

## Patterson Trust Fellowship Program in Clinical Research 2016 Award Recipients

- **Damion Grasso, Ph.D.**

Assistant Professor of Psychiatry and Pediatrics  
*University of Connecticut Health Center*

“Maternal Exposure to Violence, Pregnancy and Birth Outcomes, and Stress-Related Epigenetic Risk”

Key Words: Violence, Pregnancy, Stress, Epigenetics

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Emerging evidence implicates maternal exposure to interpersonal trauma with adverse child outcomes, a process hypothesized to begin during the prenatal period. These maternal factors may influence mothers' experience of stress and ability to regulate emotions during pregnancy. In turn, this may give rise to an intrauterine environment with the potential to modulate development of key physiological stress systems and serve an etiologic role in emergent psychopathology, which can have cascading effects across the lifespan. Research recognizes stress-related epigenetic processes as critically involved in these prenatal risk mechanisms and several candidate genetic loci have been identified. One promising candidate gene is FKBP5, a critical component of a negative feedback loop functioning to terminate the stress response at the cellular level. In adults, a common FKBP5 polymorphism has been shown to interact with retrospectively reported childhood trauma to increase glucocorticoid resistance and stress reactivity and risk for psychopathology. Further, epigenetic findings suggest that early life trauma exposure and the risk genotype interact to reduce DNA methylation of FKBP5, producing relative cortisol insensitivity, which then compromises the negative feedback loop. Although these epigenetic changes are hypothesized to depend on sensitive periods in early childhood, they have not yet been examined in children. Studying infants of mothers exposed to trauma may elucidate these epigenetic processes, which may play a key role in initiating an adverse biobehavioral cascade to psychopathology. The proposed study involves a pregnancy cohort and focuses on three primary aims: To examine whether maternal exposure to interpersonal violence is associated with (1) known prenatal risk factors (i.e., psychopathology, tobacco, alcohol and drug use, perceived stress, co-occurring life stressors) and birth outcomes, and (2) stress-related epigenetic changes in FKBP5 (i.e., demethylation), and (3) whether these relationships are moderated by the timing of mothers' exposure to interpersonal violence (i.e., childhood, adulthood, during pregnancy).

- **Carolyn Greene, Ph.D.**

Assistant Professor, Department of Psychiatry  
*University of Connecticut Health Center*

“The Role of Parental Emotion Regulation in Evidence-Based Treatment for Children with PTSD”

Key Words: PTSD, Children, Parents, Emotion Regulation, Treatment

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Early detection and intervention with traumatized children is essential in order to prevent PTSD from undermining healthy development (D'Andrea et al., 2012) and becoming a debilitating lifelong impairment and threat to physical as well as mental health (Anda et al., 2010). Parents can play a crucial role in enhancing the effectiveness of PTSD prevention or therapeutic interventions. However, parents also experience severe secondary traumatic stress when their child has been traumatized, and may have trauma histories of their own. Resulting parental stress reactions and depression may inadvertently contribute to their traumatized child developing PTSD (Morris, Gabert-Quillen, & Delahanty, 2012; Trickey et al, 2012). Conversely, when parents are able to provide emotional support and security in the wake of trauma, a traumatized child is more likely to be resilient to or recover from PTSD. The proposed study is designed to address a crucial gap in the treatment of traumatized children by providing an empirical test of the potential mediating role that parental emotion regulation may play in the child's development of PTSD or in enhancing the child's recovery from PTSD. The study will examine (1) the mediating roles of parental emotion regulation and parents' ability to provide emotional support and security to their traumatized child ("emotion socialization") in the association between parental trauma history and traumatic stress reactions and the severity of traumatized children's PTSD symptoms; and (2) the mediating role of parents' participation in treatment in the association between parents' emotion regulation and the ability of evidence-based PTSD therapy to enable children to recover from PTSD. Data will be collected from parents, teachers, and child clinicians at the outset of TF-CBT in order to test the first hypothesis, and follow-up data will be collected from child clinicians at the completion of TF-CBT to test the second hypothesis.

