

**Patterson Trust Mentored Clinical Research Awards
and William O. Seery Foundation Clinical Research Award for Cancer Research
2017 Award Recipients**

• **Lynnette A. Averill, Ph.D.**

Associate Research Scientist / Clinical Research Psychologist

Department of Psychiatry, *Yale University*

Clinical Neurosciences Division, National Center for PTSD, VA Connecticut

“Connectivity Networks Underlying Ketamine–Induced Improvements in Suicidal Ideation”

Key Words: Suicidal Ideation, Ketamine, PTSD, Neurobiology, Connectivity

This innovative, multidisciplinary proposal is the first to implement state-of-the-art neuroimaging methods; novel, data-driven Coupled Intrinsic Connectivity Distribution Analysis (Coupled-ICD); and advanced clinical assessment to demonstrate sustained ketamine-induced improvements in suicidal ideation (SI; aim 1) and confirm functional connectivity normalization post-treatment in posttraumatic stress disorder (PTSD; aim 2). This proposal capitalizes on a large ongoing randomized double-blind clinical trial ($n=198$) of Veterans with treatment-resistant PTSD. In the parent trial the study drug will be administered twice/week for 4-weeks under one of three parallel treatment conditions (intravenous placebo, 0.2 mg/kg ketamine or 0.5 mg/kg ketamine infused over 40 minutes). In the proposed add-on study, 45 Veterans ($n = 15$ per dosing condition) will complete three evaluation sessions (baseline, 24-hours post-1st infusion and post-last infusion) that include state-of-the-art rs-fcMRI studies, SI and symptom inventories, and a brief neuropsychological battery as evidence suggests SI may be related, at least in part, to impaired cognition and cognitive control. The randomization schema will be adapted to stratify randomization on consent to participate in this separate study so as to insure that 15 subjects per treatment arm can be achieved. The rapid effects of ketamine on functional connectivity provide a unique paradigm to examine the underlying neurocircuitry relative to suicidal ideation. Coupled-ICD offers increased power for detecting changes in connectivity pre/post-intervention. Equally important, this paradigm also allows us to look beyond the general antidepressant effects of ketamine to evaluate the potential for specific rapid reductions in suicidal thinking, advancing our understanding of SI in PTSD and its relationship to connectivity, informing novel drug development and psychosocial treatment interventions, and having significant positive implications for improved outcomes in PTSD and other psychiatric disorders including depression and schizophrenia, devastating illnesses afflicting millions of individuals worldwide.

- **Kumar Dharmarajan, M.D.**

Assistant Professor of Medicine (Cardiology)

Department of Internal Medicine

Yale School of Medicine

"Recovery after Cardiopulmonary Hospitalization: The REACH Study"

Key Words: Health Status, Function, Mobility, Symptoms, Quality of Life, Hospital Care, Geriatrics

Improvement in health status, including function, mobility, symptoms, and health-related quality of life, is increasingly considered a primary goal of health care. Yet little data exist describing detailed trajectories of recovery in health status in the month after hospitalization. Moreover, no studies have examined if common experiences related to hospitalization, including sleep disruptions, immobility, frequent orders to fast, and high levels of ambient light and sound, impair health status recovery after hospital discharge.

Our objective is to perform a pilot study describing variable trajectories of recovery in health status within the first month after hospitalization and the relationship of common hospital experiences with health status recovery. We will enroll 50 patients ≥ 65 years-old hospitalized with the most common acute diagnoses, characterize their exposure to adverse hospital experiences, and track health status recovery at 1, 2, 3, and 4 weeks after discharge. We will use daily interviews and state-of-the-art technology to assess sleep quality, mobility, periods of forced fasting, and levels of ambient light and sound during hospitalization.

We hypothesize that health status recovery will occur variably across patients and that different domains of health status (function, mobility, symptoms, and health-related quality of life) will have variable recovery patterns with respect to one another. We also hypothesize that more frequent sleep disruptions, greater immobility, more fasting orders, and higher levels of ambient light and sound while hospitalized will trend with lower health status 1 week after hospital discharge.

This pilot will be the first to characterize patients' diverse experiences of recovery in health status in the month after hospitalization and the relationship of common hospital experiences with health status. This foundational work will guide future research and help develop targeted interventions to improve patient-centered outcomes, including efforts to make the experience of hospitalization more humane and recovery more complete.

