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"

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

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echanisms that impact clinical and

and have a history of SV. Identifying

oid outcomes also represents the first

mprove 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"

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(g)-7. (a)-8 (se)-4,r1.78 (lly,U)-1s16d97 (u)3.6 hig

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"

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

Stephanie Wemm, Ph.D. - 2023 Awardee

Department of Psychiatry
Yale University

"Investigating Real-world Stress-related Mechanisms In Heavy Cannabis Users"

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 cannabisrelated contexts in their day-to-

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"

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-

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”

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 d evelopmental 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-progrl 9.759 (e i[(t)3.6.4 (e)-1 (l)-2.1 [(p)-5.4 (r)-6.6 me)-6.9 (t)-3.3(he)-7 (r)-6.6 (i)-14.2 (f)-8.3 (a)-

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

School of Nursing
University of Connecticut

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Patrick Cudahy, M.D. - 2022 Awardee

Department of Medicine, Section of Infectious Diseases

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

Pathology
Yale University

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

My goal is to perform research focused on the molecular mechanisms underlying dysregulation in immune interactions associated with neurodegenerative and neuropsychiatric disease. The

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

Department of Neurology, Tc 0 Tw Tc 0 Tw Tc 0 Tw Tc 0 Tw

Garrett Ash

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"

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"

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"

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]EKAP 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"

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 xenobiy uics.[h 6n.8 (b)-3.1.3 (y a4 (D)-1n5 (t)-1.3 (h)6

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"

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 w ill 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 hypertensione (i)4.i4. We wit6 (r)-4.6 (y r(y w)0.7(a)-3 (10 (bl)0.5 (a.7(a)-3 (f e (en)6re4.9 -4.9 (7y,)-5 if)-6..5 (t)3.7 (en)

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"

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

Stephanie Kerrigan , Ph.D. - 2021 Awardee

Psychiatry
Yale School of Medicine

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

Physical activity is a critical health behavior for all adults. In particular, individuals at high risk for health complications, including those with overweight/obesit y 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.lbngb.3 (io)1ncy ose aysicac de a(g)-2.2 (.)-7icn (y 14)1.9 c 0.0[lbsicly. D()-8.3

Brienne Miner , M.D. - 2021 Awardee

Geriatrics
Yale School of Medicine

"Evaluating Poor Sleep Quality in Persons with Advanced Age"

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

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"

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

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”

Patients with type II diabetes mellitus (0 Tc 0 Tw r(e)]TJ .9 (t)-13 0.004 Tc -0.0C -0.00215.3 (sdCTj 0.)-13.3 dTi(sdCTj5 (s

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"

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"

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 cces,enro(i)-12.6 ()-3.4 (e)-4n3 (h)-107 (it)-13.1 (a)-8 (n)1.7 (d)-5.4 (la)-8 (t)-1-8 (t)-1.9 (r)-4.t2 (O)-1i.2 (o)1.8 (n)17 (s.)-T

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

Department of Nephrology
Yale University

“Pathways Mediating Renal Lymphocyte Survival in Hypertonic Conditions”

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

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"

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

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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atments 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"

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 CHA2DS2VASc 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

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"

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

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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"

Emergency departments (EDs) are facing increasing numbers of mental health visits, with 1.7 million associated episodes of patient agitation occurring annually in a

Anika Anam, M.D. -

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

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

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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"

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-

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"

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

Sherry Mansour , D.O. - 2019 Awardee

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"

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

Juan Vasquez, M.D. - 2019 Awardee

Pediatric Hematology/Oncology
Yale University

"Leveraging Oncometabolite-Induced DNA Repair Defects for Immunotherapy Sensitization"

Chongguang