



Mountain West Regional Chapter  
Society of Toxicology

August 12 - 13, 2026

Tucson, AZ

# 44TH ANNUAL MEETING OF MOUNTAIN WEST SOCIETY OF TOXICOLOGY

**Safeguarding Tomorrow: Advancing Toxicology  
for Early Life and Future Generations**

Featuring:  
Invited Speakers  
Oral and Poster Presentations  
2026 MWSOT Legacy Award





# TABLE OF CONTENTS

**Leadership & Sponsors**

**Welcome**

**2026 MWSOT Legacy Award**

Jay Gandolfi, PhD

**Conference Map**

**Conference At-A-Glance**

**Invited Speakers**

- I. The Future of Toxicology
- II. Immunotoxicology
- III. Neurotoxicology
- IV. Reproductive & Metabolic Toxicology
- V. Community Engaged Research
- VI. Systems & Mechanistic Toxicology

**Oral Presentation Schedule**

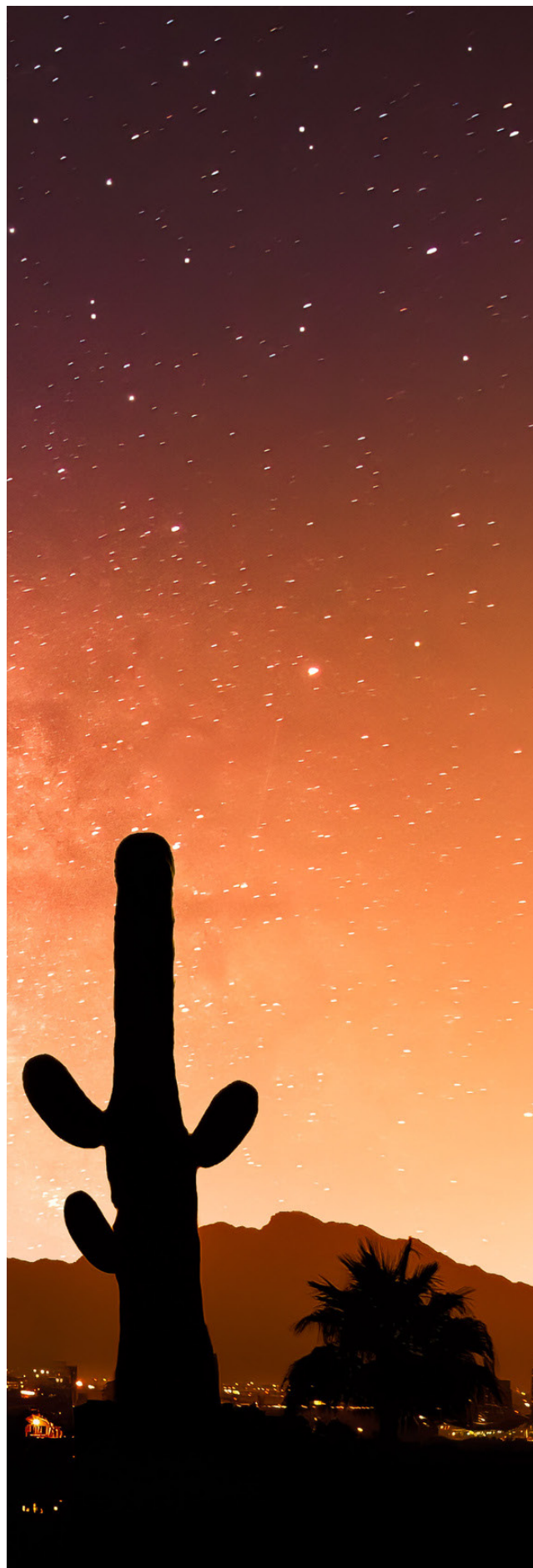
**Oral Presentation Abstracts**

**Poster Presentation Overview**

**Poster Presentation Abstracts**

**Tucson Eats**

**Acknowledgments**





# LEADERSHIP & SPONSORS

## Planning Committee

|                    |                   |
|--------------------|-------------------|
| Zelieann Craig     | Sebastian Medina  |
| Julie Moreno       | Derek Drechsel    |
| Alessandro Venosa  | Jocelyn Cuthbert  |
| Michael Lumpkin    | Maribel Hernández |
| Charlotte McVeigh  | Ember Suh         |
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## 2026 MWSOT Officers

|                                                                               |                               |
|-------------------------------------------------------------------------------|-------------------------------|
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# WELCOME

## Tucson, Arizona

Welcome to **Tucson**, where desert beauty and vibrant culture come together! Known as the first U.S. city to be designated a **UNESCO City of Gastronomy**, Tucson celebrates its rich culinary heritage influenced by **Native American, Mexican, and Spanish traditions**. Surrounded by stunning landscapes, the city is home to the iconic **Saguaro National Park**, where towering saguaro cacti create a truly unique desert skyline. Tucson also hosts the world-famous **Tucson Gem, Mineral & Fossil Showcase**, drawing visitors from across the globe each year. With a lively downtown, historic barrios, and the renowned **University of Arizona**, the city blends youthful energy with deep-rooted history. From its colorful sunsets to its thriving arts scene and outdoor adventures, Tucson offers an unforgettable experience in the heart of the **Sonoran Desert**.