- **Caitlin Hansen, M.D.**

Associate Research Scientist, Department of Pediatrics  
*Yale School of Medicine*

“Development of a School-Based Health Center HPV Vaccination Intervention”

Key Words: Human Papillomavirus, Human Papillomavirus Vaccine, Adolescent,  
School-Based Health Center

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Human papillomavirus (HPV) is a common sexually transmitted virus that can lead to six types of cancer (of the cervix, oropharynx, anus, penis, vagina, and vulva) and genital warts. Vaccines that protect against HPV infection are safe, effective, and recommended for routine use in adolescents, but remain underutilized: nationwide, only 40% of girls and 22% of boys completed the three-dose vaccination series in 2014. In contrast to the US experience, countries with high HPV vaccination rates have achieved this success largely through school-based vaccination. Expanding vaccination through use of school-based health centers (SBHC) in the US could help improve uptake. We previously conducted formative work with parents and adolescents to assess perceptions of a potential SBHC intervention to increase uptake of HPV vaccination, which participants found to be acceptable. Now, we will develop and pilot test a HPV vaccination intervention to increase completion rates of HPV vaccination by using SBHCs in New Haven, Connecticut. The current proposal will take a systematic approach to intervention development and implementation by 1) assessing baseline rates of school-based HPV vaccination in New Haven, CT; 2) developing and implementing an intervention to optimize the use of SBHCs to complete the 3-dose HPV vaccination series in New Haven, CT adolescents; 3) evaluation of the intervention, specifically for feasibility, acceptability, and effectiveness. Outcomes will include: ability to enroll participants in the school-based HPV vaccination intervention, acceptability of the intervention assessed via qualitative follow-up interviews, and HPV vaccine series completion rates (compared to baseline). While the potential benefits of SBHC-located HPV vaccination are great, limited data exist on how SBHCs can be used to promote HPV vaccination. Improved HPV vaccination coverage will help maximize the full preventive potential of vaccines in reducing HPV infections, HPV-related cancers, and their associated morbidity and mortality.

- **Kelly Hawley, Ph.D.**

Postdoctoral Research Fellow, Department of Pediatrics  
*University of Connecticut Health Center*

“Elucidating Innate and Adaptive Immune Interplay in Human Syphilis.”

Key Words: Syphilis, Macrophage, Lymphocyte, Laser Capture Microdissection, RNA Sequencing

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Syphilis, a multi-stage sexually transmitted disease caused by the spirochetal bacterium, *Treponema pallidum* (Tp), is a major global health concern. The World Health Organization estimates that approximately 10.6 million new cases of syphilis occur annually worldwide. It is generally accepted that the clinical manifestations associated with syphilis are a direct result of the host inflammatory response. Syphilitic lesions consist of a complex cellular infiltrate of CD4+ T cells, CD8+ T cells, Natural killer cells and macrophages. Studies with an ex vivo model demonstrate that human macrophages are able to phagocytose Tp in the presence of opsonic antibodies elicited during syphilitic infection and that interferon-gamma dramatically enhances the macrophage's opsonophagocytic capacity and its ability to secrete proinflammatory cytokines following internalization and degradation of spirochetes. These results imply that both spirochetal clearance and generation of tissue-damaging inflammation depend upon interactions between the innate and adaptive arms of the immune system at the site of infection. Our long-term objective is to elucidate these complex interactions in situ in humans. To accomplish this objective, we have formulated Specific Aims in which we will investigate the immunophenotypes and transcriptomes of (i) macrophages and (ii) lymphocytic subpopulation in skin biopsies from secondary syphilis patients seen at our translational research study site in Cali, Colombia. Immunophenotyping will be done by immunohistochemical and immunofluorescence analysis. For transcriptional analysis, individual cell subpopulations will be isolated by laser capture microdissection followed by deep RNA-sequencing (RNAseq). Over the years, we have shown that animal models of syphilis poorly replicate the cellular immune response that occurs in humans. Because these studies are performed in humans, the information they provide will be of unquestioned relevance to the clinical setting.

