Harold Amos Medical Faculty Development Program

Name: Tasce Bongiovanni, MD, MPP

Current Institution: UCSF

Mentor(s): Mike Steinman, MD

College: Santa Clara University

Medical/Dental/Nursing PhD School: UCSF

Residency: UCSF

Fellowship: UCSF/SFGH

Title of Project: Postoperative Prescribing of Pain Medication Among Older Adults

**Introduction:** In response to the opioid epidemic, surgeons have increasingly initiated multimodal pain regimens with the intent of reducing opioid use in the postoperative period, including by prescribing gabapentinoids. We sought to describe trends in postoperative prescribing of both gabapentinoids and opioids after a variety of surgical procedures. Given that like opioids, gabapentinoid use may be prolonged after this initial postoperative prescription, we also sought to describe prolonged use of postoperatively prescribed gabapentin and characterize associated risk factors.

Figure 1: Gabapentinoid Prescribing Over Time

**Methods:** We conducted a retrospective analysis of gabapentinoid prescribing from 2014-2018, using a 20% Medicare sample. We included gabapentinoid naïve patients ≥ 66 years at time of the procedure undergoing one of 14 common non-cataract surgeries performed in older adults. We measured rate of postoperative prescribing of gabapentinoids (with days supply) and opioids (with oral morphine equivalents (OME)), defined as a prescription filled between 7 days before procedure to 7 days after discharge. We assessed concomitant postoperative prescribing of gabapentinoids and opioids. We also assessed the incidence of and risk factors for prolonged use of gabapentinoids.

**Results:** The total study cohort included 494,922 patients, with a total of 18,095 (3.7%) receiving a new gabapentinoid prescription in the postoperative period. Of those receiving a new gabapentinoid prescription, 61% (n=10,956) were women and the majority were white (n=15,529). After adjusting for age, gender, race and procedure type in each year, the rate of new postoperative gabapentinoid prescribing increased from 2.3% in 2014 to 5.2% in 2018 (p value<0.01) (Figure 1). While there was variation between procedure types, almost all procedures saw an increase in both gabapentinoid and opioid prescribing. In this same period, opioid prescribing increased from 56% to 59% (Figure 2). Both days supply for gabapentinoids (34 to 27 days) and opioid OME (436 to 379, a difference of 7 tabs of 5mg oxycodone) decreased slightly. In the cohort of patients who received a gabapentinoid, 22% demonstrated prolonged use. Risk factors for prolonged use included being female, having a higher Charlson comorbidity score, having an opioid prescription at discharge and at >90 days and having a higher care complexity.

Figure 2: Opioid Prescribing Over Time

**Discussion:** New postoperative gabapentinoid prescribing is rising and despite national attention to decreasing opioid use there is not a downward trend in the proportion of patients receiving postoperative opioids. Further, patients receiving gabapentinoids are at risk for prolonged use, with almost one quarter of patients still receiving gabapentinoids >90 days after surgery. Our findings suggest that broad-based shifts in pain management to avoid opioid prescribing has potential long-term effects. Close attention needs to be paid to medications meant to be used short-term in the post-surgical discharge period, especially those that are potentially inappropriate medications for older adults.

Harold Amos Medical Faculty Development Program

Name: Crystal E. Brown, MD MA

Current Institution: University of Washington

Mentor(s): Bessie Young

College: University of Washington

Medical/Dental/Nursing PhD School: Case Western Reserve University

Residency: University of Chicago

Fellowship: University of Washington

Title of Project: Perspectives About Racism and Patient-Clinician Communication Among Black Adults with Serious Illness

**Introduction:** Black patients with serious illness experience higher intensity care at the end of life. Little research has used critical, race-conscious approaches to examine contributing factors.

**Objective:** To understand the lived experiences of Black patients with serious illness and how various factors impact patient-clinician communication and medical decision-making.

**Methods**: We conducted one-on-one, semi-structured interviews with twenty-five Black patients with serious illness hospitalized at an urban academic medical center in Washington State between January 2021 and February 2023**.** We asked patients to discuss experiences with racism, how those experiences affect the way they communicate with clinicians, and how it impacts medical decision-making. Public Health Critical Race Praxis was used as framework and process.

**Main Outcomes and Measures**: The experience and impact of racism as described by Black patients with serious illness on patient-clinician communication and medical decision-making within a racialized healthcare setting.

