critical health behavior for all adults. In particular, individuals at high risk for health complications, including those with overweight/obesity and prediabetes, may experience mitigated risk for diabetes and cardiovascular disease with increased physical activity. Despite this, treatments often do not effectively increase activity. One problem may be that one-size-fits-all prescriptions for activity fail to consistently motivate behavior. Adaptive goals offer promise for addressing this problem. However, studies have not attempted to optimize such goals across the frequency of adaptation (e.g. new goals could be presented daily or weekly) or the method of adaptation (e.g., are goals anchored to a standard goal or dependent only on prior behavior). Moreover, such goals have not been tested among individuals with prediabetes specifically, who may carry additional complications compared to those without specific increased disease risk. The present study will address this gap by enrolling 140 adults with overweight/obesity and pre-diabetes in a randomized-controlled trial testing variations in frequency (daily vs. weekly) and adaptation algorithm against a static goal for step counts. All participants will have monthly check-in calls with researchers to discuss initiating weight loss and have goals for step counts for three months. Participants will be provided with a device for monitoring step counts and a scale that connects via Bluetooth for use during the study. Primary outcomes will be change in step counts over time. Secondary outcomes will include changes in weight (measured via Bluetooth scale at least monthly) and markers of diabetes (fasting glucose and HbA1c; N=50 patients will complete blood draws at baseline and post-intervention). Results from this pilot trial are designed to provide initial effect size estimates for a large-scale clinical trial evaluating low-intensity physical activity interventions for individuals at high risk for diabetes.

**Lisa Korn, M.D., Ph.D.** - 2021 Awardee

*Department of Medicine, Rheumatology Section  
Yale School of Medicine*

“Cytokine Regulation Of Intestinal Nutrient Transport In Atopic Diseases”

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Atopic diseases, including asthma, allergy, and eczema, are common conditions that cause significant illness and interfere with quality of life. One hallmark of these diseases is increased levels of the type 2 cytokines, IL-4 and IL-13. Receptors for IL-4 and IL-13 are expressed on small intestine epithelial cells (IECs) that have important metabolic functions such as nutrient sensing, nutrient uptake, and production of enteroendocrine hormones. Though type 2 cytokines have also been linked to metabolism, their relationship to IEC metabolic function is not well understood. IEC nutrient sensing and handling is mediated by specialized nutrient transporters that are expressed on the IECs. In preliminary data from mouse 3D intestinal organoids, we identified a novel IL-4 and IL-13 driven IEC nutrient transporter gene expression program for amino acids. As IECs are functionally heterogenous, we asked if this program applied to a specific IEC cell type. Using publicly available single cell RNA sequencing (RNA seq) data, we found it applied across absorptive, secretory, and sensory cells. We further examined enteroendocrine cell hormone gene expression and found these were also affected. We hypothesize that a coordinated IL-4 and IL-13 (type 2 cytokine)-mediated nutrient transporter program regulates local nutrient metabolism and systemic metabolic signals in atopic diseases. We propose using human derived 3D intestinal organoids to thoroughly define the program and to metabolically profile it, addressing specific questions of amino acid uptake and enteroendocrine hormone production. We further plan to validate the program in small intestine samples from patients with atopic diseases. Defining altered nutrient handling as a feature of type 2 cytokine-driven atopic diseases is an important first step in determining exactly how it participates in disease and how it can best be treated.

**Brienne Miner, M.D.** - 2021 Awardee

*Geriatrics*

*Yale School of Medicine*

“Evaluating Poor Sleep Quality in Persons with Advanced Age”

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Poor sleep quality in older adults is common, distressing, and associated with many adverse outcomes, including cognitive and physical decline. Sleep quality is usually assessed by self-report. However, discrepancies between self-reported and objectively measured sleep in older adults suggest that sleep problems may be even more prevalent and severe than reported. The addition of objective sleep measurement may more effectively identify poor sleep quality and gauge its severity, leading to improved treatment and prevention of adverse outcomes.

Polysomnography and actigraphy are widely used objective measures of sleep, but both have substantial limitations in older adults. Polysomnography, which measures electroencephalography (EEG) to detect sleep-wake states, is the gold standard, but is expensive and cumbersome. Actigraphy does not measure EEG, instead inferring sleep from the absence of limb movements. It may generate inaccurate estimates, especially in older adults with poor sleep quality. Thus, there is an unmet need for EEG measures of sleep that can be successfully applied in older populations.

EEG-measuring sleep headbands have the potential to overcome the limitations of polysomnography and actigraphy in older adults. These devices provide a user-friendly design for at-home use. Sleep headbands may be an appealing and more robust alternative to objectively measure sleep, but they have not been validated in adults 65 years and older.

We will collect data from older adults with poor sleep quality to: 1.) pilot test use of a sleep headband at home; 2.) validate the headband against gold standard polysomnography; and 3.) compare the agreement among self-reported and EEG measures of sleep quality. The long-term goal of this research is to improve the evaluation of sleep quality in older adults by complementing self-reported measures with feasible objective measures. This work may change the current paradigm by establishing the need for and feasibility of measuring sleep objectively in older persons.

**Oluwabunmi Olaloye, M.D. - 2021 Awardee**

*Division of Neonatal-Perinatal Medicine  
Yale University*

“Deep Profiling the Peripheral Immune System Development of Preterm Infants at Risk of Necrotizing Enterocolitis”

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Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease of prematurity with 20-30% mortality and an annual burden of \$1 billion. Non-specific clinical instability after intestinal damage often precedes the diagnosis. No definitive therapy exists, but management involves cessation of feeds, treatment with antibiotics, and surgical resection of the necrotic intestine in severe cases. Preventative strategies are limited to exclusive human milk feeds, though some infants receiving exclusive human milk still develop NEC. This disease is complex, and its exact pathophysiology is poorly understood. Immune dysregulation is a contributing factor with several studies identifying intestinal immune defects in affected neonates. Yet, a biomarker that accurately predicts infants at risk of NEC development and progression is lacking. This proposal will provide an in-depth insight into NEC's pathogenesis in premature infants using state-of-the-art tools such as mass cytometry (CyTOF) that allows for simultaneous single-cell analysis of a large number of cellular populations. We hypothesize that NEC is characterized by immune dysregulation in peripheral blood before disease onset. To address this, we have designed a prospective cohort study of infants born at Yale New Haven Hospital, where we will obtain longitudinally collected blood samples over the first month of life to define the developmental trajectory of peripheral immunity in premature infants and identify differences in immune development that increase susceptibility to NEC. The following two aims will address our hypothesis:

Aim 1: Define the developmental path of classical, non-classical peripheral monocytes, and effector memory T cells in preterm neonates.

