

Robert E. Leet and Clara Guthrie Patterson Trust
Mentored Research Award: Clinical, Health Services and Policy Research
and
William O. Seery Foundation
Clinical Research Award for Cancer Research

• **Jennifer Dearborn–Tomazos, M.D., M.P.H.**

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“Intentional Weight Loss in Obese Patients after Ischemic Stroke: a Feasibility and Safety Study”

Key Words: Obesity, Stroke, Weight loss, Clinical Trial

Despite decades of research on secondary prevention of stroke, approximately 200,000 Americans with a history of stroke will have a recurrence each year. New treatments are needed to reduce this burden and one potential treatment is obesity management (i.e. weight loss). Obesity is highly prevalent in patients with stroke and is associated with adverse metabolic effects that are known to increase risk for progressive vascular disease, including insulin resistance, hyperglycemia, dyslipidemia, hypertension, vascular inflammation and vasomotor impairment. Although blood pressure and lipid lowering agents ameliorate some of the adverse effects of obesity, they do not fully reverse the underlying pathophysiology or fully reduce risk. Treating obesity with weight loss rapidly improves these metabolic consequences and may represent an effective therapy for preventing recurrent stroke.

This mentored award would support the candidate in completing a phase II randomized clinical trial to test the feasibility and safety of weight loss implemented soon after an ischemic stroke in obese patients who have a residual motor deficit. The two hypotheses to be tested are that weight loss: 1) is feasible and 2) does not impair motor recovery. The first hypothesis is grounded in the theory that patients with a recent ischemic stroke may not be sufficiently motivated to participate in a weight loss program or may have distinct barriers to successful participation. Assessing percent weight loss at 90 days will test this hypothesis. In other populations, 5% weight loss is sufficient to show significant improvement in vascular risk factors. The second hypothesis is grounded in the observation that intentional weight loss leads to loss in both fat and lean body mass. If loss in lean body mass occurs after stroke there is a theoretical concern that motor recovery may be impaired. Measuring the Fugl–Meyer Upper Extremity Scale (UE–FM) at baseline and 90 days and identifying the mean difference between the intervention and control groups will test this hypothesis.

- **Mary Driscoll, Ph.D.**

Research Psychologist
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“An Ecological Momentary Assessment of Relational Demand and its Implications for a Pain Self-Management Intervention Among Women Veterans with Chronic Back Pain”

Key Words: Relational Demand, Pain Self-Management, Women Veterans

Women Veterans represent the fastest growing segment of Veterans Healthcare Administration (VHA) utilizers. Relative to their male counterparts they report higher rates of pain, more pain-related interference in everyday life, and less satisfaction with their pain care. Women also prefer non-pharmacologic modalities for pain treatment. Addressing women's unique healthcare needs is a VHA priority. Research suggests that social factors (i.e., support, relational demand) may be salient intervention targets for women with chronic pain. In particular, support facilitates pain self-management, while relational demand, defined as a press to prioritize the needs of others above self, may be a barrier to engagement in pain self-management. Relative to support, much less is understood about relational demand in the context of chronic pain.

Building upon this research, a reciprocal peer support pain self-management intervention (Project CONNECT) that includes modules on managing relational demand was developed for women Veterans with chronic back pain and funded by a VHA Career Development Award. While this pilot focuses on the broader feasibility and acceptability of the intervention, and the peer support component, it is not designed to evaluate relational demand. Because little is known about variation in this construct, its association with pain or its potential implications for treatment, a mixed-methods approach including ecological momentary assessment and qualitative inquiry is proposed to a) elucidate momentary associations between relational demand and pain, b) evaluate whether Project CONNECT attenuates these associations, c) explore pre-post intervention changes in relational demand and pain intensity, d) understand participant perceptions of the interplay between relational demand and pain and e) examine the acceptability of the relational demand modules.

Findings will inform efforts to tailor the Project CONNECT intervention and highlight the potential importance of addressing relational burden in future effectiveness trials.

