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## PERFORM: Persistent effects of intrauterine growth restriction (IUGR) on infant brain development: A comparative magnetoencephalography (MEG) study

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OBJECTIVES/GOALS: Evaluate the impact of intrauterine growth restriction (IUGR) on neonatal brain development using magnetoencephalography (MEG) and correlate findings with NICU Network Neurobehavioral scale (NNNS) scores at 1 month METHODS/STUDY POPULATION: In this prospective cohort study, we will enroll 30 participants, consisting of 15 neonates diagnosed with IUGR and 15 healthy controls, matched by gestational age, from the University of Arkansas for Medical Sciences. We will perform MEG scans at three key developmental stages: during fetal life, at 1 month, and at 3 months of age and a Bayley IV exam at 12 months of age. The NNNS assessments will be conducted at the 1-month visit to evaluate neurobehavioral outcomes. All MEG data will be synchronized with clinical evaluations and maternal health records to ensure comprehensive analysis. RESULTS/ANTICIPATED RESULTS: We anticipate that the study will reveal significant differences in brain maturation and neural activity patterns between IUGR-affected infants and healthy controls. Specifically, we expect to find altered neural connectivity and delayed maturation in the delta and theta frequency bands during the early neonatal period in the IUGR group. These anticipated neuroimaging findings will be correlated with NNNS scores to assess functional implications of the observed brain activity differences. If our hypotheses are confirmed, the study will provide robust biomarkers for early identification of neurodevelopmental delays in IUGR-affected infants, paving the way for targeted early interventions. DISCUSSION/SIGNIFICANCE OF IMPACT: This study could significantly enhance early detection and intervention strategies for IUGR, potentially reducing long-term neurodevelopmental challenges and improving clinical outcomes

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## Factors influencing pharmacokinetics of tacrolimus in hematopoietic stem cell transplantation: The integration of microbiome and pharmacogenomics

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OBJECTIVES/GOALS: Tacrolimus (TAC) is an immunosuppressant used after hematopoietic stem cell transplant (HSCT). Recently, TAC was found to be metabolized to a novel, less active metabolite by common gut microbiota. Our objective is to determine a microbiome signature that influences oral TAC pharmacokinetic (PK) and to develop a clinical tool to select the TAC dose. METHODS/STUDY POPULATION: This is an observational IRB approved microbiome-pharmacogenomic study using banked biospecimens and clinical data, TAC dose, and PK information from the electronic health record. Adult HSCT patients with pre-transplant DNA and stool specimens were included in this analysis if they received TAC in the first 100 days post-HSCT. A global diversity array was used for DNA pharmacogenomic (PGx) genotyping, and metagenomic shotgun sequencing was used for stool microbiome analysis. Spearman correlation will be used to identify potential stool microbiota associated with TAC PK. TAC trough concentrations at steady state will be modeled using nonlinear mixed effects (NLME) modeling to identify potential genetic and microbiota covariates that influence TAC clearance. RESULTS/ANTICIPATED RESULTS: We identified 53 eligible patients who had available DNA and 90 stool samples. The majority (n = 49, 92.5%) were of European ancestry. These patients had 920 (oral = 622, IV infusion = 298) TAC trough blood concentrations. We expect that patients who have high abundance of bacteria that metabolize or reduce the absorption of TAC will have lower blood concentrations and will require a higher IV to oral dose conversion ratio than those with lower abundance. Those patients will also require higher oral TAC daily doses. Low stool microbial diversity is expected to be associated with high oral TAC trough intra-patient variability in the first 100 days post-transplant. In the NLME model, PGx when combined with potential bacterial signature will better explain variability in TAC clearance. DISCUSSION/SIGNIFICANCE OF IMPACT: Combining PGx and microbiome biomarkers will provide a better understanding of the factors influencing TAC PK and lead to models for individualized dosing. To our knowledge, this is the first study to investigate the combined influence of microbiome and PGx on drug PK. The study is limited to the availability of samples in the biobank.

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## Elucidating individual complement activation products in driving inflammation and progressive hydrocephalus in murine neonatal germinal matrix hemorrhage*

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OBJECTIVES/GOALS: Germinal matrix hemorrhage (GMH) is a devastating disease of infancy that results in brain-related pathologies. Following rupture of vasculature in the brain, red blood cell (RBC) lysis, and hemoglobin breakdown results in heme/iron-related toxicities. We hypothesize that these cellular pathologies are mediated in part by the complement system. METHODS/STUDY POPULATION: Post-natal mice on day 4 (P4) were subjected to collagenase induced-GMH and treated with various complement inhibitors that function at different points in the complement pathway and differentially prevent the generation of specific complement activation products. The principle bioactive complement activation products are C3 opsonins (C3b, iC3b, and C3d), the proinflammatory anaphylatoxins (soluble C3a and C5a peptides), and the terminal cytolytic membrane attack complex (MAC). Experimental groups consisted of: Wild-type (WT) naïve mice, and WT GMH-mice treated with either PBS (vehicle),

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