Aim 2: Identify differences in monocyte and effector memory T cell development in infants with NEC.

Ultimately, we will define the peripheral immune trajectory in preterm infants and identify alterations that increase susceptibility to NEC that will serve as potential diagnostic and therapeutic targets.

**Denalee O'Malley, M.S.W., Ph.D. - 2021 Awardee**

*Department of Family Medicine, Research Division  
Rutgers University Robert Wood Johnson Medical School*

**“Developing Implementation Approaches to Target Colorectal Cancer Screening among Patients with Diabetes in Safety-net Primary Care Settings”**

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Patients with type II diabetes mellitus (T2DM) have an estimated 27% elevated risk of developing colorectal cancer (CRC) and are disproportionately Non-Hispanic blacks (NHBs) and Hispanic. NHBs are less likely to survive CRC and are more likely to be diagnosed at late stages compared to Non-Hispanic Whites. CRC screening reduces mortality by 13% to 68%, depending on the screening tool used. Failure to implement CRC screenings translates to ~6.5 years of lost life for CRC patients.

Federally qualified health centers (FQHCs), struggle to implement CRC screening programs (44.1% vs. the national average 67.3%) for average-risk patients, and primarily serve as primary care for priority populations (low income and racial/ethnic minorities). Patients with T2DM and CRC, suffer greater morbidity, all-cause, and cancer-specific mortality. Therefore, implementation strategies to target this population for CRC prevention are needed.

This study aims to: (1) examine the effects of CRC screening implementation on racial/ethnic disparities among primary care patients with T2DM, and (2) identify multi-level change objectives to implement targeted CRC screening for patients with T2DM in FQHCs. For this proposal, we will use the Medical Expenditures Panel Survey data, to compare differences in overall and test specific CRC uptake among patients with T2DM who receive majority of their care in FQHCs vs patients in traditional primary care settings. For Aim 2, using an iterative community participatory research strategy, an implementation planning group (patients, clinicians, staff) will be assembled. The group will use multiple data inputs (Aim 1 results, FQHC organizational survey, semi-structure interviews among key actors) to produce an implementation map and toolkit. This implementation toolkit and strategy will be tested using a hybrid effectiveness-feasibility pilot in the next phase of this research. The proposed research can be adapted to develop targeted cancer prevention strategies in additional chronically ill priority populations.



**Rozalyn Rodwin, M.D., M.H.S.** - 2021 Awardee  
William O. Seery Foundation  
*Pediatrics, Section of Hematology/Oncology*  
*Yale University*

“A Symptom-Based Survey to Screen for Peripheral Neuropathy in Childhood Cancer Patients”

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There are nearly half a million childhood cancer survivors in the United States, and over 60% of survivors experience at least one late complication of their cancer therapy. Peripheral neuropathy is a debilitating side effect of chemotherapy that affects at least 20% of children with cancer, and can persist years after treatment has ended. Peripheral neuropathy impairs activities of daily living, but once detected there are interventions available that can improve symptoms. Currently available methods for detection of peripheral neuropathy in children with cancer require specialized examinations that are not part of routine care. A major barrier to detection of peripheral neuropathy in children with cancer is the lack of a validated, symptom-based survey to screen for peripheral neuropathy.

The goal of this project is to construct and validate a symptom-based survey to screen for peripheral neuropathy in routine oncology visits. A recent Children’s Oncology Group multicenter clinical trial of children with leukemia collected data regarding reported symptoms of peripheral neuropathy at the same time-point that physical therapists performed specialized examinations to detect peripheral neuropathy. Using these data, our aims are to 1) construct a symptom-based survey to screen for peripheral neuropathy by examining the association between survey responses and abnormal specialized examinations and 2) externally validate this symptom-based survey in children treated for cancer at our institution. We hypothesize that survey questions will be associated with exam-identified peripheral neuropathy. A symptom-based survey is needed to enable oncology providers to quickly identify patients who may benefit from interventions for their peripheral neuropathy.

**Stephanie Samuels, M.D.** - 2021 Awardee

*Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes  
Yale-New Haven Hospital*

**“A Pilot Virtual/Telehealth Adaptation of the Bright Bodies Intervention for Childhood Obesity”**

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Childhood obesity is a prevalent public health problem associated with short-term and long-term health complications, with recent estimates of nearly 1 in 5 children in the United States affected by obesity. Disparities persist, with higher prevalence of obesity and its associated cardiometabolic sequelae impacting low-income communities, racial/ethnic minorities, and rural populations. Positive impacts of multidisciplinary pediatric weight management interventions may be limited by low access, enrollment and attrition. The COVID-19 pandemic — with associated stay-at-home mandates, school closures, and decreased access to quality foods and physical activity — has the potential to exacerbate the epidemic of childhood obesity. The current pandemic has highlighted the urgent need for effective childhood obesity prevention and treatment interventions that can be delivered remotely to families.

The Bright Bodies program at Yale is a family-based pediatric weight management program tailored to racially/ethnically diverse, urban children. The United States Preventive Service Task Force cited the Bright Bodies program as one of a few effective interventions in its 2017 report concluding that comprehensive, high-intensity behavioral interventions for childhood obesity can help reduce body mass index (BMI) in children.

During the COVID-19 pandemic, participants enrolled in Bright Bodies have participated in some web-based activities organized by program leadership. In Aim 1, we will use mixed (quantitative and qualitative) methods to evaluate the experience of staff and families who have participated in Bright Bodies during the pandemic; findings will inform adaptations and optimization of intervention delivery via mobile and remote technologies. In Aim 2, we will conduct a prospective pilot study of this novel adaptation for telehealth, with outcome measures of feasibility, acceptability, and efficacy. Findings from this preliminary study will be used to design a larger trial to assess the effectiveness of a virtual Bright Bodies intervention in reducing BMI and improving metabolic outcomes for youth with obesity.

**Nkiruka Atuegwu, Ph.D.** - 2020 Awardee

*Department of Internal Medicine  
University of Connecticut Health Center*

“Predictive Modelling to Identify Variables Associated with E-cigarette Initiation, Use and Cessation in Young Adults in the US Population: A Machine Learning Analytic Approach”

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The use of electronic nicotine delivery products, commonly known as e-cigarettes, is increasing at an alarming rate among the youth and young adults. E-cigarettes usually contain nicotine that increase the risk of developing nicotine addiction, psychiatric disorders, attention deficits and future addiction to other drugs in youth and young adults.