## Mountain West Society of Toxicology

The **Mountain West Regional Chapter of the Society of Toxicology (MWSOT)** encompasses the beautiful states of Arizona, Colorado, Utah, Southern Idaho, Nevada, New Mexico, and Wyoming. Toxicology-related programs, companies, and firms from the Mountain West region attend and participate in MWSOT-hosted events and meetings: University of Arizona, Colorado State University, University of Colorado, Fort Lewis College, Idaho State University, University of Nevada, University of New Mexico, University of Utah, Utah State University, University of Wyoming, and Exponent.

## University of Arizona

It is an honor and pleasure for the **University of Arizona (U of A) R. Ken Coit College of Pharmacy** and the **College of Agriculture, Life & Environmental Sciences** to host the **44th Annual Meeting of the Mountain West Society of Toxicology**. The College provides front-line research and immersive education that prepares undergraduate and graduate students to create a richer, more sustainable world. With over 175 faculty researchers and about 500 annual research projects, their research focuses on One Health; animal systems; commerce; families and communities; health and food safety; plant, insect, and microbe systems; and environment, energy, and natural resources.

## MWSOT Yost/Burchiel Award

The **MWSOT Yost/Burchiel Award** is in honor of **Dr. Garold S. Yost (University of Utah)** and **Dr. Scott Burchiel (University of New Mexico)** and recognizes a predoctoral toxicology student exhibiting exceptional interest and aptitude in toxicology through participation in regional chapter activities. Every year, a pre-doctoral student working in a research laboratory of a member of the Mountain West Regional Chapter is awarded.

## 2026 MWSOT Legacy Award Jay Gandolfi, PhD



It is our honor and pleasure to announce that the 2026 Mountain West Society of Toxicology Legacy Award is awarded to **Dr. Jay Gandolfi** for his exceptional, dedicated service to the Society of Toxicology and the Mountain West

Regional Chapter. Dr. Gandolfi recognizes and nurtures each student individually based on their unique needs and capabilities and takes time to understand their goals and aspirations, strengths, and weaknesses. His commitment to the training of students in Toxicology and his long service to the unique student-oriented mission of MWSOT have been instrumental to not only at the University of Arizona but across all of the four major MWSOT sponsor universities. Dr. Gandolfi served as MWSOT senior advisor and a pillar of stability for the support of toxicology and student training over the past 40 years. With over 25 years of continuous NIH support and hundreds of peer-reviewed manuscripts detailing the mechanistic features of arsenic toxicity, Dr. Gandolfi has left a significant mark in the field of heavy metal toxicity. Furthermore, he established the Center for Toxicology (1987), the Southwest Environmental Health Sciences Center (SWEHSC, 1994), the Superfund Research Program (SRP, 1989), the Center for Indigenous Environmental Health Research (CIEHR, 2015), the Environmental Health Sciences-Transformative Research Undergraduate Experience (EHS-TRUE, 2015), the Environmental Health Sciences-Research for Indigenous Scholar Engagement (EHS-RISE, 2023), and the EPA Environmental Justice Thriving Communities Technical Assistance Center (2023). He has received the 2007 Findlay E. Russell MD, PhD, Distinguished Citizen Award from the University of Arizona, and the 2026 Toxicology Mentoring Award and the 2004 Education Awards from SOT.



