

# UAMS SHOWCASE OF MEDICAL DISCOVERIES

## **Arkansas Children's Research Institute: Making the Discoveries to Define and Deliver Unprecedented Child Health**

Feb. 11, 2026 | 4:00 – 6:00 PM

12th Floor, Jackson T. Stephens  
Spine & Neurosciences Institute

[www.archildrens.org/research](http://www.archildrens.org/research)

A Research & Innovation event featuring investigators from the Arkansas Children's Research Institute showcasing their work and discoveries.

# Welcome Message

Welcome to the first UAMS Showcase of Medical Discoveries of 2026. We are pleased to feature the Arkansas Children's Research Institute (ACRI), an institution that accelerates pediatric research breakthroughs through cutting-edge cores, collaborative networks, and innovative programs across Arkansas. Researchers at ACRI are addressing a wide spectrum of children's health concerns that impact families throughout our state.



**Daniel Voth, PhD**  
*Vice Chancellor for  
Research & Innovation*

Through specialized programs and centers—such as the Asthma and Respiratory Disorders Research Program and the Arkansas Children's Nutrition Center—paired with robust mentoring and funding opportunities, ACRI empowers investigators and partnering institutions to pioneer transformative discoveries in child health.

We are proud to highlight the exceptional work of the 35 researchers presenting at this showcase. Thank you for joining us in this opening showcase of the year as we drive pediatric innovation, health, and excellence in research at UAMS.

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## Empowering Futures: Nurturing Health Through Maternal and Pediatric Nutrition & Activity

Aline Andres, PhD, RD, CLC,  
Professor and Chief, Developmental Nutrition, Department of Pediatrics

Our research program is dedicated to examining the effects of **prenatal and postnatal nutrition** on offspring **growth, body composition, metabolism, and development**. To tackle these complex questions, we partner with research groups at Arkansas Children's Nutrition Center, Arkansas Children's, University of Arkansas for Medical Sciences and other institutions using multi-disciplinary approaches.

A longitudinal study of infant feeding followed children up to age 14 years to assess growth, development, cognitive function, metabolism, fitness and reproductive organ development, demonstrating through over 30 publications that both formulas yield similar outcomes up to adolescence.

A prenatal cohort is following mother/child pairs until age 14 years to understand how maternal health and children's lifestyle during childhood influence their growth, development and health trajectories. The study has yielded over 50 publications and demonstrated the roles of maternal and paternal health and lifestyles in shaping children's health and development.

A randomized controlled trial is investigating the benefits of antenatal breastmilk expression, or postnatal lactation-tailored healthy meals on lactation and human milk composition outcomes. The pilot study demonstrated benefits for both the mother (postpartum weight retention) and human milk composition.

Finally, a longitudinal, fully remote study will evaluate the nutritional status of mothers and children throughout the state of Arkansas to evaluate current feeding practices, access to food, childcare and healthcare.

Understanding how nutrition can program child's health will help us target specific interventions that can be implemented in the community to enhance maternal and child health in Arkansas and beyond.



**Translational Animal Research Core (TARC)**  
**Department of Animal Research**  
**Arkansas Children's Research Institute**

Umesh Wankhade, PhD  
Assistant Professor, Department of Pediatrics

The Translational Animal Research Core (TARC) at Arkansas Children's Research Institute (ACRI) provides comprehensive rodent and large-animal research infrastructure to support innovative, high-quality translational science focused on improving child health. The program operates within a 35,000-square-foot AAALAC-accredited animal research facility, supported by specialized surgical suites, a modern large-animal ICU, and 24/7 veterinary care. TARC offers expertise in rodent metabolic phenotyping, environmental and physiological monitoring, and full-service preclinical study execution. Large-animal capabilities include advanced surgical training, transplantation models, cardiopulmonary and critical care research, and device validation studies. Collectively, these resources position TARC as a regional hub for collaborative, compliant, and impactful preclinical research.



# Engineering Immune-Modulated, Growth-Capable Partial Heart Transplants

Jayden Carter, Alm Kassier, Herra Javed, Simon Chung, Elizabeth Hartman, Gabriella ten Have, Rushita Bagchi, Konrad Rajab

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Assistant Professor  
Department of Pediatrics

**Background:** Partial heart transplantation (PHT) allows implantation of living donor valves capable of growth, but lifelong immunosuppression carries significant risks including increased infection rates, nephrotoxicity, impaired somatic growth, and malignancy. Donor endothelial cells play a crucial role in allograft rejection and drive graft rejection by presenting alloantigens and recruiting leukocytes to the graft-host interface. Targeted endothelial modification through allograft engineering can reduce graft immunogenicity while preserving the cellular viability required for adaptive growth and remodeling.

**Methods:** Porcine pulmonary valves were treated *ex vivo* with mechanical abrasion, enzymatic digestion with collagenase-P (ColP), or detergent-based treatment using polidocanol (PDOC) or sodium dodecyl sulfate (SDS). Endothelial integrity was evaluated by CD31 immunohistochemistry, tissue injury by TUNEL, and architecture by hematoxylin and eosin staining. Complementary *in vitro* cell viability assays with human valvular endothelial and interstitial cells evaluated cell-type-specific sensitivity to treatment.

**Results:** Endothelial modification strategies produced distinct patterns of cellular injury and tissue preservation. Mechanical abrasion and ColP treatment resulted in inconsistent endothelial disruption accompanied by variable structural damage. SDS exposure caused near-complete, non-selective cellular removal across the valve. In contrast, PDOC treatment led to partial endothelial removal, with remaining CD31-positive endothelial cells exhibiting evidence of apoptosis localized to the luminal surface while largely preserving underlying leaflet architecture and interstitial cell populations. *In vitro*, PDOC exposure preferentially reduced endothelial cell viability over interstitial cells.

**Conclusion:** PDOC enables luminal-restricted endothelial modification while preserving underlying interstitial cell populations critical for valve growth and function. This strategy provides a targeted allograft engineering approach that could dramatically reduce immunogenicity and systemic immunosuppression, offering the first viable path toward growing, immune-tolerant pediatric heart valves.



# **GUARD (Generating Understanding and Awareness for Responsible Drug Use): A Novel Adolescent Nonmedical Prescription Drug Use Prevention Program**

Ronald G. Thompson, Jr., PhD, Judy Andrews, PhD, Srinivasa Gokarakonda, MD, MPH, J. Thostenson, MS, Alison H. Oliveto, PhD

Ronald G. Thompson, Jr., PhD  
Associate Professor, Department of Psychiatry,  
College of Medicine, UAMS

Nonmedical prescription drug use (NPDU) continues to be a major public health problem in the US. Due to the serious consequences of NPDU and its unique etiology relative to other substances, implementing accessible, focused adolescent NPDU prevention efforts are warranted. Thus, we developed GUARD (Generating Understanding and Awareness for Responsible Drug Use), a technology-enhanced adolescent NPDU prevention intervention. GUARD is comprised of two independent yet complementary research-based components: (1) a game-based application (app) intervention for adolescents (GUARD-T) that incorporates game design techniques, thinking, and mechanics in nongame contexts (given that digital media-based prevention programs are promising approaches to improve health outcomes and potentially a more efficacious and preferred delivery method to reach today's adolescents) to engage and motivate them while simultaneously promoting pro-health attitudes and behavior (delivered over Chromebook); and (2) a video-based educational program for their caregivers (GUARD-C) to educate them about the dangers of NPDU and provide tools for addressing this issue with adolescents in their care (delivered via email/text links to brief videos over the same time period as adolescents complete GUARD-T), given that caregivers can have a major influence on adolescent drug-use behaviors during early adolescence. We are preparing to conduct a mixed methods study with 30 Arkansas 8th grade students and 30 caregivers to obtain input on the usability, acceptability, and appropriateness of GUARD-T and GUARD-C, respectively, as well as any knowledge gains and attitude/intention changes after accessing the interventions. Participants will complete surveys prior to and immediately following access to the respective intervention and attend a virtual focus group with others in their cohort to provide additional feedback on the intervention. Results will be reviewed with a community advisory board (CAB) of expert stakeholders who will provide feedback before real world testing. Findings, if positive, will provide support for extramural grant submissions to further evaluate GUARD across the state and country.




# Epidemiological Assessment on Birth Outcomes and Birth Defects Among Marshallese Immigrants in Arkansas

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**Background & Purpose:** Marshallese immigrants are a unique group of Pacific islanders in the context of historical activities and foreign policies of the United States. In the past, the U.S. military conducted extensive nuclear weapons testing in the Marshall Islands. The operation had long-term economic and health impact in the region. Republic of Marshall Islands (RMI) became independent in 1986 under the Compact of Free Association (COFA). The COFA allows people in these territories to freely enter, lawfully reside and work in the US without visa. A large proportion of these immigrants are resided in Arkansas. The data on the birth outcomes and prevalence of birth defects among Marshallese immigrants is very scarce. The purpose of study is to investigate the birth-related outcomes and prevalence of birth defects among Marshallese in the comparison to other Asian and Pacific Islanders. The findings will help identify areas for tailored intervention.