- **Tae Kon Kim, M.D., Ph.D. (Seery Foundation Fellow)**  
Clinical Fellow, Department of Hematology/Oncology  
*Yale University*

“Overcoming Immune Evasion in Acute Myeloid Leukemia (AML) with DNA Methyltransferase (DNMT) Inhibition and PD-1H Blockade”

Key Words: Acute Myeloid Leukemia, Immune Evasion, Immunotherapy, PD-1H

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The goal of immunotherapy in cancer is to enhance the ability of the immune system to recognize and eradicate malignant cells. Although immune checkpoint blockade has been successful in some solid tumors, its use in hematologic malignancies such as acute myeloid leukemia (AML) has been hampered by poor immunogenicity and may be due to epigenetic silencing of immunologic antigens and co-stimulatory ligands. Additionally, while much attention has been focused on PD-L1, it is unknown whether other co-inhibitory pathways might also contribute to immune evasion, especially in patients who are resistant to current checkpoint blockades. Programmed death-1 homolog (PD-1H) is a novel co-inhibitory molecule that is predominantly expressed in hematopoietic cells but its role in conferring immune tolerance in cancer, including AML, is unknown. We hypothesize that PD-1H co-inhibitory signaling along with epigenetic silencing of co-stimulatory molecules induces immune evasion in AML. To achieve our long-term goal of developing an immunotherapeutic approach for the management of AML, our specific aims are to: 1) investigate whether a DNMT inhibitor (DNMTi) can enhance immunogenicity against murine AML; 2) determine whether a DNMTi can enhance antigenicity against murine AML; and 3) evaluate whether combination PD-1H blockade and DNMT inhibition confers a synergistic effect to control AML progression. Immunogenicity will be assessed by studying secondary engraftment of AML cells into mice that have been immunized with AML cells treated with a DNMTi. Ex vivo analysis of proliferation and cytotoxicity of T cells from DNMTi treated mice against DNMTi treated AML cells will be done to measure antigenicity. Subsequently, in vivo proliferation of AML cells will be evaluated in PD-1H knock-out mice with and without DNMTi treatment to demonstrate a synergistic effect with PD-1H blockade. These studies will provide a pre-clinical foundation for developing novel combined immune checkpoint blockade/epigenetic approaches for the treatment of hematologic malignancies.

- **Kevin Manning, Ph.D.**

Assistant Professor of Psychiatry

*University of Connecticut Health Center*

“Physical Mobility and Driving in Subjective and Mild Cognitive Impairment”

Key Words: Aging, Automobile driving, Mild Cognitive Impairment, Subjective Cognitive Impairment, Postural stability, Gait, Activities of Daily Living.

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Decline in cognition, vision, and motor functioning increase unsafe driving in older adults. Impairment in physical mobility and executive functions are the strongest predictors of on-road performance in older healthy drivers and those with mild cognitive problems. Common vascular risk factors in the elderly (e.g., hypertension) are associated with deterioration in executive and physical functioning and increased risk of later dementia diagnosis. More research is needed to understand how earlier-stage cognitive impairment and sensitive measures of physical disability are associated with driving performance in older adults with vascular disease who are at risk of future cognitive and functional decline. We recently used driving simulation to examine intersection approach speed in 8 drivers with subjective cognitive impairment (SCI), who performed in the average range on neuropsychological tests and did not meet criteria for mild cognitive impairment (MCI), and 10 healthy control participants (HC). Compared to HC, SCI participants engaged in behavior associated with a higher probability of accidents. These pilot data did not include physical mobility measures and the association between physical disability, predementia, and driving has not been investigated. The primary aim of this study is to investigate the effect of physical mobility in conjunction with cognitive status on driving behaviors in HC and adults with predementia (SCI, MCI). Statistical analyses will include normal regression models investigating effects of group (HC, SCI, MCI), gait speed, and group by gait speed interaction on three driving performance variables associated with increased accident risk (intersection approach speed, significant deceleration, and premature stopping) at the .05 level of significance. This research will identify the earliest driving changes in older adults who are likely to eventually relinquish their driving privileges. Older adults with subtle cognitive and physical changes are excellent candidates for targeted interventions to prolong driving cessation and postpone deterioration associated with reduced mobility.

- **Carlos Oliveira, M.D., Ph.D. Candidate**  
Clinical Fellow, Department of Pediatrics  
*Yale University*

“Clinical Effectiveness of the Human Papillomavirus Vaccine”

Key Words: Vaccine Effectiveness, Human Papillomavirus, Cervical Cancer.

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**Background:** Current recommendations are that all adolescents 11–12 years old receive 3 doses of human papillomavirus (HPV) vaccine (ideally before sexual debut). Although highly efficacious in preventing precancerous high-grade cervical lesions (HGCL) in clinical trials, the full potential of HPV vaccines to prevent HGCL is not being realized. This is because of poor uptake (<25% girls receive 3 doses by 13 years of age) and delayed administration, as the vaccine is not effective in women already infected with HPV. The extent to which delayed administration and number of doses received impacts the effectiveness of the vaccine is not known.