# CONFERENCE MAP

[Click here to go to the Google Map list of the meeting locations!](#)

**The Graduate by Hilton Tucson**

930 E 2nd St, Tucson, AZ 85719

**The Moonstone @ Graduate by Hilton Tucson  
Student Union**

14th Floor, 930 E 2nd St, Tucson, AZ 85719

**Bear Down Gym**

1303 E University Blvd, Tucson, AZ 85719

1428 E University Blvd Tucson, AZ 85721







## CONFERENCE AT-A-GLANCE

| Time                        | Event                                                                                  | Location                                        |
|-----------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>WEDNESDAY, AUGUST 12</b> |                                                                                        |                                                 |
| 7:00 PM                     | Optional Welcome Social                                                                | The Moonstone<br>(Graduate Hotel's rooftop bar) |
| <b>WEDNESDAY, AUGUST 12</b> |                                                                                        |                                                 |
| 7:00 AM - 9:00 AM           | Breakfast & Registration                                                               | Student Union<br>Kachina Room                   |
| 8:00 AM - 8:20 AM           | Welcome & Opening Remarks<br>(Additional Welcome by ADRs)                              | Student Union<br>Kachina Room                   |
| 8:25 AM - 8:40 AM           | MWSOT Legacy Award                                                                     | Student Union<br>Kachina Room                   |
| 8:45 AM - 10:30 AM          | Session I - The Future of Toxicology                                                   | Student Union<br>Kachina Room                   |
| 10:45 AM - 12:15 PM         | Session II - Immunotoxicology                                                          | Student Union<br>Kachina Room                   |
| 12:15 PM - 1:30 PM          | Lunch<br><i>Optional Trainee Lunch Event at Sabino Room</i>                            | Student Union<br>Kachina Room                   |
| 1:35 PM - 3:00 PM           | Session III - Neurotoxicology                                                          | Student Union<br>Kachina Room                   |
| 3:30 PM - 4:45 PM           | Session IV - Reproductive & Metabolic Toxicology                                       | Student Union<br>Kachina Room                   |
| 5:30 PM - 7:30 PM           | Poster Session & Light Reception<br>(Refreshments available at 5:15 PM for presenters) | Bear Down Gym<br>Bear Down Court                |
| 7:30 PM                     | Dinner (On Your Own)                                                                   | N/A                                             |
| <b>THURSDAY, AUGUST 13</b>  |                                                                                        |                                                 |
| 7:00 AM - 9:00 AM           | Breakfast & Registration                                                               | Student Union<br>Kachina Room                   |
| 8:00 AM - 8:30 AM           | Opening Remarks & Yost/Burchiel Award                                                  | Student Union<br>Kachina Room                   |
| 8:30 AM - 10:00 AM          | Session V - Community Engaged Research                                                 | Student Union<br>Kachina Room                   |
| 10:25 AM - 11:55 AM         | Session VI - Systems & Mechanistic Toxicology                                          | Student Union<br>Kachina Room                   |
| 12:00 PM - 12:15 PM         | Session VII - Risk Assessment                                                          | Student Union<br>Kachina Room                   |
| 12:20 PM - 12:30 PM         | Final Remarks & Trainee Presentation Awards                                            | Student Union<br>Kachina Room                   |
| 12:30 PM                    | Lunch (On Your Own) & Departures                                                       | N/A                                             |





# INVITED SPEAKERS

## THE FUTURE OF TOXICOLOGY

Wednesday, August 12 | 8:45 AM – 10:30 AM

Student Union Memorial Center, Kachina Room

**Pregnancy exposure to 10 classes of priority chemicals in the ECHO Cohort: associations with birth outcomes and dietary guideline adherence**

**Diana Pacyga, PhD, MS**

Assistant Professor

University of Arizona

R. Ken Coit College of Pharmacy

Department of Pharmacology & Toxicology



**Prenatal Dibutyl Phthalate Exposure Dysregulates Fetal-Placental Vascular Function and Placental Vasculature-Specific Lipid Metabolism**

**Chi Zhou, PhD**

Assistant Professor

University of Arizona

School of Animal and Comparative Biomedical Sciences

Department of Physiology & Obstetrics and Gynecology



**Data Sharing for New Approach Methodologies: What is metadata and why is it important?**

**Karen Watanabe, PhD, MS**

Associate Professor

Arizona State University

School of Mathematical and Natural Sciences





# INVITED SPEAKERS

## IMMUNOTOXICOLOGY

Wednesday, August 12 | 10:45 AM – 12:15 PM

Student Union Memorial Center, Kachina Room

### Tungsten and Cardiometabolic Disease: Bridging Epidemiology and Mechanistic Insights



**Alicia Bolt, PhD**

Associate Professor  
University of New Mexico  
College of Pharmacy  
Department of  
Pharmaceutical Sciences