**Results***:* Twenty-five Black patients with a mean age of 62.0 years and significant socioeconomic disadvantage were interviewed. Participants had low levels of wealth, income, educational attainment, and health literacy. Participants reported high levels of medical mistrust and high frequency of discrimination and microaggressions experienced in healthcare settings. Participants reported epistemic injustice as the most common manifestation of racism—silencing of their own knowledge and lived experiences about their bodies and illness by healthcare workers (HCWs). Participants reported these experiences made them feel isolated and devalued, especially if they had intersecting, marginalized identities such as insurance status or being unhoused. These experiences exacerbated existing medical mistrust and contributed to poor patient-clinician communication. Participants described various mechanisms of self-advocacy and medical decision-making based on prior experiences with HCW mistreatment and medical trauma.

**Conclusion and Relevance**: In this qualitative study of Black patients, experiences with racism, specifically epistemic injustice, were associated with their perspectives on medical care and decision-making during serious illness and end-of-life. Race-conscious, intersectional approaches are needed to improve patient-clinician communication and support Black patients with serious illness to alleviate the distress and trauma of racism as they near the end of life.

Harold Amos Medical Faculty Development Program

Name: Erin Ealba Bumann DDS PhD MS FAAPD FACD

Current Institution: University of Missouri-Kansas City

Mentor(s): Sarah Dallas PhD

College: University of Michigan

Dental School: University of Michigan

PhD School: University of California San Francisco

Residency: University of Michigan (Pediatric Dentistry)

Title of Project: Dynamics and Molecular Mechanisms of Jaw Bone Development

Abstract: Defects in jaw bone length are associated with problems in mastication, breathing, and quality of life. The only treatment option currently available is multiple, invasive surgeries. Therefore, identifying the molecular and cellular mechanisms through which skeletal elements in the jaw achieve their proper length is critically needed. Our laboratory discovered a previously unknown role for osteoclasts, which resorb bone, in regulation of jaw length. Our data showed that short-jawed quail have higher resorptive activity compared to long-jawed duck at equivalent developmental stages and confirmed this data in chimeric avian models, suggesting that increased resorption is associated with a shorter jaw. WNT family member 5A (WNT5A) noncanonical signaling is a major player in craniofacial development, as well as osteoblast-lineage and osteoclast differentiation and activity. Mutations in humans and mice have shown a key role for the WNT5A signaling pathway in jaw length. For example, *WNT5A* mutations cause micrognathia and maxillary hypoplasia in Robinow Syndrome. Together, these observations lead us to the hypothesis that WNT5A noncanonical signaling directs osteogenesis and osteoclast resorption dynamics to control jaw bone length. To determine the effects of WNT5A on lower jaw development during the initiation of bone mineralization, quail were injected with one systemic injection of recombinant WNT5A (25ng/uL). An approximate 5% decrease in lower jaw was seen when compared to controls. To confirm our avian studies, we used a mouse transgenic model to determine the effect of WNT5A overexpression in osteoblast-lineage cells and osteoclasts using CTSK-cre in postnatal day 10 pups. The data recapitulates what we see in the quail model and the craniofacial phenotypes in patients with Robinow Syndrome, including micrognathia (~4% decrease), macrocephaly (~5% increase), midface hypoplasia (~5.5% decrease), and low set ears (~3% decrease) (p<0.05). Additional craniofacial phenotypes noted in the mutant mice include midface asymmetries seen in over 60% of the mutant mice and sex differences in the cranial base, with females being ~4% greater than males (p<0.05). Interestingly, WNT5A overexpression did not affect whole skull size or bone mineral density. Our ongoing research aims to determine the molecular mechanisms behind these craniofacial changes and the impact of WNT5A/ROR2 noncanonical signaling on osteoclast & osteocyte dynamics using high-resolution techniques. To support future experiments, we have developed new techniques to visualize osteoclasts in vivo, including a chorioallantoic membrane assay where we can visualize GFP-positive osteoclasts in developing non-fluorescent chimeric lower jaws, as well as novel methods for 3D imaging of bone formation over multiple stages. Elucidating the role of noncanonical WNT5A signaling in craniofacial bone development will improve patient care and facilitate the development of less invasive therapeutic treatments.