Prior models of e-cigarette use and cessation either use known information or exploratory guesses to select variables to include in the models. This standard approach may lead to the exclusion of significant variables that can improve our understanding and prediction of e-cigarette use. The emergence of machine learning algorithms can reduce this limitation and provide the capability to explore and gain a deeper insight from data. Our central hypothesis is that machine-learning techniques can be used to create accurate predictive models of e-cigarette initiation, use and cessation in young adults. To the best of our knowledge, this will be the first study that will create these predictive models in young adults.

Our long-term objectives are to provide accurate and comprehensive models that will help physicians and policy makers develop programs to better target young adults at risk for e-cigarettes use, develop cessation programs to better address e-cigarette addiction, and to develop policies that will help in effective e-cigarette regulation.

The project will use a nationally representative, longitudinal database (Population Assessment of Tobacco and Health (PATH) survey). Specifically, we aim to use the first two Waves of PATH data to identify variables and to create models that predict e-cigarette initiation, use and cessation in young adults. The final prediction models will be validated using the third and fourth Waves of PATH data.

The project will employ logistic regression, support vector machines and tree-based classification algorithms to select variables and also to create models of e-cigarette initiation, use, and cessation.

**Irene Chernova, M.D., Ph.D.** - 2020 Awardee

*Department of Nephrology  
Yale University*

“Pathways Mediating Renal Lymphocyte Survival in Hypertonic Conditions”

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Systemic lupus erythematosus (SLE, lupus) is a multi-organ autoimmune disease characterized by antibody deposition in target organs. SLE nephritis is a leading cause of morbidity and mortality in this population with 10% of those afflicted progressing to end stage renal disease. Kidneys of these patients are characterized by a profound lymphocytic infiltrate with the degree of infiltrate correlating with tissue damage and disease severity. The kidneys are also characterized by a high salt environment not found elsewhere. Thus infiltrating lymphocytes are presented with the unique challenge of surviving in a high salinity environment. The goal of this research is to define the molecular mechanisms utilized by immune cells when faced with this hostile microenvironment.

In our animal data, lymphocytes from lupus-prone mice have enhanced survival when exposed to a high salt environment (compared to wildtype). In aim 1, we propose to replicate this finding in lymphocytes taken from the blood of lupus patients and healthy controls and to further characterize these cells via RNA sequencing and flow cytometry. Our animal studies have also revealed high expression of Fxyd2, a subunit of Na-K-ATPase known to be involved in kidney cell survival in conditions of high salt, on lymphocytes from lupus-prone mice. We hypothesize that Fxyd2 is necessary for immune cell survival in the high salt environment of lupus kidneys. In aim 2, we will look at human kidney biopsy specimens to determine whether Fxyd2 is upregulated in immune cells. In aim 3, we will create lupus-prone mice that genetically lack Fxyd2 and examine the effects on the presence of immune cells in the kidneys as well as on the animals' disease course. Altogether these studies will provide us with an enhanced understanding of the renal immune compartment and the pathways used by immune cells to survive in hostile non-lymphoid tissue environments.

Joao De Aquino, M.D. - 2020 Awardee

*Department of Psychiatry, Division of Addictions  
Yale University*

“Cannabinoid Modulation of Pain Sensitivity in Humans with Co-occurring Chronic Pain and Opioid Use Disorder”

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Individuals with co-occurring chronic pain (CP) and opioid use disorder (OUD) suffer from abnormal pain sensitivity and tend to ruminate about pain, feeling helpless about the experience (pain catastrophizing), which contributes to the risk of dying from opioid overdose. Safer analgesic compounds are, thus, urgently needed for this critical population.

As awareness of the dangers of opioids grows, medicinal use of cannabinoids for CP and OUD is garnering public acceptance, with several U.S. states authorizing medicinal cannabis for these conditions. Converging preclinical evidence indicates opioid-sparing effects of delta-9-tetrahydrocannabinol (THC), the main component of cannabis, reducing the dose of opioids required for analgesia and their abuse liability, with potential implications for preventing fatalities.

Although experimental studies indicate cannabinoids increase pain threshold and tolerability in healthy humans, the analgesic effects of cannabinoids in humans with co-occurring CP and OUD have never been studied.

As a first step in systematically investigating the opioid-sparing effects of cannabinoids, this proposal aims to examine the acute analgesic effects of oral THC (dronabinol) in humans with co-occurring CP and OUD on methadone maintenance treatment (MMT), the most common opioid agonist treatment for OUD, and also a treatment for CP.

This is a randomized, double-blind, placebo-controlled human laboratory study investigating the acute effects of dronabinol in 36 outpatients with co-occurring CP and OUD on MMT. Across 3 test sessions, participants will be randomized to a sequence of a single dose of dronabinol (10 mg, 20 mg) or placebo using a crossover design.

Subsequently, participants will undergo laboratory testing of well-validated measures of: 1) Analgesia, 2) Pain catastrophizing/facilitation, and 3) Safety outcomes (abuse liability, cognitive performance, respiratory rate and pupillary diameter). Insights gained through this study may help develop improved treatments for co-occurring CP and OUD, potentially reducing the high rates of mortality by opioid overdose in this population.

**Julie Gaither, Ph.D., M.P.H.** - 2020 Awardee

*Department of Pediatrics  
Yale University*

“Pediatric Opioid Poisonings: Family, Home, and Community Risk Factors”

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Nearly 10,000 children and adolescents died from prescription and illicit opioid poisonings between 1999 and 2017, and as we found in the first national studies to examine pediatric opioid-related morbidity and mortality, hospitalizations for opioid poisonings doubled in recent years and the mortality rate nearly tripled. Yet, the dangers that opioids pose to children are not reflected in the current policies and practices in the U.S. today; adults are the focus of virtually all of the public health measures enacted over the past two decades to contain this epidemic—a reflection of what little is known about the risks for opioid poisonings in children. Therefore, we aim to address these extensive gaps in the literature by building on our two prior epidemiologic studies with two additional studies—one quantitative, one qualitative. The aim of the first study is to determine the risks for pediatric opioid poisonings in relation to the child, family, home, and community by examining 1,592 fatality reports collected from 36 states on children who died from opioid poisonings. The aim of the second study is to elicit feedback from parents and healthcare providers on issues related to opioid safety by conducting interviews with individuals in our local community in the Northeast. By focusing on the homes where children have actually died, and in talking directly to parents and healthcare providers, we have a unique opportunity to understand the epidemic from the perspective of those who struggle daily with this unprecedented public health crisis. Long term, these detailed, real-world data will form the basis from which to develop interventions that are pediatric specific, family-centered, and tailored toward communities across the U.S., including in the Northeast—Connecticut, Maine, Massachusetts, New Hampshire, and Rhode Island are among the top ten states for opioid overdose deaths in the country.