# INVITED SPEAKERS

## NEUROTOXICOLOGY

Wednesday, August 12 | 1:35 PM – 3:00 PM

Student Union Memorial Center, Kachina Room



### **Manganese as a modulator of innate immunity in the brain**

**Ronald Tjalkens, PhD**

Professor

Barrow Neurological Institute

Department of Neurology

### **Neurological Signatures of PFAS in multi-OMIC platforms**

**Melissa Furlong, PhD**

Associate Professor

University of Arizona

Mel & Enid Zuckerman College of Public Health

Department of Environmental Health Sciences





# INVITED SPEAKERS

REPRODUCTIVE & METABOLIC TOXICOLOGY

Wednesday, August 12 | 3:30 PM – 4:45 PM

Student Union Memorial Center, Kachina Room

## Sex Differences in Phthalate Metabolism and Reproductive Toxicity



**Estela Jauregui, PhD**  
Assistant Professor  
Midwestern University  
Department of Physiology

# INVITED SPEAKERS

## COMMUNITY ENGAGED RESEARCH

Thursday, August 13 | 8:30 AM – 10:00 AM

Student Union Memorial Center, Kachina Room



### **Community-Engaged Research with Firefighters**

**Jeff Burgess, MD, MS, MPH**

Professor

University of Arizona

Mel & Enid Zuckerman College of Public Health

Department of Community, Environment and Policy



### **Captain John Gulotta**

Retired Captain of Tucson Fire Department

First Responders Center for Excellence (FRCE)

### **Building resilience together: Community science for understanding co-exposures and compounding environmental threats**

**Mónica Ramírez-Andreotta, PhD, MPA**

Professor

University of Arizona

Mel & Enid Zuckerman College of Public Health

Soil/Water and Environmental Science



### **From data to action: Co-producing water quality research with a rural, Indigenous Arizona community**

**Anupama Sethuraman**

PhD Candidate

University of Arizona

Department of Environmental Science



# INVITED SPEAKERS

SYSTEMS & MECHANISTIC TOXICOLOGY

Thursday, August 13 | 10:25 AM – 11:55 AM

Student Union Memorial Center, Kachina Room

## PFAS inhibition of retinoic acid metabolism and signaling: a novel mechanism for developmental toxicity



### Jed Lampe, PhD

Associate Professor  
University of Colorado  
Anschutz Medical Campus  
Skaggs School of Pharmacy  
and Pharmaceutical Sciences  
Department of  
Pharmaceutical Sciences



# ORAL PRESENTATIONS

## WEDNESDAY, AUGUST 12 Student Union Memorial Center | Kachina Room

| Abstract | Time     | Presenter        | Title                                                                                                                                                                | Institution                                    |
|----------|----------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| 1        | 8:50 AM  | Diana Pacyga*    | Pregnancy exposure to 10 classes of priority chemicals in the ECHO Cohort: associations with birth outcomes and dietary guideline adherence                          | University of Arizona                          |
| 2        | 9:20 AM  | Chi Zhou*        | Prenatal Dibutyl Phthalate Exposure Dysregulates Fetal-Placental Vascular Function and Placental Vasculature-Specific Lipid Metabolism                               | University of Arizona                          |
| 3        | 9:50 AM  | Karen Watanabe*  | Data Sharing for New Approach Methodologies: What is metadata and why is it important?                                                                               | Arizona State University                       |
| 4        | 10:20 AM | Miely Suarez     | Stratifying mouse ovarian follicle growth dynamics to inform computational models of folliculogenesis and environmental toxicant disruption                          | University of Arizona                          |
| 5        | 10:45 AM | Alicia Bolt*     | Tungsten and Cardiometabolic Disease: Bridging Epidemiology and Mechanistic Insights                                                                                 | University of New Mexico                       |
| 6        | 11:05 AM | Hayley Wondra    | Trichloroethylene metabolite promotes autoimmune-relevant metabolic changes in CD4+ T cells                                                                          | University of New Mexico                       |
| 7        | 11:20 AM | Katie Zychowski  | Differential Effects of Uranium and Coal Mine Dust Exposure on Innate Immune Function <i>In Vitro</i> and In Humans                                                  | University of New Mexico                       |
| 8        | 11:35 AM | Matthew Gibb     | Inhaled Agricultural Dust Exposure Precedes Proximal Tubular Transporter Dysregulation and Immune Cell Depletion in the Kidney: Relevance to CKDu                    | University of Colorado Anschutz Medical Campus |
| 9        | 11:50 AM | Ember Suh        | Wildfire Smoke as a Driver of Neurological Aging and Injury                                                                                                          | University of New Mexico                       |
| 10       | 12:05 PM | Aidan Briggs     | Juvenile manganese exposure potentiates dopaminergic neurodegeneration resulting from encephalitic arbovirus infection via astrocyte-mediated inflammatory signaling | Barrow Neurological Institute                  |
| 11       | 1:40 PM  | Ronald Tjalkens* | Manganese as a modulator of innate immunity in the brain                                                                                                             | Barrow Neurological Institute                  |