**Methods:** The study used retrospective cross-sectional data by combining vital statistics from the Arkansas Department of Health, and registry data from the Arkansas Reproductive Health Monitoring System (ARHMS). Live births to Arkansas residents from 2001-2020 were surveyed. The Marshallese were identified from birth certificates where mother's birth state or birth country recorded as Marshall Islands. Birth defect cases from ARHMS were linked to the birth certificate data using infant birth dates and names as well as mothers' names. Descriptive statistical analysis was performed for general demographic and characteristics of infants and mothers. Prevalence Ratios (PR) were calculated using Poisson modeling with maternal age and education being adjusted and other Asian and Pacific Islanders as the reference group.



**Results:** Total 5427 live births to Marshallese mothers were identified from 2001-2020. The average maternal age was 27.3 years and most (92.1%) of Marshallese mothers had secondary education, though there was significant difference in post-secondary education compared to other Asian and Pacific Islanders. The rate of prenatal care in the first trimester was significantly lower among Marshallese, and complications of labor was significant higher than the reference group. Rates of preterm birth, low birthweight, infant anemia, birth injury and hyaline membrane disease were significant higher among infants born to the Marshallese mothers. The overall birth defect risk among Marshallese was no higher than the reference group after adjusting maternal age and education. However, higher prevalence of neural tube defects was observed among the Marshallese.

**Conclusion:** When compared to other Asian and Pacific Islanders, the birth outcomes of infants among Marshallese immigrants are less ideal with higher rates of preterm births, low birthweight and birth injuries. They also show higher risk in neural tube defects. Prenatal care and related health services in the state shall be tailored to better meet their needs to improve their reproductive health.



## Arkansas Children's Nutrition Center Metabolomics and Analytical Chemistry Core

Renny Lan, PhD, Assistant Professor

Operations Director of Metabolomics and Analytical Chemistry Core

Department of Pediatrics

Metabolomics is the comprehensive study of small molecules, known as metabolites, within cells, tissues, or organisms. It aims to elucidate metabolic processes and pathways by analyzing the chemical fingerprints left by cellular activity. The Arkansas Children's Nutrition Center (ACNC) is a research facility dedicated to improving child health by investigating the relationships among diet, nutrition, and nutrient utilization across development. This mission is supported by past and ongoing mother-child research studies conducted at the USDA-funded ACNC, as well as clinical research programs within Arkansas Children's Hospital and the University of Arkansas for Medical Sciences (UAMS).

The Metabolomics and Analytical Chemistry Core (MACC) at ACNC was established to conduct both targeted and untargeted metabolomics and lipidomics studies using state-of-the-art liquid chromatography-mass spectrometry (LC-MS) instrumentation and advanced data processing tools. The primary mission of MACC is to support USDA-ARS researchers, ACRI, UAMS, and external universities through collaborative projects and testing agreements. To date, MACC has developed robust untargeted metabolomics and untargeted lipidomics workflows for hypothesis generation across a wide range of biological matrices in both preclinical and clinical studies, including large clinical cohorts with more than 700 samples. Untargeted metabolomics data annotation at MACC leverages mzCloud, NIST, and GNPS spectral libraries, in addition to an ACNC in-house spectral library comprising 433 compounds with a focus on microbiome-derived metabolites. MACC has also developed several targeted assays for hypothesis testing, including short- and medium-chain fatty acid (SCFA and MCFA) assays, a bile acid assay, a tryptophan metabolism assay, an acylcarnitine assay, a soluble vitamin assay, and a uremic solute assay. In addition, MACC offers phytochemical assays targeting more than 500 compounds, as well as a combined phytochemical and microbial metabolomics panel encompassing approximately 200 metabolites.



## **Murine Partial Tracheal Occlusion Alters Respiratory Dynamics and Potentiates Airspace Injury**

Andrea D. Edwards PhD, Elham Shahreki MD, Madeline K Frazier BS, Rashika Joshi MD, Craig Porter PhD, Basilia Zingarelli MD PhD, Brian M Varisco MD

Brian Varisco, MD  
Professor, Vice Chancellor for Research  
Department of Pediatrics

The respiratory system relies on the coordinated function of multiple components to maximize efficiency. Dysfunction of one element often has deleterious effects on the others. For example, in chronic obstructive pulmonary disease (COPD), small airways dysfunction is associated with rapid emphysema progression. Similar interactions occur in bronchopulmonary dysplasia (BPD), where cystic lung disease and tracheobronchomalacia are often comorbid. Furthermore, childhood asthma predisposes to COPD in adulthood. While mouse models have elucidated key mechanisms in respiratory disease in many lung disorders, none have specifically examined how conducting airway dysfunction influences alveolar structure and function. To address this gap, we developed a murine partial tracheal occlusion (PTO) model and a complementary esophageal pressure monitoring technique. In 8-10-week-old C57BL/6 mice of both sexes, partial closure of the cervical trachea to 50% of its original diameter using a microsurgical clip was well tolerated, did not significantly impact mouse weight or metabolism, and did not significantly alter distal lung structure despite a 10 mmHg increase in transpulmonary pressure gradient. However, following tracheal aspiration of 0.5 units of porcine pancreatic elastase (PPE), mean linear intercept (MLI) was 20  $\mu\text{m}$  greater ( $p < 0.001$ ) in PPE+PTO mice compared to PPE+Sham mice. This PTO model provides a straightforward, well-tolerated model of conducting airway dysfunction that potentiates distal lung injury and could offer new insight into the molecular mechanisms of how mechanical forces influence pathological remodeling in the distal lung.

# Quantification of Regional Lung Strain Using a Novel Point-of-Care Lung Ultrasound Analysis Technique

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Pediatric acute respiratory distress syndrome (PARDS) is a disease process involving inflammation, reduced lung compliance, hypoxemia, and pulmonary edema. We hypothesize that strain due to mechanical ventilation can increase the risk of PARDS. To test this directly, this project developed a method of quantifying lung tissue strain using point-of-care ultrasound (POCUS) cine clips. The steps in quantification are cropping, derivation of a persistence map for selection of 20 centroids, centroid classification as pleural, superficial lung, or deeper lung, tracking of centroids from high persistence frames to low, re-sorting of the frame temporal sequence, and quantifying change in distance between centroids as strain. To test the tool, we quantified images of a pig with healthy lungs and ventilated with tidal volumes of 4, 6, 8, and 10 mL/kg. It consistently determined an accurate respiratory rate and there was a direct relationship between measured strain and tidal volume. This new tool could be useful for personalized titration of respiratory support in the Pediatric ICU.

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# Multimodal Assessment Detects Early Brain Changes in Childhood Acute Lymphoblastic Leukemia

Ellen van der Plas, Simon Chung, Jason Farrar, Xiawei Ou, Amy L. Conrad, Andrew Brown, Timothy Kosciak

Ellen van der Plas, PhD  
Associate Professor  
Department of Pediatrics

**Introduction:** Up to 60% of survivors of pediatric acute lymphoblastic leukemia (ALL) face neurocognitive impairment, compromising quality of life. Given limited rehabilitation options, early identification is critical for timely intervention. The objective of this ongoing, longitudinal, multimodal study integrates neurocognitive assessments, advanced quantitative MRI, and plasma biomarkers to determine neurodevelopmental changes in ALL patients during the first year of treatment.

**Methods:** Children (aged 3–10) newly diagnosed with ALL and a healthy control group completed three visits over one year, starting 1–2 months after diagnosis. Participants provided serial plasma samples, underwent neurocognitive testing with the NIH Toolbox (standard scores; mean=100; SD=15), and completed non-sedated, non-contrast-enhanced brain MRI on a 3T scanner. MRI sequences included: T1-weighted (for neuroanatomy) QALAS (quantitative parameter mapping); diffusion-weighted (white matter integrity and tractography); magnetic resonance spectroscopy (neurometabolites); and resting-state BOLD fMRI (for functional connectivity). Single molecule array assays quantified neuroaxonal injury (Neurofilament Light, NfL) and astroglial response (glial fibrillary acidic protein, GFAP) in plasma. We used linear mixed effects models to estimate the association of ALL status and visit with neurodevelopmental outcomes.



**Results:** Fifteen patients and 27 controls completed 34 and 69 visits, respectively. Neurocognitive testing demonstrated ALL patients compared with controls had significantly lower executive processes such as inhibitory control (Estimate [standard score]=-15.04, 95%CI=-23.69, -6.40), mental flexibility (Estimate [standard score]=-10.47, 95%CI=-17.93, -3.00), receptive language (Estimate [standard score]=-8.45, 95%CI=-14.97, -1.93), and coordination (Estimate [standard score]=-9.71, 95%CI=-16.60, -2.82). Plasma NFL was ~40 fold greater in patients than controls at first study visit 1-2 months post-diagnosis with partial recovery later in treatment (group\*visit interaction:  $F_{(2, 53)}=5.62$ ,  $p<0.01$ ). GFAP levels were somewhat elevated in ALL patients relative to controls (Estimate [pg/ml]=295.56, 95%CI=1.37, 589.74,  $p=0.06$ ), with no significant group\*visit interaction. MRI confirmed early white matter and metabolic disruption. Patients exhibited lower fractional anisotropy (FA) as early as 1-2 months post-diagnosis (e.g., superior frontal white matter FA; Estimate=-0.07, 95%CI=-0.09, -0.04), indicative of white matter injury. Metabolic profiles showed disrupted energy homeostasis, evidenced by higher lactate (Estimate=0.044, 95%CI=0.02, 0.07) and lower phosphocreatine (Estimate=-0.06, 95%CI=-0.10, -0.01). Higher plasma NFL concentrations were significantly associated with lower frontal white matter FA in ALL patients (Estimate=-1.89, 95%CI=-0.0003, -6.06).