Harold Amos Medical Faculty Development Program

**Name**: Ana G. Cristancho, MD, PhD

**Current Institution:** Children’s Hospital of Philadelphia/Perelman School of Medicine at the University of Pennsylvania

**Mentor(s):** Eric D. Marsh, MD, PhD & Michal A. Elovitz, MD

**College:** University of Miami

**Medical/Dental/Nursing PhD School:** Perelman School of Medicine at the University of Pennsylvania

**Residency:** Pediatrics, Children’s Hospital of Philadelphia

**Fellowship:** Child Neurology, Children’s Hospital of Philadelphia

**Title of Project:** Unraveling the Epigenetic Sequelae of Prenatal Hypoxic Brain Injury One Cell at a Time

Pathologic transient hypoxia to the fetal brain during critical periods of development leads to a broad spectrum of neurodevelopmental disabilities, even without clinically evident cell death or structural injuries. Emerging evidence suggests that among the most critical consequences of prenatal brain injuries, including hypoxia, is the disruption of the epigenome. However, we are limited in our ability to target the epigenome therapeutically because the cell type-specific effects of hypoxia on the developing brain’s molecular phenotype are unknown. To address this gap, we performed joint single nucleus RNA-sequencing and assay for transposase-accessible chromatin sequencing from the cortex of mice immediately after a mild prenatal hypoxia exposure (8 hours, 5% inspired oxygen at embryonic day 17.5). Immediately after hypoxia, we uncovered that hypoxia has both a “shared” signature across all cell types and cell type-selective changes associated with previously described long-term deficits in the corresponding individual cell types, providing novel strategies for untangling the diverse hypoxic response. Notably, dysregulated genes in all cell types demonstrated a marked overlap with genes that cause neurological disorders, supporting a convergence of clinical phenotypic significance despite the variability of affected pathways. When integrated with the chromatin accessibility profiles, we surprisingly discovered a global disassociation between gene expression and chromatin accessibility organization selectively in glutamatergic neurons. These changes were correlated to structural and functional aberrations in these neurons one month after the injury. These findings suggest that comprehensive multi-omics single-nuclei profiling can predict long-term deficits in developing glutamatergic neurons and offer a framework for dissecting the diversity of the hypoxic response in other cell types. Ongoing analyses will test (1) whether early transcriptional and epigenetic changes in other cell types reflect lasting functional injury, (2) whether the chromatin organization shifts in glutamatergic neurons after prenatal hypoxia lead to a persistent “epigenetic scar” in juvenile mice affecting maturation or function, and (3) which motifs are present at differentially accessibility sites in all cell types, potentially indicating transcriptional regulators that may be targets for innovative therapeutic interventions.

Harold Amos Medical Faculty Development Program

Name: Utibe R. Essien, MD, MPH

Current Institution: David Geffen School of Medicine at UCLA

Mentor(s): Michael J. Fine, MD, MSc; Leslie R.M. Hausmann, PhD

College: New York University

Medical/Dental/Nursing PhD School: Albert Einstein College of Medicine

Residency: Internal Medicine / Primary Care (Massachusetts General Hospital)

Fellowship: General Internal Medicine (Massachusetts General Hospital / Harvard Medical School)

Title of Project: Achieving Pharmacoequity in Veterans with Atrial Fibrillation

Intro: Anticoagulation reduces stroke risk in atrial fibrillation (AF), yet prior studies, conducted in VA at the patient-level, show significantly lower prescribing rates for any anticoagulant and direct oral anticoagulant (DOAC) therapy for Black than White individuals. Because little is known about the magnitude of these anticoagulant prescribing disparities at the facility level, our goal was to compare anticoagulant initiation between White and Black patients with AF across VA facilities.

Methods: We identified a national cohort of patients enrolled in VA with a new outpatient diagnosis of non-valvular AF from 1/1/2020 to 12/31/2021. We excluded patients with an AF diagnosis or anticoagulation in the 2 years prior to their index AF diagnosis, pre-existing valvular disease, and those receiving hospice care or who died within 180 days of index diagnosis. For all VA facilities with >10 Black patients with AF, we calculated facility-level rates of anticoagulant initiation (any or DOAC) within 180 days of an index diagnosis and assessed the difference in anticoagulant initiation between White and Black patients. We characterized variation across VA facilities using risk differences, adjusted for year of AF diagnosis, area deprivation index, and VA enrollment priority group, CHADS2VA2Sc stroke risk score, bleeding risk, and comorbid renal and liver disease.