\*Invited speakers





# ORAL PRESENTATIONS

## WEDNESDAY, AUGUST 12 Student Union Memorial Center | Kachina Room

| Abstract | Time    | Presenter                 | Title                                                                                                                                                                | Institution                    |
|----------|---------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| 12       | 2:05 PM | William Gendron           | Glyphosate at the Human-Equivalent EPA Chronic Reference Dose Alters the Gut-Brain Axis and Exacerbates Alzheimer's Disease Pathogenesis in mice                     | Arizona State University       |
| 13       | 2:20 PM | Abigail Bibb              | Global STING knockout rescues male-specific gait and nigrostriatal neurochemical decrements in mice subjected to the juvenile Manganese model of Parkinson's disease | Barrow Neurological Institute  |
| 14       | 2:35 PM | Adam Schuller             | Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson's disease                  | Barrow Neurological Institute  |
| 15       | 2:50 PM | Melissa Furlong*          | Neurological Signatures of PFAS in multi-OMIC platforms                                                                                                              | University of Arizona          |
| 16       | 3:40 PM | Estela Jauregui*          | Sex Differences in Phthalate Metabolism and Reproductive Toxicity                                                                                                    | Midwestern University          |
| 17       | 4:05 PM | Kara Miller               | Lipid Dysregulation in Mouse Ovarian Antral Follicles After Oral Exposure to a Human Relevant Mixture of Three Phthalates                                            | University of Arizona          |
| 18       | 4:20 PM | Kylie Jones               | Integrating Toxicokinetic, Mechanistic, and Epidemiologic Evidence to Evaluate the Estrogenic Potential of Methylparaben and Propylparaben                           | Aetia Scientific Collaborative |
| 19       | 4:35 PM | Alexis Cruickshank-Taylor | Hepatic Transporter Dysfunction as an Early Indicator of Metabolic Dysfunction and Alcohol-Associated Liver Disease Progression                                      | University of Arizona          |

\*Invited speakers



# ORAL PRESENTATIONS

## THURSDAY, AUGUST 13 Student Union Memorial Center | Kachina Room

| Abstract | Time     | Presenter                     | Title                                                                                                                | Institution                                                           |
|----------|----------|-------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| 20       | 8:35 AM  | Jeff Burgess* & John Gulotta* | Community-Engaged Research with Firefighters                                                                         | University of Arizona & First Responders Center for Excellence (FRCE) |
| 21       | 9:35 AM  | Mónica Ramírez-Andreotta*     | Building resilience together: Community science for understanding co-exposures and compounding environmental threats | University of Arizona                                                 |
| 22       | 9:50 AM  | Anupama Sethuraman*           | From data to action: Co-producing water quality research with a rural, Indigenous Arizona community                  | University of Arizona                                                 |
| 23       | 10:35 AM | Jed Lampe*                    | PFAS inhibition of retinoic acid metabolism and signaling: a novel mechanism for developmental toxicity              | University of Colorado Anschutz Medical Campus                        |
| 24       | 11:00 AM | Paxton Sample                 | Impacts of Heat Strain on ADME Function                                                                              | University of Arizona                                                 |
| 25       | 11:15 AM | Dominique Farrera             | Mechanistic Evaluation of Ezetimibe-Glucuronide as a Functional Probe in Chronic Liver Disease                       | University of Arizona                                                 |
| 26       | 11:30 AM | Caroline Ho                   | Investigating the Impact of Lithium Exposure on Gut Microbiota                                                       | Arizona State University                                              |
| 27       | 11:45 AM | Xiang Xue                     | Nuclear Receptor Coactivator 4 Restricts Mitochondrial Iron Signaling by Controlling Intracellular Iron Partitioning | University of New Mexico                                              |
| 28       | 12:05 PM | Chanese Forté                 | Comparing US National Databases to Examine Health Risks Near Los Alamos National Laboratory                          | Union of Concerned Scientists                                         |

\*Invited speakers





# ORAL PRESENTATION ABSTRACTS

## SESSION I – THE FUTURE OF TOXICOLOGY

Student Union Memorial Center | Kachina Room

Wednesday, August 12 | 8:45 AM – 10:30 AM

### INVITED SPEAKER

#### 1. Pregnancy exposure to 10 classes of priority chemicals in the ECHO Cohort: associations with birth outcomes and dietary guideline adherence

8:50 AM – 9:15 AM

**Diana Pacyga**

University of Arizona, R. Ken Coit College of Pharmacy, Department of Pharmacology & Toxicology, Tucson, AZ, USA