**Michael Leapman, M.D.** - 2020 Awardee

William O. Seery Foundation

*Department of Urology*

*Yale School of Medicine*

“Intensification of Prostate Cancer Care in Older Men Associated with the Use of New Diagnostic Tests”

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Many older men ( $\geq 70$  years) who are diagnosed with prostate cancer receive treatments that do not improve or prolong their life. This is because not all cancers found through screening with prostate-specific antigen (PSA) will metastasize or cause death if untreated. Determining the optimal approach for older men with prostate cancer is particularly challenging due to the disease’s variable aggressiveness that must be weighed against an individual’s life expectancy and preferences. New diagnostic tests (prostate MRI, biomarkers, and tissue-based genomic tests) have been developed to improve predictions of cancer aggressiveness but might paradoxically worsen over-treatment in older men by over-stating the cancer’s risk. As a result, older men might receive intensified care, including greater use of prostate biopsy for suspected disease, or treatments with greater potential toxicity if the disease is diagnosed.

To test these hypotheses, and anticipate solutions to overcome their associated challenges, we will leverage two complementary data sources to explore care for older patients with prostate cancer: a population-based sample reflecting national care, and patient-level data to explain the impact of specific test results.

In Aim 1, we will examine population-level trends in the use of new diagnostic tests for prostate cancer. In Aim 2, we will examine population-level associations between the use of new diagnostic tests for prostate cancer and clinical care delivered (prostate biopsy among PSA-tested, and the intensity of therapy among treated men). In Aim 3, we will examine patient-level associations between the results of specific tests for prostate cancer and the intensity of clinical care delivered. The findings from this study will generate an understanding of how new diagnostic technologies are applied to older men. This award also supports the career development of the applicant, a urologic oncologist, whose goal is to improve the process and outcome of care for patients with cancer.

**Gregory Ouellet, M.D., M.H.S. - 2020 Awardee**

*Department of Internal Medicine, Section of Geriatrics  
Yale University*

“Does It Still Help? Benefits and Harms of Anticoagulation for Atrial Fibrillation in Patients with Advanced Dementia”

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Dementia affects 5.5 million U.S. adults 65 and older; almost 20% of them have atrial fibrillation, which significantly increases their stroke risk. A critical management decision is whether to prescribe an oral anticoagulant to reduce this risk. Current guidelines, derived from trials that largely excluded individuals with dementia, suggest evaluating the risk of stroke without treatment using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Nearly all patients with both atrial fibrillation and dementia meet the threshold for anticoagulation due to their age and comorbidities. However, this may be overly simplistic when treating individuals with dementia.

The balance of benefits and harms of anticoagulation likely shifts over the course of dementia. As dementia progresses, there is less function to lose and life expectancy shortens, attenuating potential benefits. However, no empirical evidence exists to identify the tipping point at which harms exceed benefits. Even in advanced dementia, characterized by profound disability and minimal ability to communicate, the net benefit is unknown. Nevertheless, our preliminary data suggests that 27% of decedents with advanced dementia and atrial fibrillation continue anticoagulants in the last six months of life.

As a first step in optimizing atrial fibrillation treatment in persons with dementia, we will investigate whether anticoagulation retains benefit among those with advanced dementia and quantify its harms. To assemble a large cohort of patients with advanced dementia and track longitudinal associations between anticoagulant use and the outcomes of death and bleeding, we will link data from the Minimum Data Set, an assessment of nursing home patients, and Medicare claims. Our hypothesis is that mortality benefits will be so low and bleeding risk so high that discontinuation will be warranted. However, regardless of the outcome, the results of this work are necessary to inform treatment decision-making about anticoagulation in advanced dementia.



**Craig Wilen, M.D., Ph.D. - 2020 Awardee**

*Department of Laboratory Medicine and Department of Immunobiology  
Yale University*

“Type II Immunity and Chemosensation in the Pathogenesis and Treatment of Tuft Cell-Variant Small Cell Lung Cancer”

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Small cell lung cancer (SCLC) typically presents with widespread metastases and is associated with a median survival of approximately 12 months. Chemotherapy is the mainstay of treatment but resistance quickly develops in most cases. Novel therapeutic options are greatly needed to improve patient outcomes. Recently, it was discovered that 15% of SCLCs are of tuft cell rather than neuroendocrine cell origin. Tuft cells are a rare chemosensory cell found in the respiratory and gastrointestinal tracts of people. Closely related to taste receptor cells in the taste buds, tuft cells detect small molecules in the extracellular environment and secrete diverse effector molecules in response to stimuli. Specifically, tuft cells in the intestines detect small molecules secreted from intestinal worms and parasites and in response tuft cells release the cytokine IL-25. This cytokine activates an immune cell called group 2 innate lymphoid cells (ILC2), which produce diverse cytokines including IL-5, IL-13, and amphiregulin. These ILC2-derived cytokines recruit inflammatory cells such as eosinophils and Th2 cells, increase epithelial cell turnover, and importantly cause tuft cell proliferation resulting in the establishment of a positive feedback loop between tuft cells and ILC2s. In aim 1, we will use patient tumors to test the hypothesis that the tuft cell-ILC2 feedback loop contributes to the development and metastases of tuft cell-variant SCLC. In aim 2, we will use patient-derived cell lines to test the hypothesis that existing FDA-approved drugs can inhibit tuft cell activation and proliferation. If successful, this work would lead to clinical trials re-purposing existing FDA-approved drugs to treat tuft cell-variant SCLC.