**Methods:** We will conduct a population-based, case-control study to determine the overall type-specific effectiveness of HPV vaccines, and the influence of age at the time of immunization and the number of doses received on the effectiveness of the vaccine. Cases will be women with HPV positive HGCL. Controls will be women with normal Pap smears, matched to cases by age, date of testing, and medical practice. We will interview participants and review all medical records to determine immunization status. The effectiveness of HPV vaccines, by age at the time of immunization and by number of doses received will be determined, adjusting for potential confounders with conditional logistic regression.

**Impact:** This study will be the first to evaluate how age at the time of immunization and number of doses received impacts the effectiveness of the vaccine in preventing HGCL. If results show that effectiveness is higher when immunization occurs at younger ages, it will provide strong evidence for providers and parents to assure that adolescents receive HPV vaccine at the recommended ages. In addition, if the effectiveness of two doses approaches that of 3, this could inform policy about an alternative regimen that may be both easier to achieve and less costly.

- **Georgios Pantouris, Ph.D.**

Postdoctoral Research Associate, Department of Pharmacology

*Yale University*

“Targeting Hematological Cancers Using a Small Molecule Inhibitor with a Novel Mechanism of Action.”

Key Words: Hematological cancer, Small molecule inhibitor, CD74, MIF

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Macrophage migration inhibitory factor (MIF) is an immunostimulatory cytokine with an active role in cancer. Binding of MIF to the cell-surface receptor CD74 initiates a cascade of signaling events that promote tumor survival and proliferation. In a CD74-independent manner, MIF is present in the cytosol of all nucleated cells where it interacts with p53, Jab1, and other proteins modulating the cell cycle in favor of tumor growth and invasiveness. Targeting the MIF/CD74 axis has emerged as an attractive target in hematological cancers such as acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL). Through a multidisciplinary approach, we aim to identify, characterize and optimize an MIF inhibitor that inhibits both the intracellular and extracellular functions of the protein. The long-term goal is the development of a therapeutic agent that can be used alone or in combination with other drugs for the treatment of patients with AML and CLL. Through crystallographic and kinetic analyses, we identified a potent MIF inhibitor with a novel mode of binding. Preliminary studies showed that the compound meets our expectations by both inhibiting interactions of MIF with Jab1 (intracellularly) and binding to CD74 (extracellularly). In collaboration with the NCI we tested this compound against the NCI-60 cancer cell lines. At 10  $\mu$ M our compound selectively inhibits the growth of the HL-60 cell line while the remaining 59 cell lines remain unaffected. Further characterization of this compound is currently in progress. Structure-activity relationship studies along with crystallographic analyses and in vivo studies will be carried out for the most promising derivatives.

- **Lisa Parikh, M.D.**

Clinical Fellow, Section of Endocrinology & Metabolism

*Yale University*

“Investigating the Central and Peripheral Mechanisms by which Glucocorticoids Affect Hunger”

Key Words: Glucocorticoids, Appetite, Obesity, Metabolism

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Obesity is a global epidemic affecting over 600 million people worldwide, placing them at an increased risk of developing cardiovascular disease and type 2 diabetes. Drug-induced obesity is a frequent and often overlooked, preventable cause of obesity. Synthetic glucocorticoids are among the most common offenders given their widespread use as anti-inflammatory therapy to treat several common diseases. The side effects of this drug class that contribute to obesity include increased adiposity, altered metabolism, and increased appetite. The pathophysiology of the appetite changes caused by glucocorticoids and its contribution to weight gain and obesity remain poorly understood. Cortisol is an endogenous glucocorticoid that increases during stress. By interacting with the corticolimbic-striatal system in the brain, a region critical to the regulation of reward, feeding, and memory, cortisol influences many of the behaviors associated with stress including stress-induced overeating. We hypothesize that synthetic glucocorticoids increase hunger by interacting with similar regions in the brain. To test this hypothesis, we will use functional magnetic resonance imaging (MRI) to study how synthetic glucocorticoids affect the brain's response to visual food stimuli in lean, healthy individuals. Participants will view pictures of high and low calorie foods while in the MRI and rate their "liking" and "wanting" of these foods, along with their hunger level. "Liking" refers to the pleasure obtained from a food and "wanting" refers to the motivation to seek a particular food. Using these methods, we plan to clarify the reward neurocircuitry's role in producing appetite changes after glucocorticoid administration. Since glucocorticoids can affect the production of appetite-regulating hormones, we will also measure changes in these hormones and correlate them with hunger ratings and food intake. Ultimately, understanding the pathogenesis of glucocorticoid-induced appetite changes could lead to the development of targeted obesity therapy, such as synthetic glucocorticoids with weight-sparing effects.