Pregnant women are widely exposed to reproductive/developmental toxicants. However, many chemicals remain understudied regarding their health impacts and exposure reduction strategies. We aimed to 1) evaluate associations of pregnancy chemical exposures with birth outcomes and 2) examine whether adherence to the Dietary Guidelines for Americans (DGA) is associated with exposures. In the Environmental influences on Child Health Outcomes Cohort, pregnant participants (n=5,318) provided mid-pregnancy spot urines to quantify 113 biomarkers representing 10 chemical classes, including insecticides, fungicides/herbicides, halogenated phenols, organophosphate esters (OPEs), benzophenones, bisphenols, parabens, antimicrobials, phthalates/alternatives, and polycyclic aromatic hydrocarbons (PAHs). A subset (n=1,492) reported mid-pregnancy dietary intake to calculate the Healthy Eating Index (HEI)-2015. We used linear mixed effects models to estimate associations of 1) urinary biomarkers with gestational age at birth and birth weight-for-gestational age (BW-GA) Z-scores and 2) HEI-2015 with these biomarkers. We used quantile-based g-computation to identify top HEI-2015 component contributors to associations. Overall, 35 of 113 biomarkers were detected in >70% of participants. Several phthalates were associated with shorter gestational age and lower BW-GA Z-scores. Additionally, select halogenated phenols, benzophenones, bisphenols, and PAHs were associated with lower BW-GA Z-scores. Higher HEI-2015 scores, reflecting greater DGA adherence, were associated with lower phthalate, halogenated phenol, bisphenol, PAH, and OPE biomarker concentrations, although positive associations emerged with some benzophenones, insecticides, and parabens. Higher protein, vegetable, fruit, and whole grain intake were consistent predictors of lower biomarker concentrations. Together, these findings highlight potential opportunities to leverage dietary recommendations to reduce prenatal chemical exposures and improve maternal/child health outcomes.

### INVITED SPEAKER

#### 2. Prenatal Dibutyl Phthalate Exposure Dysregulates Fetal-Placental Vascular Function and Placental Vasculature-Specific Lipid Metabolism

9:20 AM – 9:45 AM

**Chi Zhou**

University of Arizona, School of Animal and Comparative Biomedical Sciences, Department of Physiology & Obstetrics and Gynecology, Tucson, AZ, USA

In humans, prenatal dibutyl phthalate (DBP) exposure is associated with increased risks of adverse fetal outcomes as well as metabolic and cardiovascular diseases in the offspring in a fetal sex-specific manner. However, mechanisms underlying these prenatal DBP exposure-associated adverse fetal/offspring outcomes are unclear. We hypothesize that environmentally relevant low-dose prenatal DBP exposure dysregulates fetal-placental vascular function and lipid metabolism in a fetal sex-specific manner, thereby impairing placental efficiency and programming adverse offspring metabolic outcomes. Female CD-1 adult mice (8-10 weeks) were orally dosed with vehicle or an environmentally relevant low-dose DBP (0.1µg/kg/day) daily from 30 days pre-

pregnancy through gestational day (GD) 18.5. Fetal-placental vascular hemodynamics of these dams were examined using high-frequency ultrasound at multiple timepoints. The effect of prenatal environmentally relevant low-dose DBP exposure on placental efficiency, spatial transcriptomic profiles, lipid homeostasis, and placental vascular endothelial cells function in male and female fetuses were evaluated at gestational day (GD) 18.5. Our data showed that prenatal low-dose DBP exposure dysregulated the fetal-placental vascular hemodynamic indices from mid-to late gestation. DBP exposure impairs placental efficiency in male, but not female placenta at GD18.5. Further, female placentas exhibited fetal labyrinth vasculature-specific transcriptomic adaptations that preserves placental efficiency and endothelial function. In contrast, male placentas exhibited minimum transcriptomic adaptation, together with compromised placental efficiency and endothelial function associated with lipotoxic lipid profile. In conclusion, prenatal low-dose DBP exposure dysregulates placental vascular function and lipid homeostasis in a fetal sex-specific manner, with male fetuses being more susceptible to DBP exposure.