**Ambrose Wong, M.D., M.Sc. - 2020 Awardee**

*Department of Emergency Medicine  
Yale University*

“The Agitation Code Team Response (ACTR) Intervention to Improve Patient and Health Worker Safety in the Emergency Department”

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Emergency departments (EDs) are facing increasing numbers of mental health visits, with 1.7 million associated episodes of patient agitation occurring annually in acute care settings. When de-escalation fails during agitation management, patients are subject to use of physical restraints and sedatives, which are associated with apnea and physical injuries. At the same time, ED staff report workplace violence due to physical assaults during agitation events, leading to injuries, burnout, and missed workdays. In response to calls for a rigorous approach to this critical issue, we recently developed a theoretical framework to characterize ED agitation management using a human factors systems approach, which examines complex healthcare issues as a set of interrelated elements in a work system. As a result, our framework identified staff teamwork as a particularly critical component to reduce harm. In addition, we found that it was necessary to consider patient and staff safety simultaneously to effectively improve safety. Currently, no structured team response protocol for ED agitation addressing both patient and staff safety exists.

This proposal aims to develop and pilot the Agitation Code Team Response (ACTR) intervention, which will consist of a standardized, structured process with defined health worker roles/responsibilities, work processes, and clinical protocols. Using a human factors systems approach, ACTR will simultaneously address and balance patient and staff safety in the ED through two research aims: (1) Development of ACTR will occur through iterative loops of conceptual design and refinement using in situ simulated agitated patient encounters in the ED along with observations and staff focus groups to assess and improve the prototype. (2) Once ready for implementation, we will evaluate ACTR for efficacy in the clinical environment. Controlled interrupted time series analyses of patient restraint/sedative use and staff injury rates will serve as our primary and secondary outcomes.

**Anika Anam, M.D.** - 2019 Awardee

*Department of Internal Medicine  
Yale School of Medicine*

“The Role of Insulin in Endometrial Cancer Pathogenesis: Metabolic Phenotyping of Women with Endometrial Cancer”

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Obesity is an established risk factor for endometrial carcinoma (EC), which is diagnosed in over 60,000 American women annually. Although EC is an obesity-driven disease, we do not yet understand which attributes of obesity contribute to its pathogenic role. As an endocrinology fellow, I seek to determine whether metabolic dysregulation in obesity, specifically high levels of insulin, is associated with malignant transformation of endometrium. Obese women may have high insulin levels due to excess visceral fat distribution. We hypothesize that women with EC have higher stimulated insulin levels, greater degree of insulin resistance, and greater volume of visceral fat, than BMI-matched women with benign endometrium.

We propose to assess the metabolic health of post-menopausal women with EC by examining stimulated insulin levels, insulin resistance, and fat distribution. We will enroll 15 women with EC and moderate obesity (BMI 35-39.9kg/m<sup>2</sup>) and 15 BMI-matched women without EC. We will interview participants to assess lifestyle factors, reproductive, and personal/family medical history. Risk factors for EC and Type 2 diabetes will be evaluated with laboratory testing of hormones, lipids, and inflammatory markers. All participants will undergo a glucose tolerance test to quantify stimulated insulin levels and evaluate insulin resistance. Finally, MRI will quantify subcutaneous, visceral, and liver fat, and anthropometric measures will be obtained. The primary outcome will be insulin levels. Secondary outcomes will include degree of insulin resistance, visceral fat volume and ratio of visceral to subcutaneous fat, liver fat, and the frequency of metabolic dysregulation (metabolic syndrome, pre-diabetes) occurring in women with EC and BMI-matched women with benign endometrium. This study will provide initial evidence for understanding which attributes of obesity increase susceptibility to malignant transformation of the endometrium. This research has broader implications for understanding the pathophysiology of other obesity-driven cancers, including breast and colon cancer.

**Prasanna Ananth, M.D., M.P.H. - 2019 Awardee**

*Department of Pediatrics, Section of Pediatric Hematology/Oncology  
Yale School of Medicine*

“Establishing Benchmarks for High Quality End-of-Life Care in Children with Cancer”

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Although rates of cure for childhood cancer have greatly improved in recent years, thousands of children continue to suffer from incurable cancer. Ensuring high quality end-of-life care (EOLC) for children with advanced, incurable cancer, is therefore critical. Among adults with cancer, intensive—or poor quality EOLC—has been defined by quality measures such as hospitalizations in the last month of life, chemotherapy receipt in the last 14 days of life, and delayed hospice referral. These quality measures have proven particularly useful, enabling evaluation and, importantly, improvement of cancer care delivery in adults. Our prior research reveals intensive healthcare resource use near the end of life for children with cancer, which, based on current evidence, may heighten child suffering and complicate family bereavement. However, there are no existing standards for what constitutes high quality EOLC for children with cancer. We seek to address this problem in the current proposal.

The overall goal of this proposal is to develop patient- and family-centered, provider-informed EOLC quality measures for children with cancer. Specifically, we aim (1) to generate candidate pediatric EOLC quality measures, informed by focus groups and interviews with key stakeholders; and (2) To select core pediatric EOLC quality measures, using the modified Delphi technique to achieve multi-center expert consensus. Our proposed mixed methods research is conceptually innovative, introducing quality measures within a pediatric serious illness context where, to date, no metrics exist. Furthermore, the proposed work bears the potential to transform how we approach care for children with advanced cancer, informing the development of a prospective intervention to ameliorate poor quality EOLC.

**Mari Armstrong-Hough, Ph.D., M.P.H. - 2019 Awardee**

*715 Broadway  
New York University*

“Predicting and Preventing Tuberculosis Treatment Failure in an Emerging Co-Epidemic of HIV, Diabetes, and Tuberculosis”

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In settings with heavy burdens of HIV and tuberculosis (TB), type 2 diabetes (DM) prevalence is increasing rapidly. DM makes patients more susceptible to infections, including TB. DM can alter how patients respond to medications, including some used to treat TB. Patients with both DM and TB are five times more likely to die during treatment than patients with TB alone. They take longer to respond to treatment and are more likely to experience complications. DM has serious implications for TB patients' treatment outcomes.

The association between DM and TB outcomes is known. However, it is not clear which measures best identify patients at high risk of poor outcomes, how often they should be assessed, how HIV may modify the relationship, or whether change in glucose exposure over treatment period is associated with treatment outcome. The proposed project initiates multidisciplinary research to elucidate the association between glucose exposure and poor treatment outcomes for TB in a high-HIV burden setting, and to improve implementation of glucose screening, monitoring, and counseling in TB units.

