Harold Amos Medical Faculty Development Program

**Name:** Tamorah Lewis MD, PhD

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**Mentor(s):** J Steven Leeder and Jeff Reese

**College**: Boston College

**Medical/Dental/Nursing PhD School**: The Johns Hopkins University School of Medicine

**Residency**: Pediatrics, The Johns Hopkins University School of Medicine

**Fellowship**: Neonatal / Perinatal Medicine & Clinical Pharmacology, The Johns Hopkins University School of Medicine

**Title of Project:** The effects of age and genetics on exposure to nonsteroidal anti-inflammatory drugs in premature infants

**Background** With traditional mg/kg dosing of indomethacin in preterm infants, systemic plasma drug exposures range 14-fold. Given that indomethacin therapy in the NICU is associated with unpredictable clinical efficacy and toxicity, it is imperative to refine our understanding of the variables which influence the dose-exposure relationship. We aim to develop a pharmacokinetic model in preterm infants which will be used for dose-individualization in prospective studies.

**Methods** A single center prospective cohort study enrolling all infants less than 32 weeks gestational age at birth treated with indomethacin within the first month of life. After consent obtained, infants had plasma, dried blood spot and urine samples collected for quantification of indomethacin and metabolites via mass spectrometry / high-performance liquid chromatography (MS/HPLC). In addition, we collected samples for DNA isolation and genotyping. Demographic and clinical drug response was recorded. Pharmacokinetic modelling was performed in NONMEM.

**Results** 53 preterm infants had full data available for analysis. The data from the first 38 infants were used for model development and the remaining 15 were reserved for model validation. Most infants received the first dose of indomethacin at less than 24 hours after birth (range 0.01 days to 18.2 days). The median weight at treatment was 779 grams (range 445-2630 grams). The median gestational age at time of treatment was 26 weeks (range 22 weeks – 34 weeks). Based on a population pharmacokinetic model, the population estimate volume of distribution for indomethacin was 0.47 L/kg, the renal clearance 0.017 ml/kg/hr and the hepatic clearance 0.49 ml/kg/hr. Postnatal age and CYP2C9 genotype were significant covariates for clearance in the final PK model. The PK model was able to accurately capture plasma and urine drug concentrations in the validation cohort.

**Next Steps** Weight-based dosing does not sufficiently account for extremely under-developed clearance and rapid maturation of drug disposition in the first weeks after birth. This population pharmacokinetic model, also accounting for the effect of age and genotype, will be used to build a dose-individualization tool. This tool has the goal to standardize plasma drug exposure by giving each neonate a unique dose. This dose-individualization approach will be prospectively compared to standard weight-based dosing, with the hypothesis that a precision therapeutics approach will lead to improved efficacy and decreased toxicity.

Harold Amos Medical Faculty Development Program

Name: E.R. Chulie Ulloa, MD, MSc

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College: UC San Diego

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

Residency: Boston Children’s Hospital

Fellowship: Children’s Hospital of Philadelphia

Title of Project: COVID-19: Healthy School Restart

**Background:** Understanding SARS-CoV-2 infection in children is necessary to reopen schools safely.

**Methods:** We measured SARS-CoV-2 infection in 320 learners [10.5 ± 2.1(sd); 7-17 y.o.] at four diverse schools with either remote or on-site learning. Schools A and B served low-income Hispanic learners; school C served many special-needs learners; and all provided predominantly remote instruction. School D served middle- and upper-income learners, with predominantly on-site instruction. Testing occurred in the fall (2020), and 6-8 weeks later during the fall-winter surge (notable for a tenfold increase in COVID-19 cases). Immune responses and mitigation fidelity were also measured.

**Results:** We found SARS-CoV-2 infections in 17 learners only during the surge. School A (97% remote learners) had the highest infection (10/70, 14.3%, p<0.01) and IgG positivity rates (13/66, 19.7%). School D (93% on-site learners) had the lowest infection and IgG positivity rates (1/63, 1.6%). Mitigation compliance [physical distancing (mean 87.4%) and face covering (91.3%)] was remarkably high at all schools. Documented SARS-CoV-2-infected learners had neutralizing antibodies (94.7%), robust IFN-γ+ T cell responses, and reduced monocytes.

Harold Amos Medical Faculty Development Program

Name: Mabel Toribio

Institution: Massachusetts General Hospital and Harvard Medical School

Mentor(s): Steven Grinspoon and Markella Zanni

College: Duke University

Medical/Dental/Nursing PhD School: Johns Hopkins University School of Medicine

Residency: University of California, San Francisco

Fellowship: Massachusetts General Hospital

Title of Project: Cardiometabolic Effects of Gender-affirming Hormone Therapy Among Transgender Women with and at Risk for HIV

**Background:** Transgender women in the United States (US) and globally face an increased risk for HIV, with HIV prevalence rates highest among African-American/Black and Latinx transgender women. While anti-retroviral therapy (ART) has significantly increased the lifespan of people with HIV (PWH) and decreased AIDS-related mortality, rates of cardiovascular disease (CVD) have increased. In addition to ART, gender-affirming hormone therapy (GAHT) is integral to the care of transgender women with HIV (WWH). However, little is known about how GAHT affects the cardiometabolic health of transgender women with and at risk for HIV.