**Conclusion:** Newly diagnosed ALL patients demonstrate converging evidence of early neurobiological alterations (plasma NFL, white matter injury and neurometabolites) which correspond to executive dysfunction compared with healthy peers. Future studies must determine whether these early markers predict long-term outcomes to identify actionable targets for urgently needed interventions.

# Failing to Test for Sex Differences Can Result in Unsupported Conclusions: Example of the Difference in Sex-Specific Significance Error in a Reanalysis of Brain Maturation during COVID-19 Lockdowns

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Department of Biostatistics

## Background:

Consideration of sex as a variable is increasingly regarded as important for replicability and generalizability of results. To maximize rigor, sex must be incorporated using valid statistical approaches. In one example, researchers tested for effects within each sex separately, but used an inappropriate approach of declaring sex differences when statistically significant differences were independently found in one sex but not the other. This approach has, for decades, been widely recognized as invalid. When applied to sex differences, it has been called the “Difference in Sex-Specific Significance” (DISS) error, which is a specific case of the “Differences in Nominal Significance” (DINS) error. When considering two groups, DISS can result in false positive findings of difference up to 50% of the time – no better than flipping a coin.

## Objective:

To use appropriate between-sex comparisons to assess the associations between COVID-19 lockdowns and cortical thickness in female and male adolescents.

## Design/Methods:

In the original manuscript, authors generated (n=87) and validated (n=22) normative cortical thickness curves in male and female adolescents, and tested differences for each of 68 brain regions (n=54). Using shared data, code, and normed region values, we replicated results reporting cortical thinning deviated significantly from normative values in 30 regions of the “female brain” and in two regions of the “male brain” when sexes were

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analyzed independently. We further replicated overall age acceleration with confidence intervals including the null for males but not females. Thereafter, we appropriately and directly compared cortical thickness for each of the 68 regions and overall age acceleration between females and males using two-sample t-tests and the same false discovery rate correction.

**Results:**

Cortical thinning was significantly greater in females than males in only one region, not thirty (Fig. 1). In the case of overall ‘age acceleration,’ the bootstrapped 95% confidence interval failed to exclude the null (Fig. 2), meaning that, based on the original authors’ threshold of statistical significance, the data do not convincingly support the claim of a sex difference.

**Conclusions:**

The DISS error resulted in unsupported conclusions regarding the association between COVID-19 lockdowns and sex differences in cortical thickness. Appropriate between-sex tests are essential for making sex-specific comparisons. Thorough and transparent reporting of data and code permits reanalysis of results to come to rigorous conclusions.

# Omics Approaches to Identify Calcineurin-Dependent Effectors in Cell Wall and Membrane Organization in the Human Pathogen *Aspergillus fumigatus*

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Calcineurin phosphatase (CN) orchestrates growth and virulence of *Aspergillus fumigatus*, a critical human fungal pathogen responsible for life-threatening infections in immunocompromised patients making it an attractive antifungal target. Understanding the CN network of proteins in *A. fumigatus* and the mechanism of how this phosphatase regulates important fungal-specific effectors involved in cell wall and membrane biosynthesis and organization will lead to designing novel therapeutic approaches for the treatment of invasive aspergillosis. Here we utilized whole proteomic/phosphoproteomic and lipidomic approaches to define CN-dependent regulation of various cell wall- and cell membrane-related effectors. Our two-pronged proteomic approach included: (1) Quantitative LC-MS/MS analysis to identify CN interactors via CN-tagged GFP using GFP-Trap® affinity purification; and (2) Comparative whole proteomic/phosphoproteomic analysis between the wild-type versus the CN-deletion mutant to identify CN-dependent effectors. Additionally, we systematically assessed the influence of CN on membrane organization via quantitative lipidome profiling by comparing the wild-type versus the CN mutant to define CN-dependent regulation. Our whole proteomic and lipidomic results from this holistic approach will provide a mechanistic understanding of how the CN network drives cell wall and membrane organization during growth and antifungal response in *A. fumigatus*.

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# Machine Learning-Powered Metabolite Identification in R: An Automated Workflow for Identifying Metabolomics Dark Matter

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Upwards of 90% of small molecules detected in LC-MS/MS-based untargeted metabolomics are unidentified due to limitations in current analytical techniques. Although this “dark matter” can significantly contribute to disease diagnosis and biomarker discovery, current identification methods are costly and resource-intensive. This study addresses these challenges by developing a computational workflow in R to encode the tandem mass spectra into simplified structural fingerprints, which can be predicted and related to known fingerprints in molecular databases. The developed pipeline includes different R packages such as RSQLite, SF, rcdk, chemminer, caret, sparsepca, rinchi, and rpubchem which finally improves metabolite identification in untargeted metabolomics.

A total of 2,973 mass spectra of known and unknown molecules from an in-house high resolution LC-MS/MS study were extracted from an SQL database (mzVault) using the RSQLite package. The collected spectra were converted into machine-readable numbers using the rawToHex and readBin functions from the SF package. SMILES representations of known molecules were obtained by querying their names against PubChem using the rpubchem package. The set of 166 Molecular ACCess System (MACCS) fingerprints were computed for known molecules based on their SMILES using rCDK and ChemmineR packages. In the next step, 166 random forest (RF) models were trained on MS<sup>2</sup> spectra of known molecules to model

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the MACCS fingerprints using the caret package. Before training, spectral data were normalized and subjected to dimensionality reduction using robust sparse principal component analysis (rSPCA) via the sparsepca package. The trained RF models were applied to high-resolution MS2 spectra of unknown molecules to predict their MACCS fingerprints, which were then used for similarity searches in the Human Metabolome Database (HMDB) using the Tanimoto coefficient. Retrieved candidates from HMDB were further refined based on LogP, topological polar surface area (TPSA), molecular mass, and retention time.

The workflow was tested on an LC-MS/MS dataset containing 1,071 known and 1,902 unknown compounds. Despite the high dimensionality, rSPCA reduced the data to 25 principal components, preserving 97% of variance. RF models achieved a mean accuracy of 0.87 in 3-fold cross-validation. On average,  $4.1 \pm 11.31$  unique HMDB molecules were listed for each unknown molecule, and the retrieved list was prioritized using a hybrid scoring function. Applying a Tanimoto similarity threshold ( $>0.7$ ), this workflow identified at least one HMDB match for 1,079 unknowns, improving metabolite identification by 57%. The incorporation of a hybrid scoring system based on Tanimoto similarity and physicochemical properties enhanced candidate ranking and structural elucidation of unknown metabolites.



## **Ignoring Cage-to-Cage Variability Can Increase False Positive Results**

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Professor, Department of Biostatistics

In preclinical cancer research, a great many animal experiments house multiple animals per cage (or enclosure). And commonly used statistical methods for many of those experiments is ANOVA or two-sample t-tests. These statistical methods assume all the animals are independent. However, the outcome responses from cage mates tend to become more correlated the longer they are housed together and the more sensitive the outcome is to external influences. The correlation manifests as cage-to-cage variability; that is, all other factors being the same, the means of the cages will vary. Though seldom reported in animal methods, and it should be, many experiments do not mix experimental groups within a cage. When all of the cage mates are of the same experimental group, ignoring cage variability in statistical analyses can increase the probability of a false positive result (i.e., Type I error). Here, we use real mouse data to demonstrate how ignoring cage variability in the usual ANOVAs of such experiments gives artificially lower p-values, and how the false discovery rate (FDR) increases as the cage variability increases.



# **The HEALthy Brain and Child Development (HBCD) Study: Overview and Initial Data Releases**

Ashley Acheson, Xiawei Ou, Lorraine McKelvey, and the HBCD Consortium

Ashley Acheson, PhD  
Professor, Psychiatry

The HEALthy Brain and Child Development (HBCD) Study is the largest long-term study of early childhood brain in the United States. The HBCD Study is recruiting over 7,200 mother-child dyads at 26 national sites and following them from the prenatal period to at least ages 9-10 with an extensive battery of neuroimaging (MRI, EEG), behavioral, physiological, psychological, and biospecimen assessments. The HBCD Study is well-positioned to dramatically advance understanding of childhood neurodevelopmental trajectories, including understanding impacts of prenatal exposures to drugs and toxicants, maternal health conditions, parental psychopathology, stress and other adversity, and social and environmental protective factors. To address these broad objectives, the HBCD Study is enrolling women enrolled will include: 1) a varied cohort that is representative of the US population; 2) pregnant woman with use of targeted substances (opioids, marijuana, alcohol, tobacco); and 3) demographically and behaviorally similar women without substance use in pregnancy to enable valid causal inferences. In addition, the HBCD Study will identify key developmental windows during which both harmful and protective environments have the most influence on later neurodevelopmental outcomes. The large, multi-modal, longitudinal, and generalizable dataset that will be publicly available, providing an unprecedented resource to scientists worldwide. The first release of data occurred in June of 2025 and included assessments collected during prenatal, 0-1 month-old, and 3-9 month-old timepoints. The next data release is planned for February 2026 and will include data from additional participants at those timepoints as well as data collected at 9-15 and 15-30 months old. Findings from the HBCD Study are expected to improve understanding of how the brain develops and is affected by exposure to substances and other environmental, social, and biological factors during pregnancy and after birth and have lasting impacts on future generations of children.