### **INVITED SPEAKER**

#### **3. Data Sharing for New Approach Methodologies: What is metadata and why is it important?**

**9:50 AM – 10:15 AM**

##### **Karen Watanabe**

School of Mathematical and Natural Sciences, Arizona State University, Glendale, AZ, USA

Under the paradigm of New Approach Methods (NAMs) for toxicity testing and risk assessment, *in vitro* assays and *in silico* computational models are increasingly important to inform decisions about chemical adverse effects *in vivo*. *In silico* models are data intensive, and access to high-quality, data is essential for robust, predictive models. Ongoing challenges include the availability and access to high-quality data. Thus, data sharing will be increasingly important to fill these needs. The FAIR (Findable, Accessible, Interoperable, and Reusable) guiding principles for data sharing underscore the need for metadata, which is information that describes the data being shared. This includes usage licenses, creators of the data collection, as well as the methods used to obtain the data. Additionally, data repositories may have specialized metadata requirements based on the data domain. Over the course of a study, metadata are collected in different ways (e.g., lab notebooks, spreadsheets, documents.), but they often are not organized with the intent of broad dissemination via a data repository. Collating the metadata required by a repository can be time-consuming, which may become enough of a hurdle that delays or ultimately deters submission. To encourage data sharing, this presentation will focus primarily on data needs and the importance of metadata drawn from examples of *in vitro* to *in vivo* extrapolation using biologically based models for reproductive toxicity.

#### **4. Stratifying mouse ovarian follicle growth dynamics to inform computational models of folliculogenesis and environmental toxicant disruption**

**10:20 AM – 10:30 AM**

**Miely A. Suarez<sup>1</sup>**, Viviana Romero<sup>1</sup>, Talia Owen<sup>1</sup>, Xiaosong Liu<sup>1</sup>, Karen H. Watanabe<sup>2</sup>, James Sluka<sup>3</sup>, Mary Zelinski<sup>4</sup>, Adam Krieg<sup>4</sup>, Qiang Zhang<sup>5</sup>, Zeliann R. Craig<sup>1</sup>

<sup>1</sup> The University of Arizona, Tucson, AZ

<sup>2</sup> Arizona State University, Glendale, AZ

<sup>3</sup> Indiana University, Bloomington, IN

<sup>4</sup> Oregon Health & Sciences University, Portland, OR

<sup>5</sup> Emory University, Atlanta, GA

Ovarian follicles are the functional units of the ovary as they support oocyte development and reproductive hormone synthesis. Folliculogenesis, the process of ovarian follicle development toward ovulation, is required for reproductive function and overall premenopausal health in women. Unfortunately, due to its complexity and need for tight regulation, follicle development is highly susceptible to toxicity by endocrine disrupting chemicals (EDCs). There is a growing need for new approach methodologies (NAMs) to facilitate the characterization of toxicant-induced reproductive disruption while reducing the number of whole animal

studies required. Key steps towards the development of NAMs for ovarian toxicity include developing highly predictive computational models that are informed by detailed biological data derived from *in vitro* follicle maturation assays. Therefore, the objective of this study was to generate time course data corresponding to ovarian follicle diameter, cellular compartment sizes, antrum formation, and hormone outputs using follicles with distinct growth and survival trajectories. Additionally, dibutyl phthalate (DBP), a known EDC, was used as a model chemical to characterize how known toxicant exposure alters these parameters. To achieve our objective, secondary and multilayer follicles (100-250  $\mu\text{m}$ ) were mechanically isolated from 21-day old female CD-1 mice, encapsulated in alginate beads (0.5%) and cultured individually for up to 240 hours. Follicles were treated with vehicle control (0.075% DMSO), three concentrations of DBP (0.001, 0.1, and 10  $\mu\text{g/mL}$ ), or a cell death control (7600  $\mu\text{g/mL}$  hydroxyurea). Follicle diameter and brightfield images were obtained every 24 hours to assess daily growth, compartment-specific morphology and area, and antrum formation. Culture media samples were collected to measure  $17\beta$ -estradiol (E2) and testosterone (T4) concentrations over time. Follicles were stratified into three distinct growth groups based on the diameter percent change of DMSO controls at 144 hours relative to baseline. Using these criteria, individual follicles from all treatments were classified as non-growing ( $\leq 0\%$ ), slow growing (0 – 51.85%), or fast growing ( $\geq 51.85\%$ ). Finally, these growth patterns were used to compare changes in compartment morphology and hormone production between treatments.

Our results show that follicles can be stratified into biologically meaningful categories based on growth dynamics. Specifically, fast-growing vehicle control follicles secrete significantly more estradiol and have greater growth in the granulosa cell compartment compared to DBP-exposed follicles. Vehicle control fast-growing follicles are also much more likely to form an antrum compared to their counterparts. When these growth patterns are applied to DBP-treated follicles, we see a decrease in the percentage of fast-growing follicles as DBP exposure concentration increases. Fast- and slow-growing follicles exposed to high concentrations of DBP also show decreased diameter over time compared to their DMSO counterparts. This work provides experimentally derived parameters that will inform predictive computational models about different follicle populations and their responses to DBP. This will ultimately help improve predictions of disrupted follicle development in response to EDCs, contributing to improved risk assessment for female reproductive health.