- **Abhinav Seth, M.D., Ph.D.**

Postdoctoral Associate, Department of Internal Medicine  
*Yale University*

“Regulation of Follicular Helper T Cell Development and Function”

Key Words: CD4 T Cells, Lupus, NFAT, Autoantibody

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Systemic lupus erythematosus is an autoimmune inflammatory disorder characterized by a generalized loss of tolerance to self antigens and manifest by the presence of pathogenic autoantibodies that mediate damage and dysfunction of host tissues and organs. Effective treatment of lupus is challenging because the mechanisms of pathogenesis may vary between individuals and because existing therapies broadly target immune function which renders patients susceptible to the risks of immunosuppression. These challenges are highlighted by the fact that only one new treatment for lupus has been FDA approved in the past 50 years.

Follicular helper T (Tfh) cells are a specialized subset of CD4+ helper T cells that are required for B cell maturation in germinal centers and subsequent antibody formation following infection or immunization with thymus dependent antigens. Recent studies have highlighted the importance of Tfh cells in mediating pathogenic autoantibody production in lupus. Modulation of Tfh cell function can ameliorate end organ disease in murine models of lupus. A more thorough understanding of the molecular determinants of Tfh cell function may allow for the development of specifically targeted immunomodulating therapies for lupus and other autoantibody mediated diseases.

Our lab has recently completed gene expression profiling on Tfh cells that develop during acute viral infection in mice. We have found that Tfh cells exhibit a strong AP-1 independent NFAT gene signature and also have diminished T cell receptor signaling, features which are typically associated with anergic cells. The goal of this proposal is to test whether NFAT regulates the anergy-like properties of Tfh cells during normal and abnormal immune responses.

- **Reshef Tal, M.D., Ph.D.**

Clinical fellow and Instructor

Department of Obstetrics, Gynecology and Reproductive Services

*Yale School of Medicine*

“The Role of Bone Marrow and Endothelial Progenitor Cells in Implantation, Placentation and Early Pregnancy Development”

Key Words: Endothelial progenitor cells; Bone marrow; Implantation; Pregnancy

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Infertility affects 15% of women in developed countries. Recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) may be the main reason that many infertile couples will not succeed in having a child despite assisted-reproductive technology. A functioning and receptive endometrium is crucial for embryo implantation and lack of endometrial receptivity is a major factor underlying RIF. Angiogenesis, the formation of new blood vessels from pre-existing ones, is crucial for cyclic endometrial growth, implantation and normal pregnancy development. Bone marrow (BM)-derived circulating endothelial progenitor cells (EPCs) have been shown to contribute to endometrial neovascularization where they are incorporated into the vascular endothelial lining and differentiate in situ into endothelial cells, in a process termed vasculogenesis. While bone marrow-derived cells (BMDCs) and EPCs have been shown to be crucial for tumor development and ischemic injury repair, their role in embryo implantation, placentation and early pregnancy development is unknown. This project's objectives are to characterize the contribution of BMDCs and EPCs to decidualization, implantation and early pregnancy development and to investigate the mechanisms underlying their recruitment to implantation sites. A pregnant mouse model in which mice undergo bone marrow transplantation (BMT) from GFP-expressing mice will be used to characterize and quantitate the recruitment of both total BMDCs as well as EPCs to implantation sites. To explore the effects of inhibition of EPC recruitment to implantation sites on implantation and pregnancy development, wild-type mice will undergo BMT from mice harboring an endothelial-specific conditional knockout in receptors known to be important in mediating EPC recruitment (VEGFR1, VEGFR2 or CXCR4). In addition, the therapeutic potential of BMDCs will be investigated using HOXA11 knockout mice which are infertile due to endometrial-specific implantation defect. The endometrial histology, protein expression and fertility of these mice will be assessed following BMT from wild-type mice. This research may provide important insight into the role of BMDCs in implantation and provide a preclinical basis for development of stem cell-based therapeutics to treat RIF.