# The Presence of Non-pharmaceutical Interventions Correlates with Decreased Rates of Asthma Exacerbations and RSV infections in Arkansas

Katherine Caid, Grace Turner, Susanna Hartzell, Kim Cobb, Haley Long, Suzanne House, Dana Frederick, Bobby L Boyanton Jr, Rachel A Frenner, Robbie D Pesek, Akilah Jefferson, Tamara T Perry, Jing Jin, Scott Stewart, Joshua L Kennedy

Joshua Kennedy, MD

Associate Professor, Department of Pediatrics

## Rationale:

To reduce transmission of SARS-CoV-2, non-pharmaceutical interventions (NPIs), including school closures, hand hygiene, mask mandates, and social distancing, were enforced in Arkansas from 3/2020-2/2021. We hypothesized that the presence of NPIs would correlate with a decrease in asthma exacerbations and viral infections.

## Methods:

Demographic information was collected on subjects with asthma exacerbations or viral infections from 3/2018-5/2022, including age, race, ethnicity, and sex. To evaluate the effects of NPIs, three periods were considered: pre- (03/2018-02/2020), during (03/2020-02/2021), and post- (03/2021-05/2022) NPIs. ANOVA analysis and generalized linear models were performed to determine statistical significance. The stringency of NPIs was evaluated using publicly available data (Oxford Covid-19 Government Response Tracker), which allows for direct comparison of Arkansas NPI status to exacerbation data during the same time periods.

## Results:

5055 asthma exacerbations (3322 unique subjects) occurred between 3/2018-5/2022. Asthma exacerbations decreased from 3/2020-3/2021 and returned to pre-pandemic numbers by summer 2021 ( $p < 0.0001$ ). Similar downward trends occurred for respiratory syncytial virus (RSV) with out-of-season return in summer 2021 ( $p < 0.0001$ ). Rhinovirus was present throughout NPIs. The mean age of exacerbations decreased by 0.9 years when comparing the during NPIs and after NPIs periods ( $p = 0.0002$ ). An increase in the proportion of exacerbations was noted for non-black and other/unknown ethnicity subjects during and after NPIs.

## Conclusions:

Fewer asthma exacerbations occurred during the most significant NPI employment period (03/2020-02/2021), and an increase in exacerbations was seen as mitigation strategies were relaxed, which correlated with timing of increasing RSV infections.

# Food-Induced Anaphylaxis: Visualization of Airway Contractility with Allergen Exposure in Precision Cut Lung Slices from a Donor with History of Fatal Anaphylaxis to Cashew

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**Rationale:** Peanuts and tree nuts account for the majority of anaphylaxis attributable deaths. We hypothesized that exposure to peanut or cashew allergen in post-mortem lung tissue from a donor with history of food allergy would cause airway contractility.

**Methods:** Precision cut lung slices (PCLS) were prepared from a food allergic (FA) and a nonallergic control donor. PCLS maintain viability and responsiveness to contractile agonists for weeks in culture. Baseline photomicrographs measuring airway cross-sectional area were taken before and after 15-minute exposure to histamine and carbachol. PCLS with at least 50% contraction to histamine/carbachol were then exposed to 1mg/mL peanut or cashew. Airways were evaluated at 20-, 60-, and 360-minutes post-exposure. Serum was obtained from donors for specific IgE.

**Results:** The FA donor was 11yo with reported history of fatal anaphylaxis to cashew. The nonallergic donor was 20yo with no significant medical history. The FA donor had specific IgE to peanut (11.7kUA/L) and cashew (4.13kUA/L), but testing was negative in the nonallergic donor. In the FA donor, 6/7 PCLS demonstrated peak contractile responses to peanut after 60-minutes (mean 61% contraction, SD 34%) compared to 2/6 cashew exposed airways (mean 17% contraction, SD 12.2%). Despite airway responsiveness to contractile agonists, no airways responded to peanut in the nonallergic donor PCLS.

**Conclusions:** In the FA donor, peanut allergen exposure correlates with a quantifiable decrease in PCLS airway diameter. The diminished responses seen to cashew despite positive specific IgE tests may represent donor anergy, given that cashew was reported as the fatal anaphylaxis culprit antigen.

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# Intramuscular Antibiotics Administered at the Tourniquet Site Reduces Infection Rates in a Contaminated, Ischemic Limb Model

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**Introduction:** Tourniquets are sometimes necessary for hemorrhage control in the setting of traumatic limb injuries but may increase the risk of ischemic complications, including infection and impaired wound healing. Antibiotics may help to reduce infection rates in combat-associated injuries, however intravenous access is not always readily available, particularly in austere environments. This study evaluates the effect of Ertapenem administered intramuscularly at the tourniquet site on infection rates in a 24-hour porcine contaminated wound model.

**Materials and Methods:** Yorkshire pigs (n=12; 33.6±1.4kg) were anesthetized. A crush laceration injury was created in the ventral forelimb and inoculated with *Staphylococcus aureus* (SA) and *Klebsiella pneumoniae* (KP). Subsequently, a tourniquet was applied for 4 hours. Pigs were randomized into a Control group (n=6) receiving 1% lidocaine and an Ertapenem group (n=6) receiving 1% lidocaine and Ertapenem, both administered intramuscularly at the tourniquet site. Pigs were monitored continuously for 24 hours and resuscitated according to critical care guidelines. Wound cultures were obtained 4 and 24 hours post-injury and compared against baseline cultures taken prior to inoculation.

**Results:** No animal in either group had SA or KP present in the wound at baseline. 100% (n=6) of the Control animal wounds grew SA and KP in both the superficial and deep cultures at 4 and 24 hours. In the Ertapenem group, superficial swabs were positive for SA and/or KP in 67% (n=4) of the animals at 4 hours ( $X^2=2.4$ ,  $P=0.1213$ ), but were negative in all animals by 24 hours ( $X^2=12$ ,  $P=0.00053$ ). 50% (n=3) of the tissue biopsies in the Ertapenem group grew SA and/or KP at both 4 and 24 hours ( $X^2=4.0$   $P=0.0455$ ). By the study end, the mean arterial pressure in the Control (77.7±4.4mmHg) and Ertapenem groups (69.7±5.1mmHg) were similar ( $p>0.05$ ). There was no significant difference in PaO<sub>2</sub>/FiO<sub>2</sub> ratio between the Control (396.6±22.4mmHg) and Ertapenem groups (337.0±33.7mmHg;  $p>0.05$ ).

**Conclusions:** Ertapenem administered intramuscularly at the tourniquet site in a contaminated crush laceration with ischemia reduced the rates of SA and/or KP infection by 50% with no changes in hemodynamics or oxygenation. Intramuscularly administered antibiotics with tourniquet placement represents a potential therapy for combat-injured patients to reduce infectious complications, even in austere environments where intravenous access may not be readily available.



# Exploring the Use of Engineered Probiotic Yeast to Address Gastrointestinal Disease

Zachary Waldrip, PhD  
Instructor, Surgery

Gastrointestinal (GI) conditions caused by the introduction of harmful bacterial species are often mediated through the secretion of toxin proteins that can penetrate the epithelial barriers of the gut and have cytotoxic effects. This results in an array of conditions from acute colitis to distal organ failure. These bacteria and their toxins are often introduced by ingestion of contaminated foods or contact with contaminated water supplies or human waste. Various enteric toxins such as Shiga toxins are also implicated in the exacerbation of inflammatory bowel disease (IBD) and alone can induce symptoms similar to those seen in IBD. Collectively, enteric toxin-mediated infections affect tens of millions of people globally, making them a widespread problem. We are proposing the generation of a biotherapeutic agent in the form of probiotic yeast cells (*Saccharomyces boulardii*) that have been genetically modified to express antibodies on their cell surface. This yeast is already used as a probiotic to alleviate diarrhea-associated GI conditions such as IBD. Functionally, these ingestible antibody-coated yeast cells would act like a sponge to sequester the toxin proteins in the GI tract, preventing them from interacting with their target host cells and exerting their damaging effects. Our hypothesis is that probiotic yeast cells can express and display antibodies or other proteins on the cell surface that facilitate effective binding to soluble target proteins in a colonic environment. Here we have demonstrated the ability to engineer wild-type probiotic *S. boulardii* cells to express functional antibodies against the proteins Fibroblast Activation Protein (FAP) and lysozyme. To begin investigating therapeutic potential, we have used simulated colonic fluids to test antibody cell-surface expression, function, and yeast viability in vitro.