- **Alfonso Galderisi, M.D.**

Fellow in Pediatric Endocrinology
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“Pathogenesis of Youth Onset Pre-diabetes and Type 2 Diabetes: Effect of TCF7L2 on Beta Cell Function and Incretin Response”

Key Words: Prediabetes, Youth Type 2 Diabetes, Pediatrics, TCF7L2, GLP-1

Although the number of relevant type 2 diabetes (T2D) susceptibility genes has been climbing, the rs7903146 SNP in the TCF7L2 gene remains the single strongest known genetic risk factor for T2D. Remarkably, each copy of the T allele (rs7903146) is associated with a 1.914 (1.474–2.486) increased adjusted odds for IGT/T2D ($p=0.0001$), making it one of the most significant genetic findings in T2D to date in youth, with an effect size greater than that reported in adults. Additionally, recent preliminary data from our group suggest that the TCF7L2 risk genotype is associated with a reduced Disposition Index and a high odds ratio (OR 2.372 95%CI 1.059 – 5.314; $p= 0.03$) of maintaining Impaired Glucose Tolerance (IGT) or progressing to T2D. Building upon our exciting results we plan to capitalize and utilize the large thoroughly genotyped/phenotyped cohort of Yale Obesity Clinic to test the hypotheses that the risk allele at rs7903146 locus determinates a) reduced functional beta cell capacity, b) reduced incretin effect or c) reduced efficiency of GLP-1 to stimulate insulin in obese adolescents.

The Specific Aims of this proposal are:

- 1 – To delineate the effects of TCF7L2 rs7903146 on functional Beta-Cell Capacity in obese adolescents with IGT by assessing functional beta cell capacity (mass) with the use of clamp-derived glucose-stimulated C-peptide secretion and maximal C-peptide response to Arginine during hyperglycemia (AIRmax) in obese adolescent carriers of the TT and CC TCF7L2 genotype.
- 2 – To examine the functional impact of the rs7903146 variant in the TCF7L2 gene on incretin effect in obese adolescents with IGT measured by AUC of the c-peptide during OGTT and IsoG-IVGTs.
- 3 – To determine the functional impact of the rs7903146 on the ability of GLP-1 infusion to stimulate insulin secretion in obese adolescents.

- **Tracy Madsen, M.D., M.Sc.**

Assistant Professor of Emergency Medicine

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“StoP STRokE: Sex-Specific Prevention of Stroke Through Reproductive Risk Factors and Sex-steroid Effects”

Key Words: Stroke, Sex hormone binding globulin, Sex differences

Sex differences in stroke risk across the lifespan have been well-described, but the biologic basis underlying such differences is poorly understood. In the proposed research project, Dr. Madsen will investigate potential reasons for sex differences in stroke risk including the influence of sex hormones and sex hormone binding globulin (SHBG) on biologic mechanisms leading to vascular disease and stroke. Dr. Madsen will use existing stroke cohorts (Women's Health Initiative (WHI) and the Framingham Heart Study (FHS)) to study the potential sex-specific association between SHBG and ischemic stroke, controlling for known stroke risk factors and hormone use. She will then conduct an exploratory mediation analysis of the relationship between SHBG, markers of vascular risk including insulin resistance and lipid metabolism, and stroke risk in both the WHI and FHS to explore the mechanism behind SHBG levels and vascular disease. Dr. Madsen's proposed project has the potential to lead to a greater understanding of sex differences in ischemic stroke risk as well as more knowledge of how sex hormones and SHBG affect stroke risk in women and men. These findings could lead to novel ways to predict stroke risk and prevent stroke in a more personalized, sex-specific manner and potentially to the use of SHBG as a target for studies of stroke prevention.