Results: We identified 26,832 patients with AF at 82 VA facilities with at least 10 Black patients with AF. Overall unadjusted rates of any anticoagulant therapy ranged from 56.8% to 87.1% across facilities; the corresponding ranges for Black and White patients were 47.6% to 91.3% and 58.2% to 87.1%, respectively. Overall unadjusted rates of DOAC therapy ranged from 55.1% to 85.5% by facility; ranges for Black and White patients were 42.8% to 86.9% and 56.4% to 85.5%, respectively. The adjusted risk difference (ARD) between Black and White patients ranged from -29.9 (95% CI, -54.9 – -4.8) to 14.2 (95% CI, -9.1 – 25.0) across facilities for any anticoagulant therapy and from -28.8 (95% CI, -58.3 – 0.8) to 15.0 (95% CI, -8.0 – 38.1) for DOAC therapy. For any anticoagulant therapy, there were 15 (18.3%) facilities with a ≥10% clinically relevant difference, with Black individuals prescribed less than White, including 3 with a statistically significant difference. For DOAC therapy, there were 21 (25.6%) facilities with a ≥10% clinically relevant difference with Black individuals prescribed less than White, including 5 with a statistically significant difference.

Discussion: In 82 VA facilities serving Black and White patients with incident AF, we observed large facility level variation in any anticoagulant and DOAC therapy initiation, overall and by race. We also found substantial variation across facilities in adjusted risk differences for any anticoagulant and DOAC therapy initiation. Finally, we observed clinically relevant Black-White disparities in anticoagulation within nearly a quarter of VA facilities. Evaluating these facilities, as well as those where Black patients were *more* likely to receive anticoagulation, may reveal specific local drivers of differential prescribing and help guide quality improvement efforts to promote pharmacoequity in AF.

Harold Amos Medical Faculty Development Program

Name: Temidayo Fadelu, MD, MPH

Current Institution: Dana-Farber Cancer Institute, Harvard Medical School

Mentor(s): Timothy Rebbeck, PhD; Rachel Freedman, MD, MPH

College: Baylor University

Medical/Dental/Nursing PhD School: Yale University School of Medicine

Residency: Hospital of the University of Pennsylvania

Fellowship: Dana-Farber, Harvard Cancer Center

Title of Project: Developing and piloting an intervention to improve adherence to adjuvant endocrine therapy among patients with breast cancer in Rwanda.

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**Background/Study Impact**

Breast cancer mortality rates in Rwanda and other sub-Saharan African (SSA) countries remains exceptionally high, even among patients with potential curable disease. There is anecdotal evidence that many patients abandon treatment and do not complete intended recommended course of curative treatment. Adjuvant endocrine therapy (AET) is a crucial element of treatment in patients with hormone receptor positive breast cancers, leading to a mortality reduction of over 30% with 5 years of treatment given after local surgical control and chemotherapy. Despite the proven benefit and wide-availability, adherence rates in SSA are poor. The primary goal of this project is to develop and pilot AET adherence interventions grounded in the Information–Motivation–Behavioral Skills Model, a widely used framework developed for HIV medication adherence.

**Aims**

Aim 1: To identify barriers and facilitators of AET adherence in patients with estrogen receptor ER-positive breast cancer using a **sequential mixed methods** approach.

Aim 2: To develop and pilot components of a patient-facing AET adherence intervention utilizing **Intervention Mapping (IM)** procedures

**Progress towards Aim 1 and challenges.**

* We recruited 30 women for qualitative interviews on adherence, and the pilot tested endocrine therapy patient education materials.
* We conducted a retrospective review of the medical records of 206 women diagnosed with non-metastatic breast cancer between January 2019 and June 2020 to assess rates of AET initiation and discontinuation.
* We started planning for an AET decentralization pilot. Based on the results of a prior study we conducted on contributors to care delays and care discontinuation, we identified transportation (cost and process) as an overwhelming barrier to care. My local collaborators decided to prioritize piloting an AET decentralization program.

**Results**

Qualitative analyses of the interviews are ongoing. Baseline assessment of patient in the pilot noted most that patients were knowledgeable about the dose schedule (100%), intended duration (90%), and common side-effects. Patients were less knowledgeable about mechanism of action (67%). Seven patients (23%) noted missing at least one dose in the preceding seven days.

Of 206 women with non-metastatic breast cancer during our eligibility period, 52 (25%) had delays in testing for ER status, likely due to stock-outs of laboratory reagents. Of the patients who had ER testing 129 (63%) were ER positive; of these only 98 (76%) initiated adjuvant endocrine therapy (AET). Most patients 64 (65%) experienced treatment interruptions of > 30 days. At the time of data collection (a median follow-up of 2.5 years), 59 patients remained on AET; and of the remaining 39 patients, 11 had died, 19 had disease recurrence while 9 had discontinued AET. This study is the first detailed map of AET initiation, interruptions, and persistence in this population.