## Center for Childhood Obesity Prevention

Elisabet Borsheim, PhD  
Professor, Department of Pediatrics (secondary:  
Geriatrics)

Childhood obesity remains a major public health issue in the United States and is particularly severe in Arkansas, which consistently ranks among the states with the highest prevalence. Childhood obesity contributes to increased risks for diabetes, cardiovascular disease, and reduced quality of life, creating a lifelong burden on individuals, families, and health systems. Addressing this complex problem requires an integrated, multidisciplinary research strategy that links discovery science to clinical and community translation.

The Center for Childhood Obesity Prevention (CCOP) at the Arkansas Children's Research Institute (ACRI) was created to address this need. Over the first 10 years of funding from the National Institute of General Medical Sciences (Centers of Biomedical Research Excellence (COBRE) P20GM109096), the CCOP has developed a cadre of independent investigators, established shared-use infrastructure, and built enduring community partnerships. CCOP also founded three institutional cores, which now serve a multitude of investigators: Biostatistics, Metabolism & Bioenergetics, and Community Engagement.

The CCOP continues to strengthen and expand shared-use cores, supports a pilot project program, and maintains innovative mentoring and career development initiatives. The center is working toward long-term capacity to advance childhood obesity research and improve health outcomes in Arkansas and beyond.

# School Performance in Pediatric Intensive Care Unit Survivors

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Peter M. Mourani<sup>3</sup>, Clare C. Brown<sup>2</sup>, Aline B. Maddux<sup>4</sup>

Claire Foster, MD, MPH  
Fellow Physician, Pediatric Critical Care

**Background:** Children who survive critical illness are at risk of long-term sequelae, including cognitive impairment. School-based standardized testing offers a valuable way to meaningfully assess cognitive health in large cohorts of pediatric intensive care unit (PICU) survivors.

**Objective:** To evaluate the association between critical illness/injury and academic achievement.

**Design/Methods:** We conducted a single-center retrospective study evaluating PICU survivors (7-17 years-old at admission) with an admission to our PICU between 2008 and 2018. We collected statewide school data, including academic achievement testing, from the Arkansas Department of Education Data Center. Test scores were converted to z-scores based on subject, year, and grade level. We used propensity score matching to pair PICU survivors who had standardized test scores within two years before PICU admission (baseline year) with controls from the state testing data matched on gender, race, school, free/reduced lunch status, homelessness, English learner status, grade in the baseline year (3rd-10th), and baseline test score quintile. Separate matches were performed for math and language arts (LA), with 1,403 and 1,410 control students, respectively. We compared frequency (%) of PICU survivors with post-discharge test scores within two years of discharge to their matched controls using a


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chi-square test. For PICU survivors with post-discharge scores, we used difference-in-difference analysis to compare changes in scores from pre- to post-PICU discharge between PICU patients and matched controls using multivariable linear regression, adjusting for above sociodemographic and educational variables and receipt of education accommodations (e.g., Individualized Education or 504 Plan).

**Results:** Among 1,412 PICU survivors, pre-admission scores were below the state averages in math ( $z=-0.21$ ) and LA ( $z=-0.20$ ). Fewer PICU patients had test scores available after admission compared to controls for both math (58% vs 65%,  $p < 0.001$ ) and LA (58% vs 65%,  $p < 0.001$ ). PICU survivors' academic assessment z-scores declined in both math and LA (Figure 1). In adjusted analyses, PICU survivors experienced a significant decline in math scores relative to controls (-0.08 [95%CI -0.15, -0.01]). They also had a relative decline in LA but this difference was not significant (-0.06 [95%CI -0.13, 0.003]).

**Conclusions:** Relative to controls, PICU survivors were less likely to have post-admission standardized assessments and showed greater declines in math scores. Further research is needed to identify risk factors for score declines and non-return to standardized testing.

# Systems Biology of Early Atopy: The SUNBEAM Study from the NIH/NIAID Consortium for Food Allergy Research

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Stacie M. Jones, MD

Study PI, Professor, Pediatrics/Allergy Immunology

**Background:** Food allergy and atopic dermatitis (AD) are among the most common diseases of infancy. These are considered the first features of the “atopic march.” It is unclear as to why some infants develop these diseases and some do not. In order to evaluate preventative strategies, there is a need to identify risk factors that can be used to define high risk groups.

**Methods:** SUNBEAM is the first birth cohort study focused designed as a systems biology approach to defining targets of prevention for food allergy and atopic dermatitis. This study is a 12-center, longitudinal cohort study funded by the NIH/NIAID Consortium for Food Allergy Research. The study population includes pregnant mothers and their offspring, followed from the initial prenatal visit through age 6 years. Study Objectives include the following: 1) To study the role and interrelationships of established and novel clinical, environmental, biological and genetic prenatal and early-life factors in the development of allergic diseases through age 6 years, with an emphasis on food allergy and atopic dermatitis; 2) To apply systems biology to identify mechanisms and biomarkers underlying the development of food allergy, atopic dermatitis, and their endotypes, 3) To collect, process, and assay or store environmental and biological samples for current and future use in the study of allergic disease development. A wide array of survey data and biologic samples are collected throughout the study.

**Results:** Study enrollment occurred from April 2000 through December 2025. The Arkansas SUNBEAM cohort contributed a unique population of maternal-infant dyads with diversity in the study population characteristics including race/ethnicity, rurality, household income, and social determinants of health to the overall study population.

**Conclusions:** The SUNBEAM birth cohort provides a rich repository of data and specimens to interrogate mechanisms and determinants of early allergic outcomes, with an emphasis on FA, AD, and systems biology.

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# Utilizing Telemedicine for Drug Allergy Risk Stratification Among a Southern US Pediatric Cohort: Enhancing Quality and Access to Care

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Stacie M. Jones, MD

Study PI, Professor, Pediatrics/Allergy Immunology

**Rationale:** The prevalence of hypersensitivity drug reactions (HDRs) in children is rising with mislabeling and failure to de-label as contributing factors. This quality initiative study evaluated telemedicine (TM) as an alternative to in-person (IP) visits for initial drug allergy consultation employing updated risk stratification.

**Methods:** Chart review of pediatric patients from the Arkansas Children's Drug Allergy Clinic was completed over two cycles: Cycle 1 (C1:9/2023-2/2024) and Cycle 2 (C2:3/2024-9/2024). Initial visits were conducted via TM or IP to obtain HDR history, stratify risk and determine indication for skin testing (ST) and/or oral drug challenge (ODC).

**Results:** Overall, 195 HDRs were evaluated in 122 patients (median age=7 (0.53-19.78) years; C1:109 HDRs in 66 patients; C2:86 HDRs in 56 patients. TM visits doubled from C1 to C2 (33/109, (30%) vs. 53/86 (62%);  $p=0.0001$ ), yet fewer ST were ordered in C2 compared to C1 (C1:18/86 (20%) vs. 41/109 (38%);  $p=0.0125$ ). No differences in ST rates were noted across cycles for TM and IP. Likewise, ODC were conducted at a similar rate between cycles (C1:89/109(82%) vs. C2:68/86(79%),  $p=NS$ ), and between cycles for TM (75%) and IP (84%;  $p=NS$ ). Antibiotic de-labeling occurred in 120/195 (62%) HDRs overall. Of HDRs involving penicillin, delabeling increased for TM visits from C1 28/62(45%) to C2:17/21 (81%);  $p=0.0053$  and decreased for IP from C1:34/62 (55%) to C2:4/21 (19%),  $p=0.005$ .

**Conclusions:** This study supports initial telemedicine consultations for drug allergy as an efficient clinically-proven method to address HDRs providing a path to antibiotic delabeling that may benefit highly rural regions and improve access to care.

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# Ultra-High Resolution Neuroimaging of the Postmortem Human Brain

Tim Kosciak, PhD

Associate Professor, Pediatric Neurology

Understanding how the brain's layers change across a lifetime requires quantifying neuroanatomy at a scale that sits between traditional microscopy and clinical imaging. We present our systematic approach using ultra-high-resolution postmortem MRI. We achieve a 150-micron resolution—100s of times more detailed than standard clinical scans—without the tissue tearing or distortions caused by physical sectioning. This method allows for the virtual 3D reconstruction of neuroanatomy in its natural state. When paired with donor DNA and individual characterization, this collection will serve as a foundational dataset for analyzing how neuroanatomical structure changes during development and declines in later life.



## Epigenetic Stabilization of Oncogenic Transcription and Apoptotic Resistance in Fusion-Driven Pediatric AML

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Samrat Roy Choudhury, PhD

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High-risk pediatric acute myeloid leukemia driven by the CBFA2T3–GLIS2 fusion is characterized by aggressive clinical behavior despite a relatively low mutational burden, suggesting a central role for epigenetic dysregulation in disease maintenance. In this talk, I will describe how the CBFA2T3–GLIS2 fusion reprograms DNA methylation at enhancer-linked cis-regulatory elements to stabilize oncogenic transcription rather than repress it.