- **Erin Mead, Ph.D., M.H.S.**

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“Addictive Potential of Little Cigars/Cigarillos in Dual Users: Effect by Flavor and Gender”

Key Words: Tobacco control, Dual use, Little cigars/cigarillos, Flavorings, Young adults, Gender

The popularity of dual use of flavored little cigars/cigarillos (LCCs) with cigarettes among young adults has significant implications for their health, addiction, and cessation. Two likely reasons for their increased popularity are: 1) cheaper cost than cigarettes; and 2) highly appealing flavor options. The addictiveness of LCCs within the context of dual use, and moderating effects by flavor and sex, have received limited attention in the literature. Therefore, a critical need exists to characterize the addictive potential of flavored and unflavored LCCs compared with cigarettes among young adult dual users and determine sex-based differences. The long-term study objectives are to provide timely evidence to inform: (a) the development of interventions to improve cessation rates in this high-risk population; (b) policy decision-making about LCCs; and (c) future studies to assess new product characteristics in a changing tobacco environment. The specific aims of the study are: (1) to characterize the addictive potential of LCCs compared with cigarettes within the context of dual use; (2) to compare the addictive potential of preferred flavored vs. unflavored LCCs; and (3) to explore sex-based differences in the addictive potential of flavored and unflavored LCCs. The study will employ a 2-week randomized crossover design with behavioral economic assessments among 125 non-treatment-seeking young adult (18–34 years old) regular dual users (50% women, 50% men). Participants will be randomized to receive either preferred flavored LCCs or unflavored LCCs to smoke for the first week, and then switch in the second week. We will utilize a well-established tool called the Cigarette Purchase Task (CPT) that uses behavioral economic demand for cigarettes to estimate the potential for addiction. In addition to measuring the demand for cigarettes, the CPT will be adapted to estimate: the addictive potential of flavored and unflavored LCCs, and the substitutability of flavored and unflavored LCCs for cigarettes.

- **Kofi Mensah, M.D., Ph.D.**

Clinical Fellow

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“Erosive Rheumatoid Arthritis Correlates with Defective B Cell Expression of Ataxia–Telangiectasia Mutated Protein”

Key Words: B Cell, Rheumatoid Arthritis, Ataxia–Telangiectasia Mutated, Immunoglobulin Repertoire, Central Immunologic Tolerance

Rheumatoid arthritis (RA) is a common, debilitating autoimmune condition that may cause irreversible bone erosions; however, there are no reliable biomarkers to identify patients who will develop erosive disease. The importance of B cells in RA is suggested by their presence near erosions in inflamed synovium, pathogenic autoantibody production, and by the efficacy of anti-B cell therapy. Initial data from our group show a limited B cell receptor (BCR) light chain repertoire and increased autoreactive CD21–/low B cell frequency in a subgroup of RA patients. This observation suggests impaired immune tolerance mechanisms that diversify the BCR repertoire and remove autoreactive B cells. Mechanisms of impaired B cell immune tolerance and increased autoreactivity and whether these phenomena directly influence joint erosions remain unclear. Our specific aims are: 1) determine an association between the range of BCR light chain gene segment usage, autoreactive CD21–/low B cell frequency, and erosive disease in RA, 2) identify a mechanism for limited BCR light chain gene segment usage in a subgroup of RA patients, 3) identify a mechanism by which increased erosions may occur in RA patients with limited light chain repertoire and increased CD21–/low B cells. We will accomplish this via PCR–based BCR gene sequencing and flow cytometric immunophenotyping for autoreactive B cell populations. This will be correlated with radiographic evidence of erosions. Preliminary unbiased gene array in the RA subgroup with limited BCR light chain gene usage shows decreased expression of the ataxia–telangiectasia mutated (ATM) gene, which regulates DNA repair and antibody diversification. We will study B cells from ataxia–telangiectasia patients naturally deficient in ATM to examine how reduced ATM affects BCR repertoire and autoreactive B cell frequency independent of RA disease factors. We will examine how inhibiting ATM function affects B cell expression of RANKL, which is essential for development of bone–eroding osteoclasts.