- **Jessica Hollenbach, Ph.D.**

Assistant Professor of Pediatrics

Connecticut Children's Medical Center

"Interrogating the Placental Microbiome among Pregnant Women with Asthma"

Key Words: Asthma, Placenta, Microbiome, Chronic stress

Asthma affects 6.3 million children in the US and is the leading cause of school absenteeism, hospitalizations and Emergency Department visits. Asthma disproportionately affects low income children and children of color. The origins are unknown but rates are rising rapidly and the familial frequency suggest gene by environment interactions. The in utero environment has been implicated in asthma pathogenesis; studies suggest a role for the changing exposure to microbial environments prenatally in the rapid rise in disease prevalence. During pregnancy, the placenta is the maternal-fetal interface. This study will examine how pregnancy complicated by maternal asthma influences the placental microbiome.

Recent studies have described a placental microbiome and exposure to microbes via the placenta may prepare the immune system for the surge of bacteria experienced after delivery. Whether a differential bacterial community resides in the placenta of pregnant women with asthma compared to those without asthma is unknown. We hypothesize that the placentas from pregnancies complicated by maternal asthma will contain a microbiome dominated by species that predispose the fetus to asthma and allergy. We will examine Hispanic and African American, low-income pregnant women with asthma and women without asthma. We will also examine an important modifier of the association between maternal asthma and the microbiome, prenatal psycho-eco-social stress (PESS), a salient exposure among low-income, minority women. The specific aims of this study are: (1) To characterize the placental microbiota of pregnant women with and without asthma and (2) to determine whether prenatal PESS alters the association between maternal asthma and placental microbiota. This study will contribute significantly to literature on the role of the microbiome in disease development and will be used as preliminary data for a larger study to examine the effects of chronic stress on risk for adverse health outcomes in offspring including asthma, atopy, and obesity.

- **Emily McDonald, Ph.D.**

Assistant Professor (Research) of Pediatrics

Department of Pediatrics; Center for International Health Research

Rhode Island Hospital

"The Impact of Maternal Alcohol Consumption on the Placenta Microbiome"

Key Words: Microbiome, Placenta, Alcohol

Alcohol consumption during pregnancy is known to place the infant at risk for impaired neurocognitive development. The impact of alcohol is also increasingly appreciated for leading to a wide range of developmental and growth delays, collectively known as fetal alcohol spectrum disorders (FASD). The overall goal of this proposal is to explore the impact of maternal alcohol consumption on the placental microbiome as a means to identify potential mechanisms by which moderate alcohol consumption during pregnancy may have more nuanced effects on the health of the placenta and consequent birth outcomes. We will specifically evaluate the impact the placental microbiome has on fetal growth in utero. Aim 1 of this proposal will examine the impact maternal alcohol, measured by self-report and blood PEth testing, has on the composition and overall abundance of the microbial community at the maternal-fetal interface. The microbiome will be assessed through the use of 16SrRNA sequencing and whole genome shotgun approaches. Aim 2 of this proposal will use statistical Path Modeling to examine the role of the placental microbiome in the causative pathway linking various degrees of maternal alcohol consumption to fetal growth restriction and birth weight. Completion of this study will be the first to identify a link between maternal alcohol use and the placental microbiome. By exploring these hypotheses we will be able to better identify at risk infants early on in gestation, enhancing pre and antenatal care for those infants affected.

- Dennis Moledina, MBBS

Postdoctoral Associate

Department of Medicine (Nephrology)

Yale School of Medicine

"Early Non-invasive Diagnosis of Human Acute Tubulo-Interstitial Nephritis (AIN) with Cytokines Representing T-helper Cell Pathway"

Key Words: Acute interstitial nephritis, Biomarker, Kidney biopsy, Inflammation

Acute tubulo-interstitial nephritis (AIN) is a common cause of acute kidney injury. If recognized early, AIN is treatable. However, since AIN has no typical clinical feature or non-invasive diagnostic biomarker, AIN diagnosis is extremely challenging and relies on a high index of suspicion that requires confirmation by a kidney biopsy. Delay in AIN diagnosis results in increased kidney fibrosis and progression to chronic kidney disease. A noninvasive AIN biomarker will improve patient outcomes by early diagnosis and management.

Since AIN diagnosis can only be made on a kidney biopsy, biomarker discovery requires a human biopsy-based cohort. However, the current evidence in AIN is from retrospective registries and no biomarkers have been systematically evaluated in AIN. We are enrolling participants in a prospective cohort study with the aim of discovering non-invasive AIN biomarkers. We enroll patients undergoing a kidney biopsy with rise in serum creatinine. As of June 2016, we have 148 participants who have donated plasma and urine samples. Of these, 27% have AIN on clinical pathology reads.