Through integrated DNA methylation, chromatin accessibility, transcriptional profiling, and functional perturbation studies, we identify a promoter- and enhancer-biased hypermethylation landscape that persists within active chromatin and is maintained by DNMT3B downstream of the fusion. Using developmentally appropriate cord blood–derived models, we show that this epigenetic state is established early and reflects a fusion-driven process rather than a late consequence of transformation.

Functionally, targeted epigenetic editing demonstrates that enhancer-linked DNA methylation directly enforces apoptotic resistance by stabilizing expression of key survival regulators. Disruption of this DNMT3B-dependent methylation program restores apoptotic responsiveness and exposes a therapeutically actionable vulnerability. Together, these findings redefine DNA methylation as a stabilizing regulatory signal in fusion-driven leukemia and highlight epigenetic dependencies that may be exploited to overcome treatment resistance in high-risk AML.

# Development and Validation of an LC-MS/MS Assay for Simultaneous Quantification of Water-Soluble Vitamins

**Renny Lan, PhD, Assistant Professor**

Operations Director of Metabolomics and Analytical Chemistry Core  
Department of Pediatrics

**Hailemariam Abrha Assress, PhD**

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Micronutrients are essential for human health, with water-soluble vitamins of the B complex and vitamin C playing critical roles in energy metabolism, neurological function, and immune response.

Comprehensive profiling of the entire micronutrient spectrum can help identify deficiencies and imbalances, enabling more precise nutritional assessment and management. Here, we present a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method for the simultaneous quantification of ten water-soluble vitamins: thiamine (B1), riboflavin (B2), niacinamide (B3-NH<sub>2</sub>), niacin (B3-OH), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9), cyanocobalamin (B12), and ascorbic acid (vitamin C).

Chromatographic separation was performed on a Waters ACQUITY UPLC HSS T3 column (2.1 × 100 mm, 1.8 μm) at a flow rate of 0.5 mL/min using 10 mM ammonium formate with 0.1% formic acid in water (mobile phase A) and methanol (mobile phase B). Detection was carried out using multiple reaction monitoring (MRM) in both positive and negative ionization modes. All analytes were well resolved, with retention times ranging from 1.11 to 6.21 minutes. Method validation demonstrated acceptable limits of detection and quantification, as well as satisfactory precision and accuracy. This short, accurate, and reproducible LC-MS/MS assay enables simultaneous measurement of ten water-soluble vitamins and represents a valuable tool for clinical and research applications, including micronutrient screening, deficiency assessment, and dietary or supplemental management in CKD patients undergoing hemodialysis.

# Protective Mechanical Ventilation Attenuates Aspiration-Induced Lung Injury

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**Introduction:** Patients with acute respiratory distress syndrome are at risk for developing a secondary ventilator-induced lung injury from overdistension (OD) and cyclic recruitment and derecruitment (RD). In this study, we sought to determine whether lungs can be recovered after exposure to higher (↑) OD and RD by applying protective mechanical ventilation with lower (↓) levels of OD and RD.

**Methods:** 14 female pigs were anesthetized, instrumented, and placed on mechanical ventilation with airway pressure release ventilation. They had an aspiration lung injury induced by bronchoscopic hydrochloric acid instillation and were randomized into one of three groups:

- OD ↑ RD ↑ (n=5): higher OD and RD applied for six hours
- OD ↓ RD ↓ (n=5): lower OD and RD applied for six hours
- Delayed OD ↓ RD ↓ (n=4): OD ↑ RD ↑ applied for two hours and transitioned to OD ↓ RD ↓ for four hours

OD was increased by setting inspiratory airway pressure to 40 cmH<sub>2</sub>O and lessened with 28 cmH<sub>2</sub>O. RD was attenuated using a short duration of expiration (~0.3 s) and increased with a longer duration (~0.8 s).



**Results:** All groups developed mild-to-moderate ARDS following injury. OD ↑ RD ↑ caused the greatest degree of lung injury as determined by PaO<sub>2</sub>/FiO<sub>2</sub> ratio (193.2 ± 71.5 mmHg) whereas OD ↓ RD ↓ had the greatest protection (PaO<sub>2</sub>/FiO<sub>2</sub> = 351.7 ± 33.5 mmHg) and Delayed OD ↓ RD ↓ partially recovered the lungs (PaO<sub>2</sub>/FiO<sub>2</sub> = 251.4 ± 54.8 mmHg; p <0.01 among groups). OD ↑ RD ↑ required higher fluid resuscitation compared with OD ↓ RD ↓ and Delayed OD ↓ RD ↓ to maintain normotension (Fluid Balance for OD ↑ RD ↑ = 4.1 ± 0.6L; OD ↓ RD ↓ = 2.8 ± 0.6L; and Delayed OD ↓ RD ↓ = 2.0 ± 0.4L; p <0.05) yet OD ↑ RD ↑ had a higher final lactic acid level (OD ↑ RD ↑ = 5.0 ± 0.7mmol/L; OD ↓ RD ↓ = 3.0 ± 0.6mmol/L; and Delayed OD ↓ RD ↓ = 3.0 ± 0.6mmol/L; p <0.05).

**Conclusions:** Injurious mechanical ventilation with higher OD and RD can worsen underlying lung injury, however protective mechanical ventilation, even when applied later, has the opportunity to partially attenuate it.


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# Evaluating Maternal and Neonatal Pharmacokinetics of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators - The ELECTRA Pregnancy Study

**Jennifer S. Guimbellot, MD, PhD, Associate Professor**  
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**Yasmin Roye, PhD**  
Staff Scientist, Pediatric Pulmunology

Cystic fibrosis (CF) is a devastating multi-organ system disease that results in lifelong morbidity and early mortality. Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators (elixacaftor/tezacaftor/ivacaftor) have revolutionized CF patient care, restoring normal function to people with CF (pwCF) who respond. Their use also tripled pregnancy rates in pwCF, a population where subfertility and maternal complications exist at a significantly higher rate. Pregnant women with CF have an increased risk of infection, requiring prolonged hospitalizations for intravenous antibiotics and other complications, including pulmonary decline. Consequently, they are advised to continue CFTR modulator therapy to prevent maternal deterioration, despite the lack of scientific evidence demonstrating their optimal dosing in pregnancy. As such, it is critical to define the pharmacokinetics of CFTR modulators in pregnancy and postpartum, including effects on the developing fetus, the infant, and breastmilk composition. Former NIH Director, Dr. Francis Collins, highlighted critical knowledge gaps in the pharmacology of modulator drugs, and in 2022 the NIH reaffirmed these gaps to include optimal dosing, pharmacology, and use in pregnancy and lactation. Our research group's ongoing studies with the triple combination (TC) therapy (elixacaftor/tezacaftor/ivacaftor) in the adult CF population reveal substantial inter-individual variation in the concentrations of these



compounds that can affect response. Previous attempts to define the pharmacokinetics of CFTR modulators in postpartum patients have been unsuccessful due to difficulties with recruitment and retention. To address this challenge, we have identified seven geographically diverse clinical research centers across the U.S. with exceptional recruitment and retention records in both the Cystic Fibrosis Foundation/Therapeutic Development Network and the NIH/NICHD Maternal-Fetal Medicine Units Network. Led by a team of Cystic Fibrosis and Maternal-Fetal Medicine investigators, we will enroll 30 pregnant, first- trimester, patients on TC to investigate the following aims: 1) To determine the pharmacokinetics of each compound in CFTR modulator therapy, including active metabolites, in pregnant individuals in each trimester and postpartum, and 2) To evaluate the wash-out pharmacokinetics of each compound in CFTR modulator therapy, including active metabolites, from newborns of mothers taking TC. The ELECTRA Pregnancy Study is poised to generate rigorous CFTR Modulator pharmacokinetic data to inform optimal CFTR Modulator dosing to improve outcomes for pregnant patients with cystic fibrosis and their infants.

# Children with Multiple Food Allergies Exhibit Poor Diet Quality in Arkansas, a U.S. Southern State

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**Rationale:** Allergen elimination diets are key to food allergy management, making children vulnerable to nutritional inadequacies. Studies highlight the complex relationship between dietary intake, intestinal barrier function, microbiome colonization and atopy. This study assessed diet quality among multi-food allergic children compared to age-matched controls.

**Methods:** Preliminary analyses was performed on children, ages 2-11 years, enrolled into Food Allergy group (FA, n=10, multi-food allergic children [ $\geq 3$  allergenic foods] on dietary restriction) or Control group (CG, n=10, non-atopic children, unrestricted diet). Primary outcome was healthy eating index (HEI). Secondary outcomes included intestinal permeability (serum lipopolysaccharide binding protein [LPS-BP]) and stool short-chain fatty acids (SCFA). Statistical analysis: Fisher's exact and Welch's t-test.