My local collaborators conducted a readiness exercise with several district hospital and identified four district hospitals -one in each of the country’s provinces. A breast cancer and endocrine therapy training curriculum was developed for general practitioners and nurses at the respective district hospitals. There were 20 clinician participants in training that occurred in August 2023. Median knowledge score of participants increased from 62% to 89%.

**Future Directions**

Aim 1: A comprehensive survey to assess AET adherence implementation and quality of life has been developed, and it is undergoing cognitive testing. We aim to recruit 150 patients on AET to better understand adherence implementation patterns and determinants.

Aim 2: A panel of experts will be engaged with developing new intervention components through a process of Intervention Mapping. The exact components of the intervention are yet to be determined but will build on the current decentralization pilot and may include exploring approaches such as motivational reminders, remote symptom monitoring and management, and electronic delivery of educational materials to patients. The resultant menu of interventions will be piloted in 40 patients within 6 months of AET initiation.The primary endpoint will be implementation outcomesafter a 12-week pilot assessed using Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). In-depth **qualitative interviews** will be conducted to assess intervention engagement.

**Career Development and Milestones**

Promotion to Assistant Professor April 2023

Young Mentor Award from Harvard Medical School May 2023

Publications (Primary or Senior Author) since October 2022

Original Articles

Christiansen K, Buswell L, **Fadelu T**. A systematic review of patient education strategies for oncology patients in Low- and Middle-income countries. Oncologist. 2023;28(1):2-11. PMID: 36269170; PMCID: PMC9847564

Erfani P, Gaga E, Hakizimana E, Kayitare E, Mugunga JC, Shyirambere C, Milner DA, Shulman LN, Ruhangaza D, **Fadelu T**. Breast cancer molecular diagnostics in Rwanda: a cost-minimization study of immunohistochemistry versus a novel GeneXpert® mRNA expression assay. Bull World Health Organ. 2023;101(1):10-19. PMID: 36593782; PMCID: PMC9795380

Nadella P, Iyer HS, Manirakiza A, Vanderpuye V, Triedman SA, Shulman L, **Fadelu T**. Geographic accessibility of radiation therapy facilities in sub-Saharan Africa. Int J Radiat Oncol Biol Phys. 2023;115(3):557-563. PMID: 36725167

Review Articles

Erfani P, Bates M, Garcia-Gonzalez P, Milner DA, Rebbeck TR, Ruhangaza D, Shulman L, **Fadelu T**. Leveraging molecular diagnostic technologies to close the global cancer pathology gap. JCO Glob Oncol. 2022 Oct;8:e2200182. PMID: 36252158; PMCID: PMC9812500

**Fadelu, T.A.**, Buswell, L. and Anderson, B.O.. Improving adherence to adjuvant endocrine therapy in Sub-Saharan Africa: challenges and innovative nurse-driven solutions. The Oncologist 2022; 27(8), pp.607-609.

Harold Amos Medical Faculty Development Program

Name: Luis Malpica Castillo

Current Institution: The University of Texas MD Anderson Cancer Center

Mentor(s): Christopher Flowers, MD

College: Universidad Peruana Cayetano Heredia, Lima, Peru

Medical/Dental/Nursing PhD School: Medical

Residency: University of Miami/Jackson Memorial Hospital, Miami, FL, USA

Fellowship: University of North Carolina, Chapel Hill, NC, USA

Title of Project: Epidemiology of Lymphomas in Latin America

In 2020, an estimated of 40,000 people in Latin America (LATAM) were diagnosed with non-Hodgkin lymphoma (NHL), and 18,000 died from this cancer. The incidence and mortality rates for NHL in LATAM are expected to increase by 20% by 2025. These rates are 25% and 50% higher than comparable rates for the U.S. and European countries, respectively. Additional challenges exist for patients with NHL in LATAM. Geographic variations of NHL are well documented. For example, in LATAM lymphotropic viruses (EBV, HIV, HTLV-1) are a common cause of aggressive NHL, T cell NHL are commonly seen and both are associated with poor outcomes. Race and ethnicity are underreported as demographic variables particularly in genomic studies of lymphoma, and current prognostic scoring systems fail to embrace the impact of demographic, socioeconomic, biological and treatment factors. Hence, comprehensive population-specific prognostic models are needed. We hypothesized that developing prognostic and predictive models including patient-centered factors (demographic, socioeconomic, environmental, host genomic, and treatment factors) will improve understanding of the key factors associated with differences observed in treatment responses, improve representation of these populations in lymphoma research and aid in improving survival among NHL patients in LATAM. In 2017, we established the Latin American Group of Lymphoproliferative Disorders (Grupo de Estudio Latinoamericano de Linfoproliferativos, GELL), a scientific group composed of 90 medical oncologists from 14 LATAM countries and have captured data on >4,000 NHL patients. However, prospective studies are needed to address unmet needs.