We will recruit a cohort of TB patients with and without HIV at diagnosis and follow them through treatment completion or failure, tracking fasting blood glucose and glycated hemoglobin (HbA1c). We will fit hierarchical generalized linear models for TB treatment outcomes using glycemic trajectories. We will also use formative interview research with patients and health workers to identify barriers to glucose screening, monitoring, and counseling TB patients in a low-resource setting with a high burden of HIV. We will adapt each component and initiate a pilot study of a complex intervention to improve patient outcomes.

This work will improve our understanding of how glucose exposure impacts TB treatment outcomes, which indicators best predict outcomes, and how glucose screening, monitoring, and counseling can be enhanced for TB patients.

**Whitney Besse, M.D. - 2019 Awardee**

*Department of Medicine, Section of Nephrology  
Yale School of Medicine*

“The Search for Novel ADPKD Treatment Targets: Gene Discovery for Autosomal Dominant Polycystic Kidney and Liver Disease”

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Autosomal Dominant Polycystic Kidney disease (ADPKD) is the most common form of genetic kidney disease. ADPKD causes both liver and kidney cysts and kidney failure develops on average by the sixth decade of life. Pharmacologic blockade of pathways implicated in cyst pathogenesis provides only a very modest delay of kidney failure. This drives our proposal to use genetic approaches in human cohorts to implicate yet unrecognized genes and pathways in cyst pathogenesis, which will serve as novel targets for treatment.

ADPKD is caused by mutations in PKD1 or PKD2, encoding the polycystin proteins, polycystin-1 (PC1) and polycystin-2 (PC2). A spectrum of more mild ADPKD or isolated polycystic liver disease are caused by mutations in genes necessary for the full function of PC1/PC2. The existence of this phenotype, for which seven established genes explain <50% of cases, represents a tremendous opportunity to use recent advances in rare variant genetic analysis to translate a human phenotype to critical scientific knowledge.

The specific aims of this proposal are (1) to discover novel disease genes for polycystic kidney and liver disease (PKD/PLD) through large-scale genetic analysis of a human phenotype, and (2) to clinically characterize patients with candidate genotype in an exome-sequenced health system. We have demonstrated feasibility of gene discovery from an existing cohort of 102 unrelated individuals with PKD/PLD. For this proposal, we will apply tested search terms to electronic health records to identify and perform whole exome sequencing on pre-enrolled patients with the PKD/PLD phenotype. We will compare the gene burden of deleterious alleles in our cases with expected counts and controls in order to bio-statistically implicate novel genes and pathways. We will extend the translational value of our discoveries through prospective genotype-initiated clinical characterization to validate and define critical bases for biological investigation and targets for human disease treatment.

**Aarti Bhatia, M.D., M.P.H. - 2019 Awardee**

*Department of Internal Medicine, Division of Medical Oncology  
Yale University*

“Single-Arm Phase II Trial of Dual Inhibition of EGFR with Afatinib and Cetuximab with Correlative Studies in the Treatment of Advanced Squamous Cell Cancers of the Head and Neck”

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The ErbB family of receptors is significantly upregulated in the vast majority of SCCHN and this correlates with poorer outcomes for these patients. Cetuximab is an ErbB1 (EGFR) antibody and is FDA approved in the treatment of SCCHN. High expression of ErbB3 is also shown to be significantly associated with increased tumor cell survival and growth potential and poorer overall survival in these patients and promotes resistance to EGFR blockade in SCCHN. Dual targeting of EGFR and ErbB3 is able to overcome resistance to cetuximab in human tumor xenograft models by enhancing anti-neoplastic effect via parallel signaling pathways. The combination of Cetuximab and ErbB3 antibody has also shown encouraging results in early Phase and “window-of-opportunity” trials in patients with advanced SCCHN. Induction/neo-adjuvant chemotherapy has therapeutic potential in patients with locally-advanced SCCHN where upfront definitive radiation or surgery isn’t feasible or is associated with critical organ loss (e.g. eye, larynx or tongue) and associated morbidity. Prognosis is poor for this subset of patients and there is an unmet need to improve on the response rates seen with previously tested regimens and select patients who will benefit from aggressive multi-modality therapy. We therefore propose a novel induction/neo-adjuvant regimen for structure preservation using chemotherapy, cetuximab and CDX-3379 in patients with locally advanced SCCHN, with the following specific aims:

1. To identify biomarkers of therapeutic response or resistance to ErbB-targeted therapies in SCCHN patient-derived tumor specimens and clinical trial samples.
2. To determine the clinical efficacy of chemotherapy + dual ErbB family blockade when used in the neo-adjuvant setting in patients with locally-advanced SCCHN.
3. Establish whether treatment with dual ErbB family blockade counteracts cetuximab resistance.

Biomarker analysis from patient-derived tumor samples on this study will help us better elucidate mechanisms of inter-dependence among members of this important oncologic signaling pathway.

**Krysten Bold, Ph.D.** - 2019 Awardee

*Department of Psychiatry  
Yale School of Medicine*

“Evaluating the Feasibility and Efficacy of a Real-Time Smoking Intervention Using Wearable Technology”

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Cigarette smoking is a significant public health problem and is the leading cause of preventable death. Most smoking quit attempts are unsuccessful, suggesting treatment innovations are critically needed. Wearable technology has the potential to enhance tobacco treatment by allowing for passive, automatic identification of smoking behavior that can be used to trigger a real-time intervention. The proposed project will be the first randomized controlled trial evaluating the feasibility and efficacy of a real-time smoking intervention using wearable technology as an adjunct to improve standard care smoking cessation outcomes. We will recruit 50 adult daily smokers from an outpatient tobacco treatment center to participate in an 8-week intervention. Participants will be randomly assigned to a control group (standard treatment, n=25) or experimental group (standard treatment plus real-time smoking intervention, n=25). All participants will receive a smartband that will passively, continuously monitor movement for the 8-week study. Only participants in the experimental group will receive real-time feedback as soon as smoking is detected. Treatment feasibility and acceptability will be assessed by rates of adherence wearing the smartwatch and patient satisfaction ratings. Treatment efficacy will be assessed by comparing smoking cessation outcomes between the control and experimental groups. Primary outcomes include comparing rates of 7-day point-prevalence abstinence between groups at the end of the intervention (week 8). Secondary outcomes include total number of days abstinent and changes in cigarettes per smoking day from baseline to the end of the study. Study findings will provide preliminary data about the feasibility and potential efficacy of this innovative approach to augment existing tobacco treatment and will provide the foundation for an R01 application. Ultimately, identifying effective technology-based interventions could provide a novel way to enhance the reach and effectiveness of tobacco treatment to improve public health.