**Results:** Participants (FA vs. CG) were similar for age, anthropometrics, and ethnicity but differed for race (Black:70% vs. 0%; $p=0.003$ ), atopic dermatitis (AD:100% vs. 0%; $p=0.0001$ ), and caregiver health literacy (60% vs. 100%; $p=0.09$ ). Top restricted allergens were peanut/tree nut (80% each) and egg (70%) with mean dietary elimination=5.3 years (range:1-10). HEI score was low in both groups (FA 52 vs. CG 49; $p=NS$ ) with low intake of fiber, vitamin D, and calcium. FA participants had higher HEI-subscores for fruits ( $p=0.07$ ) and fats ( $p=0.06$ ) but lower for dairy ( $p=0.01$ ). FA participants had higher LPS-BP ( $p=0.02$ ) and lower stool SCFA (acetate  $p=0.02$ ; butyrate  $p=0.02$ ).

**Conclusions:** Preliminary results demonstrate very poor diet quality among Arkansas children. FA children had evidence for increased intestinal permeability and reduced SCFA, which may contribute to nutritional inadequacies in multi-food allergic children. Continuing enrollment in this study will be key to developing precision nutrition approaches for multi-food allergic children.



## **Ensuring Access to Optimal Therapy in CF: The ENACT Study (ENACT)**

**Jennifer S. Guimbellot, MD, PhD**

Associate Professor


Chief, Pulmonology and Sleep Medicine

Department of Pediatrics

**Yasmin Roye, PhD**

Staff Scientist, Pediatric Pulmunology

Cystic fibrosis (CF) is an autosomal recessive disorder caused by dysfunction of the CF Transmembrane Conductance Regulator (CFTR) channel. The care of patients with CF has rapidly evolved with the development of CFTR modulators, novel pharmaceuticals that address the basic CF defect and restore CFTR function. Most recently, a triple combination therapy, TC, has revolutionized the care of most patients (~90% of the population in the U.S.). However, as TC has been expanded in use, about a quarter of people with CF don't have the robust response that were seen in the clinical trials, and others have neuropsychological side effects that limit tolerability. The compounds of TC are metabolized by cytochrome P450 (CYP3A enzymes). Genetic variation in these enzymes cause altered activity, resulting in variation in efficacy in many drugs and side effect profiles. Our preliminary data demonstrate considerable variation in TC concentrations in patients during real-world use, which is a concern given the dose-dependence of TC effect in the lung and other tissues. This study will provide innovative data on concentration variability among the largest observational study of TC use in people with CF, as well as novel data on pharmacogenetic variation in this population, and prospective data on the utility of concentration data and dose titration to optimize the clinical response of TC in the lungs, as well as



throughout the body. Our prospective study is also designed to evaluate a balance between lung function response from TC and side effect profiles, particularly of an increasingly observed effect causing neuropsychological deterioration (i.e., worsening anxiety, depression, and cognition). The Specific Aims are: 1) Analyze population pharmacokinetics of the three TC compounds in plasma to determine pharmacokinetic parameters during real-world use and correlate drug exposure with drug response; 2) to determine novel genetic variants in relevant pharmacogenes associated with concentration or response to TC including pulmonary measures; 3) conduct a prospective study to ascertain the TC concentration relationship with neuropsychological side effects and assess the utility of dose titration to balance side effects with optimal pulmonary (and other organ system) responses to TC. To accomplish the goals of this research, the principal investigator has assembled a unique mentoring team with decades of experience in clinical trials, pharmacology, genetics, statistics, pharmacogenetics, psychology and drug metabolism. Together, we will shift the paradigm of care for CF by better understanding of the optimal concentration and dosing for individual's lung function and tolerance of therapy, and transition to a truly personalized and patient-centered approach to modulator therapy.

# Impact of CFTR Modulator Concentrations on Clinical Response in Cystic Fibrosis

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**Rationale:** Cystic fibrosis is caused by variants in the CF transmembrane conductance regulator (CFTR), leading to defective chloride ion transport and multi-organ dysfunction. CFTR modulators substantially improve chloride ion transport and disease severity, but responses vary, which may in part be due to variation in drug concentrations.


**Objectives:** This study aimed to evaluate modulator concentrations among people with CF and the potential impact of cytochrome P450 (CYP) 3A5 genotypes on sweat chloride.

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**Methods:** This multicenter study enrolled 97 children and adult participants established on elexacaftor/tezacaftor/ivacaftor (ETI) therapy. ETI drug concentrations were quantified and CYP3A5 genotypes were determined. Relationship between drug concentrations, genotype, and sweat chloride response were investigated using correlation and multivariable regression models to examine associations between drug levels and sweat chloride.

**Measurements and Main Results:** Plasma concentrations of elexacaftor, tezacaftor and ivacaftor were highly variable. Analyses revealed that CYP3A5 genotype status had no significant effect on drug concentrations. Association analysis demonstrated an association of sweat chloride with drug concentrations including after adjusting for pre-modulator sweat chloride, age, race, BMI, and sex, showing that lower drug concentrations are associated with worse outcomes in sweat chloride.

**Conclusion:** This study provides evidence that lower drug concentration are associated with worse sweat chloride levels and may be a potential indicator of therapeutic effectiveness, especially for people with high sweat chloride despite treatment. The influence of drug variability underscores the need for personalized dosing strategies to improve CF treatment outcome, although well-known CYP3A5 genotypes are unlikely to be helpful.



# Findings from the *Beginnings Study*: Body Mass Index and Dietary Intake from age 6 to 14 years

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**Background:** Early-life nutrition is a critical determinant of long-term growth and health outcomes. Breastfeeding has been consistently associated with reduced risk of later obesity and improved developmental and health trajectories (1,4). Soy-based infant formula (SF) has been widely used for decades, yet evidence on its long-term effects compared with breast milk (BF) or cow's-milk infant formula (MF) remains limited (2,3). Recent systematic reviews emphasize that early feeding practices may influence obesity risk, although findings regarding metabolic outcomes are less consistent (5,6). The *Beginnings Study* (NCT 00616395) provides a unique opportunity to examine these associations prospectively from infancy through adolescence.


**Objectives:** To examine Body Mass Index (BMI) category transitions from 6y to 14y across infant feeding groups (Soy-based infant formula, Breast Milk, and Cow's milk infant formula). And to describe energy and macronutrient intake (Carbohydrate, Fat, Protein).

**Hypothesis:** Infant feeding type influences long-term BMI trajectories. Breastfed participants were expected to maintain healthier BMI categories compared with formula-fed peers.

**Methods:** The *Beginnings Study* (NCT 00616395) was a prospective study initiated at the Arkansas Children's Nutrition Center in Little Rock, Arkansas in 2002. It was designed to evaluate health outcomes in infants and children who consumed Soy-protein based infant formula (SF), Cow's- milk based formula (MF), or Human Milk (HM) during the first year of life. The *Beginnings Follow-Up* study (NCT NCT03108014) recalled these participants at age 14 to assess health outcomes during adolescence. For the present analysis,

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children with available data at both 6 (n=385) and 14 years of age (n= 179) were included. Body mass index was calculated as weight (kg)/ height (m<sup>2</sup>) at both time points (6 and 14 years). BMI categories were defined according to age- and sex-specific criteria (WHO, 2007). Transitions in BMI categories from 6 to 14 years were examined within and across infant feeding groups. Dietary intake using 3-day food records were used to estimate total energy intake (kcal) and macronutrient intake (g). Comparisons of energy and macronutrient intake were performed among feeding groups and among BMI categories at each age. Statistical analyses included comparisons of BMI trajectories and BMI category distributions among feeding groups. Group differences in dietary intake were assessed using ANOVA followed by Tukey's post hoc tests when appropriate. Differences in BMI category distribution were evaluated using chi-square tests. Statistical significance was set at  $p < 0.05$ .

**Results:** BMI trajectories from 6 to 14 years did not differ significantly among infant feeding groups (SF, BF, and MF) ( $p > 0.05$ ). Similarly, the distribution of BMI categories at 6 years of age was comparable among groups ( $p = 0.47$ ). However, at 14 years, BMI category distribution differed significantly among feeding groups ( $p = 0.04$ ), with a higher prevalence of overweight and obesity observed in the MF group compared with the BF and SF groups. Overall, there was an increase in the prevalence of overweight and obesity from childhood to adolescence in all groups. Energy and macronutrient intake at both 6 and 14 years did not differ significantly among infant feeding groups (all  $p > 0.05$ ). However, when dietary intake was stratified by BMI category, significant differences emerged. At both ages, children in higher BMI categories exhibited greater energy and macronutrient intakes compared with those in lower BMI categories, with statistically differences ( $p < 0.05$ ).

**Conclusion:** There was an increase in the prevalence of overweight and obesity, particularly among participants in the Milk Formula group. The increase was more modest in the Soy Formula and Breast Milk groups. Dietary patterns were comparable across feeding groups, but differences emerged when stratifying by BMI categories, at 14y. These findings suggest that the association between dietary intake and BMI becomes more evident during adolescence.