- **Julia Rozanova, Ph.D.**

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“Improving HIV Prevention and Addiction Treatment in Prisons”

Key Words: HIV risk, Volatile epidemic, Persons who inject drugs (PWID), HIV prevention, Prisons, Risk environment, Transition to community, Methadone maintenance therapy (MMT), Qualitative interviews

Eastern Europe and Central Asia (EECA) is the only region where HIV incidence and mortality has increased, primarily fueled by people who inject drugs (PWID) who interface regularly with prisons. In Kyrgyzstan's prisons, HIV prevalence among opioid injectors exceeds 30%, with 85% of PWID injecting within prison. Scale-up of prison-based methadone maintenance therapy (MMT) with post-release retention is the most effective evidence-based HIV prevention strategy in PWID-driven epidemics. All 15 internationally-recommended HIV prevention strategies, including MMT, exist in prison in Kyrgyzstan, creating new opportunities to research and control HIV transmission.

Aligned with a recent international call for research to examine the "risk environment" within prisons and scale-up of MMT, the proposed longitudinal qualitative Patterson Project (PP) explores how the prison environment amplifies HIV risk in prison and post-release. It adds important contextual value to a structured implementation science study to increase MMT and post-release retention in PWID in Kyrgyzstan, by qualitatively examining "why" PWID and personnel (dis)engage with MMT in the prison and post-release transitional community contexts and "how" (dis)engagement shapes the HIV risks. Findings will optimize protocols for future behavioral peer-driven HIV prevention interventions in prison and after release by comparing PWID who do and do not start and retain in MMT and how other prisoners and personnel influence their choices. The two related research aims are to: 1) Describe the client-level factors that shape within-prison and post-release HIV risk and prevention strategies for PWID; and 2) Explore providers' perspectives on how the prison and post-release environments shape MMT uptake and retention. PP advances Drs. Rozanova's career development and new research insights by integrating qualitative methods, implementation science, prisons, and HIV prevention with MMT in Kyrgyzstan, a unique setting that has global implications for advancing HIV prevention mandates in the prison setting that perpetuates the HIV epidemic.

- **Tregony Simoneau, M.D.**

Assistant Professor of Pediatrics

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Connecticut Children's Medical Center

“Identifying Biomarkers of Allergic Asthma: What Can the Long Non-coding RNA Tell Us”

Key Words: Pediatric Asthma, Genomics, RNA, Biomarker

This study seeks to identify new biomarkers of pediatric allergic asthma by exploring the differential expression of long non-coding RNAs (lncRNAs). Pediatric asthma is a collection of heterogeneous phenotypes which are poorly defined. lncRNAs are a family of RNAs that do not encode proteins, but function as effector molecules. Some lncRNAs have been found to be important in mouse models of allergic disease. However, the role of lncRNAs has not been explored in children with asthma. We hypothesize that children with allergic asthma have altered expression of lncRNAs and this expression is differentiated further in the setting of an in vitro asthma attack.

This is a pilot prospective case control study of 7–14 year old, Hispanic Puerto Rican children with persistent asthma and indoor environmental allergen sensitization compared with non-asthmatic, non-allergic control children. Data collected includes questionnaires regarding health history and status, and environmental exposures. Subjects will perform spirometry pre- and post-bronchodilator administration and undergo a blood draw. Blood will be analyzed for IgE, peripheral eosinophils, and Immunocap allergy testing. Peripheral eosinophils and T cell subsets will be isolated from the blood and will undergo analysis with RNA-seq. To mimic an asthma attack we will stimulate cultured cells and perform RT-qPCR to assess expression changes of candidate lncRNAs identified by RNA-Seq.

The primary outcome will be the differential expression of lncRNAs compared between children with allergic asthma and those without allergies or asthma. 21 study visits have been completed thus far with a goal of 45.

The results of this study will allow us to identify biomarkers associated with pediatric allergic asthma. Alterations in the expression of those markers in the setting of an in vitro asthma attack will be explored. Future studies will explore the identified markers in other asthma phenotypes and as potential therapeutic targets.