**Methods:** We are conducting a prospective longitudinal study assessing effects of GAHT among transgender women with and at risk for HIV. Thirty transgender women will undergo abdominal and cardiac MRI/MRS, whole body DEXA, oral glucose tolerance testing, and laboratory assessments related to select coagulation parameters prior to and after 12 months of newly initiated GAHT (estrogen replacement and testosterone suppression).

**Results:** The median age of currently enrolled transgender women (N=4) is 21.5 (20.5, 22) years; and the age that these women began to identify as transgender is 15.5 (13.3, 14) years. Twenty-five percent of transgender women in this initial cohort are African-American/Black. With respect to body composition, baseline median BMI is 27.1 (23.8, 32.9) kg/m2, median total body lean mass is 63.0 (58.6, 70.2) kg and median today body fat mass is 23.9 (17.3, 30.6) kg. All transgender women in this initial cohort have normal baseline lumbar and total hip bone mineral density (data not shown) as well as insulin sensitivity [Matsuda index: 4.5 (4.1, 5.0)] and HOMA-IR: 1.7 (1.3, 2.0)]. Baseline coagulation parameters (including levels of factor II, V, VII, VII, X, Fibrinogen, Antithrombin III, von Willebrand antigen, and protein S activity) also are normal save for one participant with a low baseline factor VII activity (data not shown).

**Conclusion:** Recruitment and enrollment for this study is currently ongoing. The baseline and longitudinal results from this study will ultimately be used to investigate CVD prevention strategies tailored to transgender women with and at risk for HIV who are receiving GAHT.

**Harold Amos Medical Faculty Development Program**

**Name:** Fatima Rodriguez, MD, MPH

**Current Institution:** Stanford University School of Medicine

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**College:** University of Pennsylvania

**Medical School:** Harvard Medical School/Harvard School of Public Health

**Residency:** Internal Medicine, Brigham and Women’s Hospital, Harvard Medical School

**Fellowship:** Cardiovascular Disease, Stanford University

**Title of Project**: *Cardiovascular Disease Risk Prediction and Prevention in Diverse Populations*

**Background:** There is little data on optimal cardiovascular disease prevention strategies for Hispanic and Asian populations, the two largest and most rapidly growing minority groups in the U.S.

**Objective:** To improve risk prediction models and prevention approaches for cardiovascular disease in diverse groups, including understudied disaggregated Hispanic and Asian populations.

**Methods:** This study leveraged data from an existing EHR-based cohort in Northern California that is uniquely enriched with disaggregated Hispanic and Asian patients. First, the performance of the Pooled Cohort Equations (PCE) was tested in this cohort (measured by calibration and discrimination) for disaggregated race/ethnic subgroups. Second, an ensemble of supervised machine learning (ML) models (gradient boosting machine, random forest, Lasso penalty, and extreme gradient boosting) were developed for atherosclerotic cardiovascular disease (ASCVD) risk prediction. Finally, weighted-K-nearest-neighbor (wKNN) regression models were used to identify historical EHR patients to model statin treatment decisions for primary prevention associated with the greatest percentage reduction in low density lipoprotein cholesterol (LDL-C) at 1 year of follow-up.

**Results:** The PCE overestimated ASCVD risk across this contemporary cohort by 20-60%, with heterogeneity by racial/ethnic subgroups. The predicted-to-observed ratio of ASCVD events ranged from 1.1 for Puerto Rican patients to 1.9 for Chinese patients. The discrimination also varied by subgroup and recalibration did not significantly improve the PCE’s performance. In the second analysis, the top performing ML model (gradient boosted machine) had improved performance (AUC 0.84, 95% Confidence Interval [CI]: 0.83-0.85) as compared with the PCE (AUC 0.78, 95% CI: 0.76-0.79). Incorporating additional structured EHR variables beyond traditional risk factors did not improve the model’s performance. Models performed well for Asian and Hispanic patients. An algorithm that used historical patient data was able to identify the statin treatment decision associated with the greatest LDL-C reduction. Based on the algorithm, nearly half (48%) of patients were recommended low- or moderate-intensity statins for maximum LDL-C reduction.

**Conclusions**: There is significant heterogeneity in disaggregated risk assessment by racial/ethnic subgroup. ML models allow for risk discrimination in a larger group of patients who did not meet eligibility for PCE estimates, as is common in clinical practice. EHR-based models may be useful to guide treatment decisions in areas of clinical uncertainty among diverse patients. A data-driven personalized statin recommendation approach may inform shared decision making in areas of uncertainty and highlight statin efficacy-effectiveness gaps in real-world settings.