At the Harold AFMDP, we proposed to establish the ‘Epidemiology of Lymphomas in Latin America (ELLA)’ cohort study. Over the 4 years of award period we will: (1) capture prospective clinical data, germline DNA, and tumor samples for 2,000 newly diagnosed patients with NHL in LATAM and follow them for long-term prognosis and survivorship; (2) validate existing and develop novel prognostic scoring systems for patients with NHL in LATAM; and (3), characterize the immunologic landscape of T/NK and viral-associated NHL for epitope discovery and mass spectrometry-based immunopeptidome validation for the development of novel immunotherapeutic strategies. For example, during the first year of the AFMDP award period, we have collected retrospective data of 2,000 newly diagnosed NHL patients and collected tumor samples from 300 patients. We have conducted genomic studies of patients with HTLV-1-associated adult-T cell leukemia/lymphoma (or ATLL), a rare and lethal type of NHL, and have characterized driver mutations associated to survival, and compared these genomic features to other race and ethnicities. We are currently collecting data of other NHL prevalent in LATAM and will be presented at the meeting.

Harold Amos Medical Faculty Development Program

Name: Olurotimi Mesubi, MBBS, MPH

Current Institution: The Johns Hopkins University School of Medicine

Mentor(s): Mark E. Anderson, MD, PhD; Natasha E. Zachara, PhD

Medical/Dental/Nursing PhD School: College of Health Sciences, University of Ilorin, Ilorin

Graduate School: Harvard University, School of Public Health, Boston, MA

Residency: Case Western Reserve University (MetroHealth Medical Center), Cleveland, OH

Fellowship: University of Iowa, Iowa City, IA/Johns Hopkins University, Baltimore, MD

Title of Project: The Role of O-GlcNAcylation in Atrial Fibrillation

O-GlcNAcylation (OGN) is a reversible sugar post-translational modification akin to phosphorylation regulated exclusively by two enzymes. Excessive myocardial OGN, a hallmark of diabetes mellitus (DM) is pathologic in heart, but the mechanisms remain uncertain. DM is an important independent risk factor for atrial fibrillation (AF). I previously established a proarrhythmic role for OGN in diabetic AF. My research project is focused on investigating the mechanistic role of excessive myocardial OGN in AF, specifically through its effect on aberrant type 2 ryanodine receptor (RyR2) Ca2+ release and/or atrial energetics.

RNA-seq analysis in hearts from non-diabetic and diabetic transgenic mice with cardiac specific OGA overexpression (OGA-TG mice) and their littermate controls (OGA-WT mice) identified over > 2000 differentially expressed genes. Pathway analysis of the top canonical and biological functions identified enrichment of mitochondrial, lipid and fatty acid oxidation and metabolism as the most prominent pathways differentially affected. Several differentially expressed genes were identified that will be the basis for further mechanistic studies.

The new class of drugs – sodium glucose cotransporter 2 inhibitors (SGLT2i) have beneficial effect in DM and heart failure and are now part of the guideline directed therapy for heart failure. Some data in mouse models suggest that SGLT2i decrease OGN levels in the heart and in atrial tissue. However, conflicting evidence exists regarding their role and effect on cardiac arrhythmias including AF independent of their effect on HF and their exact mechanism(s) of action on the heart. In a type 2 DM (T2D) mouse model, Empagliflozin but not Dapagliflozin (both SGLT2i) protected from increased AF susceptibility, independent of the effects on hyperglycemia and cardiac dysfunction. In on-going work, the effect of SGLT2i on myocardial OGN and CaMKII activity is being evaluated in in vivo and in vitro systems. Specific OGN targeted compounds are also being evaluated for their effect on AF susceptibility.

Taken together, although not much is known about the role of OGN in AF, our data consistently shows it plays a role in promoting AF. The early data from this project is foundational in understanding the mechanisms through which this occurs and has potential for the development of OGN-targeted therapeutic interventions for the management of AF.

