

TIMP-1. As secondary outcome measures, the association between SPM levels with disease severity by admission GCS will be determined at 24 hours post-TBI, and the association between SPM levels and GCS and mortality will be determined at 14-days. We hypothesize that SPM levels will be positively associated with admission and 14-day GCS and will be independently associated with 14-day survival. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Using the SPM lipidome as a biomarker of disease is a novel tool for future translational research. It will inform a foundational mechanistic framework for TBI pathophysiology and attenuation of neuroinflammation post-TBI, providing rationale for pre-clinical and clinical research focused on novel therapeutics

77085

### Impact of MYH6 Variants on Development and Clinical Course of Hypoplastic Left Heart Syndrome

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**ABSTRACT IMPACT:** This work represents a novel way in which genetic information can be used to improve clinical decision making as it pertains to both treatment and management of congenital heart disease. **OBJECTIVES/GOALS:** Our lab found that MYH6 variants are both enriched in hypoplastic left heart syndrome (HLHS) and associated with decreased cardiac transplant-free survival. To elucidate the mechanisms of MYH6 variant pathogenicity, we are assessing their impact on atrial function during HLHS development and progression. **METHODS/STUDY POPULATION:** We are using 2D speckle-based tracking to retrospectively evaluate echocardiograms (echos) from 51 HLHS patients, 17 with MYH6 variants and 34 matched controls. Atrial function will be assessed by myocardial strain and strain rate at seven time points, beginning at the time of the patients' earliest prenatal echo, and ending with their last available echo before death or cardiac transplant. Early left atrial function will examine the role of MYH6 variants in the development of HLHS in vivo, while longitudinal right atrial function will be assessed in order to look for differences that could be contributing to the decreased transplant-free survival seen in MYH6 variant carriers. **RESULTS/ANTICIPATED RESULTS:** We hypothesize that MYH6 variants cause HLHS by impairing early left atrial (LA) contractility, resulting in altered left ventricular hemodynamics and consequent hypoplasia. We therefore expect to find diminished prenatal LA function in HLHS patients with MYH6 variants. We also hypothesize that MYH6 variants continue to impair right atrial (RA) function in surgically-reconstructed HLHS hearts, necessitating earlier transplantation. Accordingly, we expect variant carriers to exhibit lower RA function at birth versus controls. We expect differences between groups to persist over time, and possibly increase in magnitude. In HLHS patients with MYH6 variants, we anticipate declining RA function will precede right ventricular function and therefore be an early indicator of transplant need. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** This study represents a novel way in which genetic information can inform clinical decision-making. Identifying MYH6 variants as an early cause of HLHS offers chances for intervention. Understanding long-term effects of MYH6 on right atrial function in HLHS may aid in cardiac transplant risk stratification, thus improving patient outcomes.

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### Fluconazole distribution in CNS and gynecological tissues in HIV-related cryptococcal meningitis decedents

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**ABSTRACT IMPACT:** Plasma and CSF are not reliable estimates of drug exposure in tissue compartments relevant for treatment and prevention of infectious diseases. **OBJECTIVES/GOALS:** Globally, high dose fluconazole is widely used in the management of cryptococcal meningitis. While it is known to readily penetrate into cerebrospinal (CSF), less is known about drug concentrations in brain parenchymal tissues. Similarly, distribution of fluconazole into gynecological tissues has not been robustly characterized. **METHODS/STUDY POPULATION:** With informed consent from next-of-kin, we conducted autopsies within 24h of death for hospitalized Ugandans receiving fluconazole for treatment or secondary prophylaxis of cryptococcal meningitis. Dosing history was abstracted from medical chart and caregiver interviews. Fluconazole concentrations were determined using high-performance liquid chromatography- tandem mass spectrometry (LC-MS/MS) in plasma, CSF, 10 brain compartments (frontal, parietal, and occipital lobes, corpus callosum, globus pallidus, hippocampus, midbrain, medulla oblongata, spinal cord, and choroid plexus) and 4 female genital compartments (cervix, vagina, ovary, and uterus), depending on tissue availability. Descriptive statistics of tissue to plasma ratios were used to describe concentrations relative to plasma. **RESULTS/ANTICIPATED RESULTS:** Fluconazole concentrations were measured in available tissues of 21 individuals with detectable fluconazole in plasma. Daily doses of fluconazole were 200 mg (n=4), 400 mg (n=1), 800 mg (n=4), 1200 mg (n=9) or unknown (n=3). CSF concentrations (n=10) ranged from 93-1380% (median 100%) of plasma while brain concentrations (n=3) across all 10 compartments ranged from 45% to 89% (median 69%) of plasma. In the female genital tract, cervical concentrations (n=10) were 9-78% (median 65%) of plasma and in the 2 individuals with available tissue, concentrations in vaginal, ovarian, and uterine tissues were similar to cervix, ranging from 63-105% of plasma. **DISCUSSION/SIGNIFICANCE OF FINDINGS:** Measuring drug concentrations directly in tissues, the presumed site of action, improves estimates of drug efficacy. While fluconazole concentrations in CSF were similar to plasma, actual brain tissues were consistently lower. Concentrations were similar between upper and lower female genital tracts, but were consistently lower than plasma.

### Regulatory Science/Team Science

10122

### Development of an In Vitro in Vivo Correlation of Itraconazole Spray-Dried Dispersion Tablets

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**ABSTRACT IMPACT:** As the number of poorly water-soluble drugs in development increases, our research will expand on the science behind improving drug solubility and absorption and ensuring that promising poorly-water solubility drugs do not fail drug