Anika Anam, M.D. - 2019 Awardee
Department of Internal Medicine - Section of Endocrinology
Yale School of Medicine

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

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/m2) 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"

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
Department of Epidemiology of Microbial Diseases
Yale School of Public Health

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

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"

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 cause 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

"Predictive Biomarkers of Response to Human Epidermal Growth Factor Receptor-3 (HER3) Blockade in Patients with 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-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"

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 of the William O. Seery Foundation Award
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 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"

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 neuinfammation, 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"

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"

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"

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"

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
Department of Epidemiology of Microbial Diseases
Yale School of Public Health

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

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.