Harold Amos Medical Faculty Development Program

Name: Laneshia K Tague, MD MSCI

Current Institution: Washington University in St. Louis

Mentor(s): Andrew Gelman PhD, Brian Gage MD MS

College: Northwestern University

Medical/Dental/Nursing PhD School: Northwestern University

Residency: Loyola University Medical Center

Fellowship: Washington University in St. Louis

Title of Project: Influence of Pre-Transplant Lymphocyte Mycophenolic Acid Sensitivity on Post-Transplant Outcomes Among Lung Transplant Recipients

**Background:** Mycophenolic acid (MPA), the current anti-proliferative immunosuppression agent of choice for lung transplant recipients, demonstrates extensive variability in both therapeutic and adverse drug effects. The primary target of MPA is inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in de novo purine synthesis. Due to their dependence on this pathway, lymphocytes are particularly susceptible to MPA, making it an ideal immunosuppressant. We aim to investigate how genetic and clinical factors influence MPA effects on lymphocyte function in lung transplant recipients.

**Methods:** Lung transplant candidates were consented at the time of waitlisting and peripheral blood samples were obtained upon admission for transplantation. Lymphocytes were isolated via negative selection and cultured in the presence of varying concentrations of MPA for 72hrs under activating (IL-2, CD3/CD28) or non-activating (IL-2 only) conditions. Cells were subsequently stimulated with a cocktail of PMA and ionomycin and proliferation and effector functions at were assessed via flow cytometry. Proliferation and viability data were used to define sensitivity to MPA, and patients were followed prospectively to determine how their sensitivity to MPA influenced clinical outcomes and MPA immunosuppression management.

**Interim Results:** To date we have enrolled 33 lung transplant recipients of which 23 have undergone transplantation and have provided a pre-transplant peripheral blood sample. Median age at transplant was 63 (IQR 52-69) and the most common indication was interstitial lung disease (52%). Pre-transplant lymphocyte viability (LVR) was calculated at both low (1.0ng/ul) and high (5.0ng/ul) MPA. Overall, low MPA trended towards no effect on lymphocyte viability and effector functions. Median LVR was 1.01 at low MPA and 0.87 at high MPA. At high MPA, patients with lower LVR trended towards less proliferation and decreased cytokine production. At a median follow up of 166 days post-transplant (IQR 90-229 days), lower LVR was correlated with the development of acute cellular rejection as well as interruption in MPA administration.

**Conclusions and Future Directions:** We have demonstrated that lung transplant candidates exhibit varying sensitivity to MPA which may influence post-transplant response to MPA and other clinical outcomes. Upon completion of cohort enrollment and prospective investigation, we will determine the association of this pre-transplant lymphocyte MPA sensitivity with post-transplant outcomes including immunosuppression interruption, allograft rejection and infection. Additionally, we will assess differential gene expression among the most highly sensitive and resistant individuals to further understand pathways involved in MPA response and potentially identify predictors of MPA responsivity with the goal of guiding a more personalized approach to immunosuppression in the future.

Harold Amos Medical Faculty Development Program

Name: Kathy Wright, PhD, RN

Current Institution: The Ohio State University, College of Nursing

Mentor(s): Karen Rose, Karen M. Rose, PhD, RN, FGSA, FAAN and

Cindy Anderson, PhD, RN, APRN-CNP, ANEF, FAHA, FNAP, FAAN

College: The Ohio State University, College of Nursing

Medical/Dental/Nursing PhD School: University of Utah, College of Nursing

Residency: N/A

Fellowship: N/A

Title of Project: Improving stress and hypertension outcomes in African American female caregivers of persons living with Alzheimer’s disease and related dementias