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# **Genome-wide DNA Methylation is Predictive of Outcome in KMT2A-rearranged Acute Myeloid Leukemia**

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Structural and genetic alterations form the basis for contemporary risk stratification for pediatric acute myeloid leukemia (AML). Conversely, the impact of DNA methylation on prognostication has not been well-established. We performed genome-wide DNA methylation profiling on patients enrolled in the two most recent phase 3 clinical trials completed by the Children's Oncology Group (AAML1031 and AAML0531). Our study population comprised 1,302 patients. Within a training cohort and one or more validation cohorts, we found that methylation signatures were highly prognostic for patients with KMT2A-rearranged AML, the most prevalent fusion group in pediatric AML and a group that makes up half of patients with standard-risk disease, for which optimal frontline therapy is most often debated. Methylation signatures out-performed previously described biomarkers and the integration of other biomarkers further improved outcome prediction. Pairwise bulk and single cell transcriptome sequencing suggest that a hypermethylated state is linked to leukemia stem cell signatures and is independent from lineage specific transcriptional signatures. Our findings support the incorporation of methylation profiling into risk stratification schema for pediatric AML and the ongoing study of methylation profiling, particularly as targeted therapies (e.g., menin inhibitors and hypomethylating agents) are brought to the frontline setting for pediatric AML.



# **Laryngeal Mask Airway Surfactant Delivery: A Potential Strategy to Reduce Lung Injury and Bronchopulmonary Dysplasia in Preterm Infants**

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Bronchopulmonary dysplasia (BPD) is a chronic lung disease of prematurity and is a common cause of long-term morbidity among preterm infants. BPD is associated with early lung injury from invasive mechanical ventilation, contributing to barotrauma and oxygen toxicity. Long-term impact of BPD includes increased risk of asthma, recurrent respiratory infections, higher rate of neurodevelopmental delay, and prolonged NICU stay. Surfactant delivery can improve respiratory outcomes in preterm infants with this condition, however traditional surfactant delivery via endotracheal intubation is limiting; requiring sedation, expertise to perform laryngoscopy, and higher likelihood of airway trauma. Strategies that minimize endotracheal intubation while ensuring effective surfactant delivery may reduce ventilator-associated lung injury and improve outcomes. The laryngeal mask airway (LMA) has emerged as a potential alternative for surfactant administration in eligible preterm cohorts.

The purpose of this project is to review current evidence evaluating surfactant delivery via LMA compared with traditional endotracheal tube (ETT) administration in preterm infants with or at risk for BPD. A comprehensive review of randomized controlled trials, systematic reviews, and meta-analyses was performed, focusing on factors such as respiratory outcomes, safety, and implications for BPD. Local institutional data at the University of Arkansas for Medical Sciences in Little Rock, AR from the Vermont Oxford Network were also reviewed to contextualize disease incidence and burden.

Across multiple studies, surfactant administration via LMA was associated with decreased need for intubation and mechanical ventilation, as well as lower rates of bradycardia and oxygen desaturation during administration. Effects on BPD incidence were variable, with no consistent statistically significant reduction observed. However, given the known association between invasive ventilation and long-term pulmonary morbidity, avoidance of intubation via LMA may offer less invasive clinical benefit.

LMA-mediated surfactant delivery appears to be a safe and feasible alternative to ETT administration in eligible preterm infants. Due to current underpowered studies, further research and trials are needed to better define patient selection criteria and evaluate long-term pulmonary outcomes, including BPD severity.

# Single-Sample Prediction of Average Drug Concentration in ETI Therapy Using Supervised Machine Learning

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## Introduction:

Elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) are medications used together to treat cystic fibrosis (CF). To facilitate studies of these drugs on real-world exposure-response relationships, including for side effect profiles or precision therapy, investigators need better tools to estimate pharmacokinetic parameters from limited sampling. One useful measure is the average drug level in the blood ( $C_{avg}$ ), but collecting full sets of blood samples over time is often not practical. This study looks at whether  $C_{avg}$  can be accurately predicted using just one blood sample taken at any time within 12 hours after a dose. This method supports simpler, real-world ways to monitor drug concentrations in research studies. Additionally, accurately predicting missing drug concentrations may facilitate  $C_{avg}$  estimation in from single samples in other datasets, even when some time points are unavailable or differ from those in the original dataset.

## Methods:

Data from 26 cystic fibrosis patients, including both transplant and non-transplant individuals, were used to create a comprehensive dataset. Plasma concentrations of ELX, TEZ, and IVA were measured at nine time points over a 12-hour period after dosing (0h to 12h). The primary outcome  $C_{avg}$  was calculated separately for each drug. Supervised learning using Leave-One-Out Cross-Validation (LOOCV) was applied to evaluate model performance. First, separate models were created for each drug to predict  $C_{avg}$  using data from just one time point. Then, other models were used to predict concentrations at missing time points (3h, 7h, 9h, and 11h) using data from the other time points. The model's performance was measured by  $R^2$ , average bias (mean prediction error), and precision (coverage rate).



## Results:

In the first task, we found that the  $C_{avg}$  of each drug could be predicted well using just one blood sample at certain timepoints. For ELX and IVA, the best results came from samples taken at 6 hours after dosing, where  $R^2$  values reached 0.91 and 0.92, respectively, with low bias and high precision. TEZ worked best at 8 hours ( $R^2 = 0.87$ ). Earlier time points did not predict  $C_{avg}$  as well. In the second task, we used data from nearby time points to predict drug levels at missing times (3h, 7h, 9h, and 11h). These predictions were also accurate with  $R^2$  range between 0.93-0.98, showing that we can still estimate full drug profiles even if some time points are missing

## Conclusion:

These analyses shows that predictive models of supervise machine learning can be used effectively for two important tasks with limited blood samples: (1) predicting the  $C_{avg}$  from just one blood draw, and (2) estimating drug levels at missing time points between 0 and 12 hours after a dose. This approach can help estimate drug exposure more easily and fill in missing data, making it a useful and practical tool for studies of ETI therapy.

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## Metabolism and Bioenergetics Core

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The Center for Childhood Obesity Prevention (CCOP) at Arkansas Children's Research Institute (ACRI) supports investigators in performing translational research focused on the prevention and treatment of obesity across the lifespan. The Metabolism and Bioenergetics Core (MBC) of the CCOP is central to this mission by making cutting-edge biomedical research services available at ACRI. The services are also available to non-CCOP investigators with the goal of transitioning the MBC into a sustainable core facility at ACRI. The MBC supports translational research aimed at better understanding the metabolic consequences of obesity and the identification of novel anti-obesity prevention strategies and therapies. Training and support can be provided to researchers and their teams to utilize these approaches and resources. Services are also available on a fee-for-service basis.

Key services offered by the MBC include:

**Clinical Chemistry:** The MBC also provides comprehensive clinical chemistry services including complete blood cell counts, isolation of specific blood fractions, and several hormone, cytokine and metabolic panels.

**Stable isotope approaches:** A unique aspect of the MBC is the ability to support users in the application of stable isotope techniques to compute metabolic fluxes and substrate turnover rates in vivo. This allows the direct determination of various metabolic processes, e.g., total energy expenditure, protein turnover, or fat oxidation.

**Respirometry:** Another key MBC service line relates to the comprehensive analysis of bioenergetics in isolated mitochondria, cells, and tissues. The MBC currently operates five Oxygraph O2K respirometers (Oroboros Instruments) and two Seahorse XFe96 instruments (Agilent) to support these services.



## **ACRI's Rodent Metabolic and Behavioral Phenotyping Core**

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Professor

Director, Rodent Metabolic and Behavioral Phenotyping Core

Department of Pediatrics

Arkansas Children's Research Institute (ACRI) is home to a state-of-the-art 35,000 ft<sup>2</sup> animal facility, accredited by the American Association for the Accreditation of Laboratory Animal Care and overseen by board-certified veterinarians. Within a dedicated 7000 ft<sup>2</sup> wing this vivarium, ACRI operates a Rodent Metabolic and Behavioral Phenotyping Core (RMBPC) – supported by a team of four full-time personnel trained in all aspects of animal husbandry and specialized phenotyping techniques. The goal of the RMBPC is to support translational preclinical research at ACRI by providing users with access to state-of-the-art phenotyping platforms and scientific expertise.

The RMBPC utilizes state-of-the-art instrumentation to collect detailed physiological and behavioral data for our animal researchers. This includes two state-of-the-art Promethion Core platforms (Sable Systems) that can perform 24-hr assessments of total energy expenditure and its components via indirect calorimetry, as well as recording feeding and movement behaviors in real time. Both Promethion systems (able to run up to 32 mice or 16 rats simultaneously) are housed within environmental chambers allowing for control and monitoring of key extrinsic variables such as temperature. The RMBPC also operates both Echo MRI and DEXA platforms to assess body composition. Services offered by the RMBPC are available to investigators at both ACRI and UAMS on a fee-for-service basis.



Research & Innovation

## Research Support Teams

- **Biomed Buildings Research Space & Buildings Management**
- **BioVentures**
- **Division of Laboratory Animal Medicine (DLAM)**
- **Institutional Animal Care and Use Committee (IACUC)**
- **Institutional Review Board (IRB)**
- **International Compliance & Conflict of Interest**
- **Office of Research Integrity (ORI)**
- **Office of Research and Sponsored Programs (ORSP)**
- **Office of Research Regulatory Affairs (ORRA)**
- **Research Security**
- **Science Communication Group (SciCom)**

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