**Harold Amos Medical Faculty Development Program**

Name: Gabriela Hobbs

Institution: Massachusetts General Hospital, Harvard Medical School

Mentor (s): Ann Mullally, Daniel Deangelo

Medical School: Mount Sinai Medical School

Residency: Brigham and Woman’s Hospital

Fellowship: Memorial Sloan Kettering Cancer Center

**Title of Project:** Improving allogeneic stem cell transplant outcomes in patients with myelofibrosis

**Background:**

Myelofibrosis (MF) is a lethal hematological malignancy associated with somatic mutations in JAK2, CALR or MPL. Ruxolitinib is the first JAK1/2 inhibitor approved for treatment of MF. Ruxolitinib does not prevent disease progression and thus, allogeneic hematopoietic cell transplantation (HCT) remains the only curative treatment. Ruxolitinib discontinuation, in preparation for HCT is challenging as patients experience return of symptoms/splenomegaly. Therefore, ruxolitinib is often continued during and after HCT in an off-label fashion, yet little is known about the safety of this approach.

Outcomes for patients with MF undergoing HCT have historically been poor, with overall survival (OS) estimates of 40% at 2 years. The leading causes of morbidity and mortality after HCT include infection, relapse and graft versus host disease (GVHD), which are not unique to MF. However, prolonged cytopenias after HCT are a particular challenge for MF patients due to poor graft function related to splenomegaly, which is common in MF, and underlying fibrosis that takes months to reverse.

The primary goal of this project is to investigate the safety and efficacy of ruxolitinib administered during transplantation. The exploratory aims of this research are to investigate the role of genetic testing after transplant to predict outcomes of patietns with MF undergoing HCT.

**Methods:**

I am conducting a phase II, multi-center, investigator-initiated trial investigating ruxolitinib given pre-, during- and post-HCT for patients with primary or secondary MF(NCT03427866). The accrual goal is 48 patients with 1-year GVHD free and relapse free survival (GRFS) as the primary endpoint. Secondary endpoints include overall and progression free survival, engraftment and incidence of acute and chronic GVHD, respectively. Patients will remain on ruxolitinib 5 mg BID until blood counts engraft at which point they may escalate to 10 mg BID.

Patient samples are collected before and at day 100 after HCT and an extended next generation sequencing (NGS) panel is utilized to investigate changes in genetic mutations with HCT. In addition, single-cell profiling at the same timepoints will be done to evaluate changes in the bone marrow composition with HCT.

**Results:** Between September 2018- and January 2021 26 patients have enrolled. Median age was 66 (range 46, 75) and 65% were male. 88% had 8/8 matched related grafts, and 92% had intermediate-2 or high risk disease by Dynamic International Prognostic Scoring System (DIPSS) at the time of HCT. At HCT, 58% had JAK2, 12% CALR, 12% MPL, and 35% ASXL1 mutations (Figure A). Ruxolitinib was well tolerated. The most common grade 3/4 hematologic adverse events (AE) were anemia (n=4), thrombocytopenia (n=3). There were few grade 3/4 non hematologic AEs that included infection (n=2) and hypertriglyceridemia (n=1). Median time to neutrophil engraftment was 15 days (range 11-38) after HCT. All but one patient achieved successful neutrophil engraftment. Clinical outcomes are summarized in Figure B. With median follow-up among survivors of 12 months (range 3, 24), 1-yr GRFS was 65%. OS, PFS, and cumulative incidence of NRM and relapse were 77%, 71%, 13% and 17%, respectively (Figure C). Cumulative incidence of grade II-IV and grade III-IV acute GVHD was 35% and 4%, respectively. There was no grade IV acute GVHD and only one case of grade III acute GVHD. Cumulative incidence of all chronic GVHD and moderate-severe chronic GVHD was 14% and 5%, respectively. There was no severe chronic GVHD and only one patient developed moderate chronic GVHD.

In terms of genetic testing; results are available for 14 patients with paired samples, including 6 with ASXL1 mutations. All but one patient, who remains in remission at last follow up, no longer had mutations detected by NGS at day 100 (Figure D). No patient samples have been successfully processed for single cell profiling thus far as the protocol was recently amended to allow sample collection for this purpose and the trial was on hold but due to reopen at the end of 2021.

**Discussion:**

Allogeneic HCT is the only curative treatment for patients with MF. Therapies that improve the morbidity and mortality associated with HCT are critical. Thus far, the results of the multicenter study demonstrate safety of ruxolitinib administration pre, during and post-HCT with very favorable engraftment rates and no unexpected toxicities of ruxolitinib use. In addition, the results of PFS, OS and GRFS are superior compared to historical reports. Incidence of severe acute and chronic GVHD are thus far minimal indicating excellent GVHD control with prophylactic ruxolitinib use. In terms of changes in mutational profile, most patients have lost their pre-HCT mutations. In terms of remission assessment and exploratory analysis, most patients appear to have a significant change in mutational status with HCT. One patient that had a detectable JAK2 mutation at day 100 remains in remission. Therefore, further investigation will include single gene PCR to more accurately detect the presence of mutations after transplant. At the completion of the trial, we will correlate 1 year survival and progression data with mutational profiles at day 100 after transplant.