- **Jennifer Tsui, Ph.D., M.P.H.**

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“Improving Health Care Delivery Processes to Enhance Care Quality for Underserved Cancer Patients in New Jersey”

Key Words: Cancer Care Delivery, Quality of Care, Safety-Net Health Systems, Underserved/Vulnerable Populations, Mixed-Methods Research

Low-income and racial/ethnic minority cancer patients in the United States, particularly those with Medicaid insurance, experience lower quality cancer care and worse survival compared to other groups. Poor transitions from primary care to specialty oncology (PC-SC) care following initial diagnosis may be a key contributor to disparities in cancer outcomes for underserved populations, but factors associated with care transitions within safety-net settings are understudied. System and practice-level initiatives, including Medicaid Accountable Care Organizations, to improve care and speed the adoption of best practices are gaining momentum within state Medicaid programs, but cancer has only recently emerged as a focus of such initiatives. The proposed mentored research project aims to identify organizational factors and care delivery processes that influence PC-SC transitions for underserved breast cancer (BC) or colorectal cancer (CRC) patients across varying Medicaid settings using a multistage mixed methods approach and identify care improvement strategies for effective practice and policy change through stakeholder engagement activities. Specific study aims are: (1) To determine primary care practice-level BC and CRC guideline concordance rates and identify variations in the relationship between organizational factors and guideline concordance rates using a state Medicaid-cancer registry linked dataset; (2) To identify health care delivery processes associated with PC-SC transitions and guideline concordance through comparative case studies of high and low performing primary care practices, identified from the linked dataset; (3) To engage stakeholders in identifying strategies for practice or policy change to improve care transitions among Medicaid cancer patients. Study findings will inform critical care delivery improvement strategies for cancer and other complex chronic conditions within safety-net health care settings and lead directly to the development of a larger research proposal to implement evidence-based strategies or evaluate policies to improve cancer care transitions for Medicaid patients.

Funded by the William O. Seery Foundation:

• **Yu Zhang, M.D.**

Postdoctoral Fellow

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“Evaluating the Effect of Anti-Program Death Immune Therapy on Anti-Tumor T Cell Responses in Non-Small Cell Lung Cancer Patients”

Key Words: Non-small cell lung Cancer (NSCLC), Cancer Immunotherapy, Programed Death-1 (PD-1), Programed Death Ligand-1 (PD-L1), T cell response

Immunotherapy with antibodies targeting program death-1 and program death ligand-1 (anti-PD therapy) has improved the prognosis of advanced non-small cell lung cancer (NSCLC), the second most common cancer and leading cause of mortality in the US. However, few patients achieve a prolonged durable response. Of the 20-45% advanced NSCLC patients who respond to immunotherapy, more than 50% eventually become resistant to immunotherapy. The underlying mechanism of recurrence/acquired resistance is unknown, but likely occurs through immunoediting, where tumor variants not recognized by the immune response, escape elimination and are selected for growth. Ideally, the generation of a polyclonal T cell response to a broad spectrum of antigens would prevent tumor escape from immunity. However, few T cell clones are generated in response to diverse antigens. There is also a hierarchy of responses: antigens producing strong T-cell responses are "dominant" and weaker antigens are "subdominant".

Our studies in mice showed that anti-PD therapy strengthened the response to the dominant tumor antigen, but suppressed the response to the subdominant antigen. Ironically, while anti-PD therapy is effective in promoting anti-tumor immune responses, the decrease in the overall scope of the anti-tumor response led to the development of tumor variants and to tumor escape from immunity. However, it is still unknown whether this occurs in patients receiving anti-PD therapy.

We will evaluate whether anti-PD therapy decreases the breadth of the anti-tumor immune response in NSCLC patients by comparing the T cell receptor sequences of tumor infiltrating lymphocytes from patient tumors and from their peripheral blood pre- and post-anti-PD therapy. If it is the case, then it would be important to explore new approaches that prevent tumor recurrence by enforcing responses to subdominant tumor antigens. This would have major treatment implications that could lead to changes in the current design of therapeutic strategies with anti-PD therapy.