No demographic group is more at risk for the double jeopardy of caregiving stress and hypertension than African American women caring for a family member with Alzheimer’s disease and related dementias (ADRD). Both situations lead to reduced quality of life and cardiovascular disease—a complication of uncontrolled hypertension. Maintaining the health of these caregivers is critical to support the well-being of the care recipients. Although some multi-component interventions have addressed ADRD caregiver's stress and quality of life, gaps remain in targeting interventions to address the complexity of chronic caregiving stress and hypertension self-care (adoption of healthy behaviors) in African American women. This pilot study funded by the National Institutes on Aging (1R21AG077069) builds on my earlier work which showed that stress, blood pressure knowledge, and complex diet information deficits all interfered with older African American women’s hypertension self-care. My Stage I pilot study is based on the scientific rationale that addressing stress reactivity/stress resilience, the psychological and physiological response of the body to stress, as the underlying mechanism will facilitate behavioral change. In this way we can improve health outcomes (stress, quality of life, cardiovascular disease risk). A small-scale two-group randomized controlled (RCT) pilot study of 28 African American female caregivers, age 40 and older with hypertension, is used in the ongoing study. Participants are randomized to either Mindfulness in Motion plus the Dietary Approaches to Stop Hypertension (MIM DASH) or Alzheimer’s Association Caregiver Training (attention control) in 8-weekly, 1-hour group sessions via telehealth (video and telephone access). After completion of the intervention, both groups receive four bi-monthly follow-up calls over the 9-months. To my knowledge, this is the first study that a) systematically employs one of the Science of Behavioral Change key mechanisms underlying successful adoption of health behaviors—stress reactivity/stress resilience and b) focuses solely on African American female caregivers of people living with dementia. The aims are a) determine the feasibility and acceptability of MIM DASH and Caregiver Training for African American female caregivers with hypertension; b) explore the impact of MIM DASH as compared to Caregiving Training on caregiver stress and quality of life; quality of life; and c) explore the potential mediation effects of stress reactivity/stress resilience between MIM DASH or Caregiver Training and self-care behaviors. Enhancing the health of family caregivers is essential amid rising demand for ADRD care. Study findings will inform the infrastructure for a R01 submission February 2024. Following the National Institute on Aging's stages of health behavior intervention development, my study aims to contribute to scalable solutions in the future that control cardiovascular disease risk factors such as hypertension in African American family caregivers.

Harold Amos Medical Faculty Development Program

Name: Debra Nana Yeboa

Current Institution: MD Anderson Cancer Center

Mentor(s): Dave Grosshans

College: Spelman

Medical/Dental/Nursing PhD School: UPenn SOM

Residency: Yale

Title of Project: Innovating brain cancer management by revolutionizing stereotactic radiotherapy for surgical brain metastases

**Purpose/Objective(s):** Postoperative stereotactic radiation therapy/radiosurgery (SRT/SRS) is being evaluated in comparison to Preoperative SRT for brain metastases (mets) in a limited number of prospective clinical trials. Our objective is to address the significant knowledge gap concerning the logistics of preoperative SRT in comparison to postoperative SRT in a randomized controlled study.
**Materials/Methods:** Patients with brain mets with at least 1 surgically operable met were randomized (1:1) to Preop vs Postop SRT. In this abstract we present non-primary endpoint data on the trial concept and logistics of treatment for this data safety monitoring board reviewed study. Patients enrolled had 1-2 lesions resected and <15 lesions treated at time of SRT to best reflect the standard population that receive SRT and surgery at our institution.
**Results:** From 12/2018 to 1/2023, 103 patients with 1-2 operable brain mets were enrolled and randomized to Preop (n=51) or Postop (n=52) SRT. Males represented 55% of the cohort compared to females, and median age was 59 years. The most frequent histologies enrolled were lung (29%), renal cell (15%), melanoma (14%), and breast (12%) cancers. The majority of patients (81%) had 1-4 brain mets on their baseline MRI and 91% subsequently had a single lesion resected. Eighty-three patients completed both SRT and surgery, while 9% received no therapy due to drop out before study therapy initiation. Among patients receiving both therapies in the combined cohort, 69% received Gamma Knife (GK) to the randomized cavity lesion compared to 31% receiving LINAC based SRT. Patients receiving treatment of a lesion or cavity with single fraction SRT alone was 51% in the Preop arm vs 29% in the Postop arm. Patients receiving treatment with multi-fraction (3-5 SRT) alone was 65% in the Postop cohort in contrast to 47% in the Preop cohort. Time from randomization to surgery was 11.7 days vs 12.8 days in the Postop vs Preop cohorts (p=NS). The average time from RT to surgery was 7 days in the Preop arm and 23.2 days in the Postop arm (to allow for incisional healing time). Postoperative morbidities were not significantly different between the two groups (p =0.875) with 30-day any event rates of 55 vs 53% in the Preop vs Postop cohorts.

**Conclusion:** In one of the early initiated randomized prospective cohorts of Preop vs Postop SRT, we demonstrated logistical feasibility with an efficient clinical trial workflow for study treatment. Differences in Preop vs Postop logistics reflect clinical practice differences in time-to-treatment. Importantly Preop did not delay or change the time to surgery, and postoperative morbidities were not significantly different between the two groups.

These highlight this novel approach may offer at least equivalent logistics with potential benefits in the primary tumor control outcomes still to be determined in this ongoing phase III trial. Our data provides insights in the practical management of patients receiving these two modalities of therapy, and further data at the completion of trial will address relevant primary outcomes.