**Christopher Bunick, M.D., Ph.D.** - 2019 Awardee

William O. Seery Foundation

*Department of Dermatology*

*Yale University*

“Development of First-in-class Anti-cancer Therapeutics Targeting Keratin Intermediate Filaments”

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Keratin intermediate filaments (KIFs) are commonly used as diagnostic and prognostic markers in tumor pathology. They are over-expressed in more than a dozen cancer types, including skin, breast, colon, liver, lung, pancreatic, and prostate cancers, and have been implicated in cancer cell metastasis. Our laboratory recently determined the first higher-order human keratin x-ray crystal structure: the keratin 1/keratin 10 helix 1B heterotetramer. The 1B subdomain is the critical region of keratin for initiating higher order KIF assembly (dimers to tetramers to protofibrils to 10-nm KIFs). Our crystal structure revealed a novel hydrophobic pocket-anchoring knob mechanism for KIF assembly that offers a new potential target for anti-cancer therapy. Thus, our overall goal is to develop keratin-specific therapeutics that disrupt cancer cell function (e.g. invasion, migration, immune evasion) and viability by directly inhibiting tetramer formation during KIF assembly. Preventing the formation of the KIF cytoskeleton is anticipated to have profound anti-cancer effect, and is analogous to the anti-cancer effect from taxanes and vinca alkaloids which disrupt microtubules. Specifically, we aim to develop two different types of therapeutics that bind into the hydrophobic pocket: small-molecule compounds and peptides. To identify small molecule inhibitors we will use a chemical library screening approach at the Yale Center for Molecular Discovery. To develop peptide inhibitors we will create a set of peptides around the anchoring knob and test for inhibition of tetramerization using light scattering and electron microscopy. Small-molecule and peptide inhibitors will be validated against human cancer cell lines using cell-based assays. The Patterson Trust Mentored Research Award will help this translational laboratory research develop and demonstrate efficacy of keratin-targeted anti-cancer therapies. Based on our work showing the hydrophobic pocket-anchoring knob mechanism of tetramer assembly is conserved across all type II IFs, we believe our anti-cancer strategy will be broadly applicable to multiple cancer types.

**Shelli Farhadian, M.D., Ph.D. - 2019 Awardee**

*Department of Medicine, Section of Infectious Diseases  
Yale University*

**“Central Nervous System Immune Activation During Virologically-Suppressed HIV”**

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Despite major advances in combination antiretroviral therapy (ART), adults living with HIV infection continue to suffer from the effects of long-standing viral infection and associated immune activation. Persistent immune activation in the central nervous system (CNS) during HIV infection has been linked to neurocognitive impairment. Indeed, the prevalence of neurocognitive disorders in adults with HIV remains unchanged in the ART era: an estimated 50% of adults with virologically suppressed HIV have some form of neurocognitive impairment. Understanding the cellular basis for persistent CNS immune activation is thus critical for reducing neurological morbidities in the growing population of adults with HIV on treatment. In Aim 1, we will use single cell transcriptomics and complementary techniques to analyze spinal fluid and blood from adult volunteers with and without HIV disease, to characterize novel or rare cell populations in the CNS during treated, suppressed HIV. In Aim 2, we will examine associations between immune cell subsets and markers of neuroinflammation, neuronal damage, and neurocognitive impairment. This study will define CNS immune activation in exquisite detail, including cellular populations that distinguish HIV infection during ART. This research has the potential to provide critical targets for therapeutic intervention for residual neurologic impairment during HIV treatment.

The investigator is a physician scientist, with specialized training in Neuroinfectious disease and a PhD in Neurogenetics. Her career goal is to become an independent investigator studying neurological sequelae of infectious diseases, with a special focus on neurological effects of HIV infection.

**Alicia Little, M.D., Ph.D.** - 2019 Awardee

*Dermatology*  
*Yale School of Medicine*

“Role of T Follicular Helper (Tfh) Cells in Chronic Cutaneous Lupus Erythematosus”

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Chronic cutaneous lupus erythematosus (CCLE) is a disfiguring autoimmune skin disease that causes permanent scarring, alopecia, hypopigmentation, and atrophy. No targeted therapies exist, and available treatments are often ineffective. CCLE may be skin-limited or may occur in the setting of systemic lupus erythematosus (SLE), a severe multiorgan autoimmune disease. The CCLE inflammatory infiltrate is predominantly T cells admixed with clusters of B cells, but studies of T-cell subsets in CCLE have been limited. The recently-identified T follicular helper (Tfh) cells provide essential help to B cells, promoting their selection and survival via co-stimulatory molecules and cytokine production. Tfh cells have been found to play a fundamental role in promoting pathogenic B-cell responses in autoimmune diseases including SLE. Tfh cells are found in the circulation and renal infiltrates of SLE patients and lupus-prone mice, with pathological Tfh-B cell contacts likely occurring in the kidney. Our preliminary data suggest the presence of Tfh cells in CCLE lesions. We hypothesize that Tfh cells play a critical role in the pathogenesis of CCLE, and in this proposal, we outline a strategy to elucidate this role using human tissue samples.

Our specific aims are to characterize cutaneous and circulating Tfh cells relative to other T-cell subsets in CCLE patients using single-cell transcriptomic and cytometric analyses. We will investigate T-cell cytokine signatures, surface molecules and transcription factor expression in lesional and non-lesional skin biopsies as well as in blood. We also aim to dissect the role of Tfh cells in the development of skin disease using a lupus mouse model that develops CCLE-like skin disease. Ultimately, we hope to achieve an understanding of the role of Tfh cells relative to other T-cell subsets in mediating CCLE, which would represent a critical step towards the development of targeted therapies for this devastating chronic autoimmune skin disease.