In aim 1, three renal pathologists will adjudicate kidney biopsy slides and establish a "gold standard" AIN diagnosis. We will also collect renal interstitial histologic features using a standardized data collection tool and develop an AIN histology score based on the predictive value of these interstitial features to diagnose adjudicated AIN.

In aim 2, we will test plasma and urine samples to discover biomarkers of AIN. Since prior studies show that the majority of cells infiltrating the interstitial space in AIN are CD4+ cells, we will test samples for selected cytokines involved in CD4+ T-helper cell pathway. These cytokines were obtained from literature review of preclinical and clinical data in AIN, and include IFN- γ , TNF- α , IL-4, IL-5, and IL-17.

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• **Sarah Moughalian, M.D.**

Assistant Professor of Medicine
Department of Medical Oncology
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"Improving Adherence to Endocrine Therapy in Breast Cancer Using Mobile Technology"

Key Words: Breast Cancer, Adherence, Endocrine Therapy, Hormone Therapy, Estrogen Receptor, Hormone Receptor, Medication Adherence, Text Messaging, Mobile Application, MHealth

Background: The standard of care (SOC) for stage I–III hormone–receptor positive breast cancer (BC) includes 5–10 years of endocrine therapy (ET). It is estimated that up to 40% of women in the United States are not adherent to ET or discontinue the medication prior to 5 years; non-adherence and early discontinuation may contribute to BC recurrence.

Innovation: We have developed a bidirectional intervention of system-generated text messages and patient responses. Patients receive: (1) medication reminders, (2) messages about side effects (SEs) and severity, and (3) messages about barriers to taking medication; patients respond directly to each message using a mobile device. Not only do we collect real-time actionable adherence data, but we also assess SEs and barriers to adherence. For missed doses or more severe SEs, triage nurses are alerted to contact patients directly, and for less severe SEs, patients are provided with an educational and a phone number for assistance. Patient-reported barriers to adherence are also addressed in real time. We have tested this intervention in a 100-patient pilot study in which patients found the intervention helpful and easy to use.

Approach: We propose a phase II randomized control clinical trial to assess ET continuation after one year of ET in 400 patients with stage I–III HR positive BC. The intervention group will receive SOC follow-up plus the intervention; the control group will receive SOC follow-up alone. The primary endpoint is continuation rates at one year in both arms. Secondary endpoints include adherence to ET, quality of life, financial burden, and trends of discontinuation and adherence over time.

Significance: This is the first prospective randomized trial of a bi-directional text messaging intervention that addresses adherence, SEs, and barriers to medication adherence in breast cancer. We hypothesize that continuation rates will be at least 10% higher in the intervention arm.

• **Jessica Nouws, Ph.D.**

Postdoctoral Associate

Department of Pediatric Endocrinology

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"Insulin Resistance of Adolescent Obesity: Role of Inflammation and Fat Storage Capacity"

Key Words: Insulin Resistance, Obesity, Type 2 Diabetes, Inflammasome, Fat patterning

By investigating key alterations in metabolic pathways leading to the pathogenesis of insulin resistance (IR) in adolescent obesity, our group described a "distinct endophenotype" in obese adolescents characterized by a thin superficial layer of abdominal subcutaneous adipose tissue (SAT), increased visceral adipose tissue (VAT), marked IR, inflammation, and fatty liver. To further gain insight into this endophenotype, we began to unravel the cellular/molecular mechanisms associated with this phenotype and its relations to IR. We demonstrated a key role of "impaired subcutaneous abdominal adipogenesis" in the pathogenesis of IR in obese adolescents supporting the hypothesis that the ability to retain fat in the subcutaneous depots seems to be associated with decreased VAT, reduced ectopic fat deposition, and a more favorable metabolic profile.

These findings lead to 2 major hypotheses: Hypothesis 1: Increased transcription of key inflammasome genes translate into higher activity of the inflammasome machinery (transcription and activation of caspase-1) in both abdominal and gluteal SAT depots of obese adolescent girls with different patterns of AT distribution, thereby contributing to IR. Hypothesis 2: The storage capacity of gluteal SAT is a determinant for the level of VAT/SAT fat distribution in obese adolescents. Approach: In two groups of obese adolescent girls with similar overall body fat but with an altered pattern of body fat distribution we will measure the activation of caspase-1 protein and expression of its downstream targets. We will employ the novel method of $^{2}\text{H}_2\text{O}$ to quantify *in vivo* triglyceride synthesis, and adipocyte proliferation. This will be combined with measures of adipocyte size distribution, gene expression, regional fat distribution, and measures of insulin sensitivity in obese adolescents with a high VAT/SAT ratio compared to an age and pubertal stage matched group with a low VAT/SAT ratio. The studies outlined here will provide a better understanding of IR in adolescent obesity.