- **Gwendolyn Thomas, Ph.D.**  
Associate Research Scientist  
*Yale School of Public Health*

“An Enhanced Behavioral Intervention to Increase Daily Exercise Adherence in Breast Cancer Survivors”

Key Words: Exercise, Physical Activity, Breast Cancer Survivors, Exercise Adherence, Smartphone Intervention

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Breast cancer is the most common cancer diagnosis among American women, accounting for 30% of cancer diagnoses with an estimated 232,340 invasive cases diagnosed in 2013. Approximately 50% to 64% of breast cancer survivors are currently overweight or obese and highly sedentary. These survivors are at greater risk of cancer recurrence, cardiovascular disease, and developing other comorbid chronic diseases.

Physical activity is a modifiable lifestyle factor which has been shown to decrease risk for breast cancer, increase survival rates and improve quality of life after diagnosis. Over half of breast cancer survivors report wanting to exercise, but significant barriers to exercise participation exist. Common barriers include a lack of information about exercise, a lack supervision of exercise, and a lack of prioritizing exercise in their daily schedule. Identifying novel approaches that may increase adherence to recommended exercise activity would be a significant step in promoting better long-term outcomes in breast cancer survivors.

The aims of this proposal seek to address these issues by implementing a smartphone based exercise intervention in women who are breast cancer survivors. This proposal will: 1. Examine the feasibility of implementing a smartphone based exercise intervention with breast cancer survivors to promote physical activity and exercise activities in daily life, and 2. Monitor which self-reported barriers impede exercise behavior occurrence in day to day life. These findings will inform the further development of an exercise intervention for breast cancer survivors that can be widely disseminated with the aim of supporting recommended levels of physical activity to increase quality of life, decrease health issues, and reduce mortality in breast cancer survivors.

- **Andrey Zinchuk, M.D.**

Fellow in Pulmonary and Critical Care Medicine  
*Yale University*

“Identification and Validation of Clinically Relevant Obstructive Sleep Apnea Phenotypes.”

Key Words: Adverse cardiovascular outcomes, Cluster analysis, Obstructive sleep apnea, Phenotypes, Polysomnography, Prognosis, Variable reduction.

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Obstructive sleep apnea (OSA) is a common, highly morbid sleep disorder that is increasingly recognized as a complex and heterogeneous syndrome. However, significant gaps exist in our understanding of OSA's heterogeneity (phenotypic variation) and corresponding implications for prognosis and outcomes. To help address these gaps, we hypothesize that routine sleep study (polysomnography) data can be used to identify unique OSA phenotypes that are associated with different risks of developing adverse outcomes (stroke, acute coronary syndrome and death).

To test this hypothesis, we propose an evaluation of OSA's heterogeneity in a large (N>1500), U.S. veteran study cohort. Our aims are to 1) determine the unique features (e.g., sleep fragmentation index, apneas with hypoxia only index) within the entire range of polysomnography data, 2) identify patient phenotypes that differ in polysomnographic and clinical features and 3) determine whether these OSA phenotypes independently predict the risk of developing adverse outcomes.

The study cohort is extensively characterized in polysomnographic, demographic and clinical domains. Incidence of the primary outcome (stroke, acute coronary syndrome or death) was ascertained with median follow up of 4.4 years. Unique polysomnographic features will be identified from among >80 variables via variable reduction methods (e.g. principal components analysis (Aim 1). Using these features and cluster analysis (e.g. K-means), polysomnographic phenotypes of OSA patients (clusters) will be identified (Aim 2). Clinical relevance of the OSA phenotypes will be assessed using cross-sectional associations with treatment adherence, specific risk factors for and comorbidities in patients with OSA. Finally phenotype relationship with incidence of adverse outcomes will be examined using Cox proportional hazards models, adjusting for traditional risk factors (e.g. age, diabetes, hypertension, atrial fibrillation etc.).

We anticipate that the results of this work will enable more individualized prognostication of those afflicted with OSA and provide insight into pathophysiological mechanisms and personalized treatment approaches.