**Sherry Mansour, D.O.** - 2019 Awardee

*Internal Medicine, Division of Nephrology  
Yale University*

“Phenotyping Deceased Donor Acute Kidney Injury to Predict Recipient Outcomes”

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The growing number of patients on the kidney transplant waiting list and the relatively unchanging donor kidney pool raises the need for better organ utilization and allocation. Despite several studies showing the safe and effective use of kidneys from deceased donors with acute kidney injury (AKI), routinely defined by a single measurement of creatinine, up to 30% of AKI kidneys are discarded as compared to 18% of non-AKI kidneys. In an effort to better assess donor AKI kidney quality, we propose to utilize longitudinal data on donors using DonorNet database to better phenotype donor AKI by serial creatinine measurements. We will also use the largest multi-centered prospective deceased donor AKI cohort, known as Deceased Donor Study to adjudicate AKI etiology and measure novel urine repair biomarkers at time of organ procurement to further phenotype donor AKI. We will assess the role of deceased donor AKI phenotypes in predicting allograft failure and mortality as reported by United Network Sharing of Organs and Scientific Registry of Transplant Recipients. We hypothesize that phenotyping donor AKI by longitudinal creatinines, AKI etiology and novel repair biomarkers will better risk stratify donor AKI kidneys for allograft failure and mortality as compared to existing methods, which rely on a single creatinine measurement. This study will have vast clinical impact since; if our hypothesis is proven to be correct, it will provide a model to risk stratify donor AKI kidneys into those at risk for allograft failure versus survival. As a future direction, we will examine if this model will influence clinical decisions regarding kidney discard. We plan to randomize surgeons and clinicians involved in allocation decisions of deceased donor AKI kidneys to automated electronic medical alerts utilizing our derived risk predication model to evaluate its effect on discard rates.

**Mohamed Sherif, M.D., M.Sc. - 2019 Awardee**

*Department of Psychiatry  
Yale University*

**“An Electrophysiological Investigation of Mechanisms Underlying the Rapid Antidepressant Effect of Ketamine”**

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Ketamine is a breakthrough treatment for treatment resistant depression (TRD). Multiple clinical trials show the benefit of repeated doses of ketamine. However, ketamine presents a number of unmet needs including a limited duration of the antidepressant effect following termination of treatment, and low remission rates. This proposal aims to investigate the electrophysiological modifications associated with the antidepressant effect of repeated ketamine infusions as a first step in elucidating the neurobiological basis of ketamine’s antidepressant effect in patients. The long-term goal is to use this understanding to identify interventions that can prolong ketamine’s antidepressant effect and increase its remission rates.

Data from animal studies suggest that increasing synaptic plasticity underlie ketamine’s antidepressant effect after a single treatment. However, it is not clear how enhanced synaptic plasticity reduces depressive symptoms. Understanding the mechanisms underlying the connection between enhanced synaptic plasticity and improvement in depressive symptoms carry the potential to overcome the limitations of ketamine pharmacotherapy.

One possible mechanism that might underline the connection between enhanced synaptic plasticity and improvement in depressive symptoms is increased flexibility in changing behavioral responses when presented by different affective stimuli (affective flexibility). Neither changes in synaptic plasticity nor in affective flexibility following repeated ketamine infusions have been studied in patients.

We propose using electroencephalography (EEG) to assess electrophysiological modifications associated with 1) changes in synaptic plasticity, using long term potentiation (LTP), a standard form of synaptic plasticity, and 2) changes in affective flexibility, using an affective Go/NoGo EEG task, following a course of six ketamine infusions in patients diagnosed with TRD. EEG measures will be collected at two time points: before the beginning of the treatment and at the end of the treatment. Patients will be recruited from the ketamine clinic at the VA Connecticut Healthcare System.

**Juan Vasquez, M.D.** - 2019 Awardee

*Pediatric Hematology/Oncology*  
*Yale University*

“Leveraging Oncometabolite-Induced DNA Repair Defects for Immunotherapy Sensitization”

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Immune checkpoint inhibitors are a promising new cancer therapy, but only a subset of patients will respond. Tumors with a high number of mutations and more infiltrating immune cells are more likely to respond, but most cancers are non-inflamed with a low number of mutations. Our lab recently discovered that neomorphic mutations in isocitrate dehydrogenase-1 and -2 (IDH1/2) result in accumulation of 2-hydroxyglutarate (2-HG), which induces homologous recombination (HR) defects and confers exquisite sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. These findings subsequently were extended to two structurally related oncometabolites, fumarate and succinate. Collectively, these findings reveal a novel pathway by which tumors acquire an HR-defective phenotype. Therefore, we hypothesize that oncometabolite-induced DNA repair defects can be exploited with PARP inhibitors to sensitize tumors to immune checkpoint inhibitors. In Aim 1, we will profile the immune landscape of oncometabolite-producing tumors to test whether we can detect baseline evidence of immune activation. In Aim 2, we will perform a series of cell line studies to test whether oncometabolites induce elevated levels of mutation rates and consequent neoantigen formation, either alone or after treatment with PARP inhibitors. Finally, in Aim 3, we will correlate these data with studies of specimens from an ongoing trial testing the efficacy of the PARP inhibitor, olaparib, in IDH1/2-mutant tumors.

**Chongguang Yang, Ph.D.** - 2019 Awardee

*Yale School of Medicine*

“The Role of Internal Migration in the Transmission Dynamics of Multidrug-Resistant Tuberculosis in Urban China”

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Global targets for tuberculosis (TB) control established by the World Health Organization and the United Nations cannot be met without achieving major gains in high-TB burden countries like China, which currently ranks third in estimated incidence of TB and second in the estimated incidence of multidrug-resistant TB (MDR-TB). Two major challenges to improved TB control in China have been recognized: (1) the emergence and spread of MDR-TB and (2) internal population movement of individuals from high TB incidence western and central rural provinces to eastern urban centers where TB notification rates have been substantially lower.

Currently, only a small minority (<10%) of estimated MDR-TB cases are detected and effectively treated in China and rural-to-urban migrants experience serious structural barriers when attempting to access health care services in cities. Our preliminary research has revealed that primary transmission of MDR-TB is now the dominant mechanism driving the incidence of MDR-TB disease and we have also documented how recent patterns of rural-to-urban migration have affected the transmission dynamics in highly-populated, dense urban centers in eastern China.

In this project, we will build on previous work to understand where and amongst whom MDR-TB is being transmitted in Shanghai, a large eastern city in which greater than 40% of the population has migrated from high TB incidence rural provinces. We will conduct a population-based study of all diagnosed cases of MDR-TB in Shanghai. This study will have both retrospective (2009-2017) and prospective (2018-2020) components and will include approximately 800-900 individuals diagnosed with MDR-TB. The objective of this study will be to understand the key drivers of urban MDR-TB transmission by using cutting-edge phylogenetic and spatial analytic methods to identify host- and pathogen-specific determinants of transmission and to formally assess how recent patterns of rural-to-urban migration have affected the transmission dynamics of MDR-TB.