• **Nikhil Singh, M.D., Ph.D.**
Postdoctoral Research Fellow
Department of Nephrology
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“Cellular and Molecular Characterization of Human Acute Kidney Injury”

Key Words: Acute Kidney Injury, Acute Tubular Injury, Mass cytometry

Acute kidney injury (AKI) is a significant cause of morbidity and health care expenditure, and an important risk factor for the development of chronic kidney disease. In spite of our knowledge of its importance- and our increasing adeptness at early diagnosis of AKI- no treatments exist for acute tubular injury (ATI, the most common form of AKI in hospitalized patients). This lack of therapeutic options stems largely from significant gaps in our knowledge about the pathophysiology of human ATI. While several useful mouse models exist and have furthered our knowledge of the interplay between murine tubular cells and the immune system during injury and repair, little analogous work has been done to explore the biology of the acutely injured human kidney.

We propose experiments to define the cell types comprising the normal and injured human kidney, precisely delineate their spatial relationship, and further describe the activation state of these cells during homeostasis and injury. To this end, we will first develop a monoclonal antibody panel to accurately identify the individual cell types in normal human kidney biopsy samples, including markers of tubular cells, fibroblasts, and immune cells. Mass cytometry uses time-of-flight mass spectrometry to simultaneously identify dozens of markers in a cell population, and Yale has obtained an imaging mass cytometer that will allow us to use this powerful technology in human tissue sections. After defining and validating our antibody panel, we will use imaging mass cytometry to determine the populations and activation states of cell types in the normal kidney. Finally, we will perform identical analysis on human ATI samples, and create the first ever spatially-preserved cellular profile of human ATI. These experiments comprise critical steps towards investigating the biology of the acutely injured human proximal tubule – an area of great importance as we strive to develop therapeutic targets for AKI.

- **Samuel Wilkinson, M.D.**

Postdoctoral Research Fellow
Department of Psychiatry
Yale School of Medicine

"Examining the Efficacy of Cognitive Behavior Therapy to Sustain the Antidepressant Effects of Intravenous Ketamine"

Key Words: Ketamine, Cognitive Behavior Therapy, Major Depressive Disorder, Neuroplasticity

Ketamine has generated considerable excitement as a rapid-acting antidepressant, yet legitimate concerns about safety exist, especially given the lack of long-term data of repeated dosing. Based on promising pilot data we have collected, we propose to examine the efficacy of cognitive behavior therapy (CBT) to sustain ketamine's rapid and powerful antidepressant effects. Our rationale for using the combination of ketamine and CBT derives from ketamine's ability to induce neuroplasticity and the potential of CBT to harness such a state to produce lasting positive changes in neuro-circuitry that may be associated with remission and recovery from depressive symptoms.

Patients with treatment-resistant depression will be treated with open-label ketamine (0.5mg/kg intravenous, 6 total treatments given twice weekly). Those who achieve clinical response (50% reduction in depressive symptoms compared to baseline, per depression ratings) will be randomized to CBT (16 sessions) or medication management with non-directive supportive therapy (control). Twenty-eight patients will be randomized; to achieve this target enrollment for randomization, we expect to enroll 40 patients. Depression severity will be assessed weekly using the Montgomery-Asberg Depression Rating Scale (MADRS). By convention, relapse is defined as <50% improvement over baseline in MADRS ratings for 2 consecutive visits.

As a proxy of enhanced learning and neuroplasticity, patients will also undergo cognitive tasks (assessing executive function and working memory, representing cognitive flexibility). The primary specific aim of this project is to evaluate the efficacy of concurrent ketamine and CBT to sustain antidepressant effects of ketamine. The primary outcome will be group differences in relapse rates at 4, 8, and 12 weeks following final ketamine exposure. Secondary aims will explore the delayed effects (12–72 hours following exposure) of ketamine on learning and memory and the impact that ketamine-induced changes in cognition may have on efficacy of CBT to maintain antidepressant response.