**SESSION II - IMMUNOTOXICOLOGY**  
**Student Union Memorial Center | Kachina Room**  
**Wednesday, August 12 | 10:45 AM – 12:15 AM**

**INVITED SPEAKER**

**5. Tungsten and Cardiometabolic Disease: Bridging Epidemiology and Mechanistic Insights**

**10:45 AM – 11:00 AM**

**Alicia Bolt**

University of New Mexico, College of Pharmacy, Department of Pharmaceutical Sciences, Albuquerque, NM, USA

Abstract not available.

**6. Trichloroethylene metabolite promotes autoimmune-relevant metabolic changes in CD4+ T cells**

**11:05 AM – 11:15 AM**

**Hayley Wondra**, Marena Montero, Laura Santos-Medina, Crystal Cevering, Sarah J Blossom

University of New Mexico, College of Pharmacy, Department of Pharmaceutical Sciences, Albuquerque, NM, USA

**Background and Purpose:** Autoimmune and hypersensitivity disorders have been on the rise, and while the causes are not known, studies suggest that genetic and environmental factors contribute to disease etiology. One of these environmental factors, Trichloroethylene, an industrial solvent, has been studied and linked to immunotoxicity and T-cell-driven autoimmunity. Preliminary data have established that TCE promotes autoimmune disease pathology by increasing proinflammatory cytokine-secreting Th1-like CD4+ T cells in autoimmune-prone mice. RNA sequencing was conducted to determine the direct effects of TCAH (a key metabolite of TCE metabolism *in vivo* and used in *in vitro* experiments) on gene expression in polarized Th1 and nonpolarized CD4+ T cells *in vitro*. Because RNA sequencing revealed alterations in metabolic pathways, including those related to glycolysis, it is hypothesized that trichloroethylene metabolites may influence autoimmunity by modulating T-cell imbalance through metabolic reprogramming.

**Methods:** RNA was isolated, and sequencing was conducted to determine the direct effects of trichloroacetaldehyde hydrate (TCAH) on gene expression in polarized Th1 CD4+ T cells *in vitro*. Th1 cells were compared with anti-CD3/anti-CD28-activated CD4+ cells (activated but non-polarized) to analyze whether TCAH altered gene expression in male and female MRL mice.

Extracellular flux assays (Seahorse assays) were conducted to confirm these findings and observe metabolic alterations in TCAH-treated non-polarized CD4+ and Th1 T cells. Agilent Seahorse T cell metabolic assays were conducted to assess the metabolic function of resting, anti-CD3/CD28-activated, and Th1-polarized cells in the presence or absence of TCAH. Seahorse assays were conducted on purified splenic CD4 cells from female MRL mice cultured +/- 0.5 mM TCAH over 4 days. Female C57 mice were also used as a strain comparison. Treated CD4+ T cells were analyzed via flow cytometry using activation markers (CD44 and CD62L) to assess activation state and characterize effector/memory phenotypes associated with metabolic alterations.

**Results:** RNA-sequencing results revealed that in non-polarized CD4+ and Th1 cells treated with TCAH, there was significant enrichment of differentially expressed genes involved in metabolic pathways. Metabolic assays demonstrated that cultured cells from nonautoimmune-prone and autoimmune-prone MRL/MpJ mice had a transient peak in metabolism at 48 hours. Alongside these temporal changes, TCAH enhanced basal glycolysis and respiration compared to activated controls through 48-96 hours, in a dose-dependent manner, suggesting a prolonged activation-associated metabolic programming. TCAH also enhanced glycolytic and oxidative metabolism in the absence of full costimulatory signaling, suggesting that TCAH promotes elevated metabolic programming independent of maximal T cell activation. Flow cytometric analysis performed at 24 and 48 hours in non-autoimmune-prone C57BL/6 mice identified differences in Th1-like effector cell populations and overall CD4+ T cell activation status following TCAH treatment, which may contribute to the observed metabolic alterations. Metabolic and flow cytometric analyses of autoimmune-prone MRL/MpJ mice are currently

underway to determine whether these immunometabolic responses are further amplified in a lupus-prone background.

**Conclusions:** Our findings suggest that a key TCE metabolite alters metabolic activity in CD4<sup>+</sup> T cells in nonautoimmune-prone mice, suggesting that enhanced effects would be expected in autoimmune-prone mice with underlying susceptibility. Metabolic reprogramming may enhance survival of CD4 cells, including autoreactive CD4s, and amplify responses to weak or self-antigens, promoting an autoimmune-relevant environment. Mechanistically targeting TCE-induced alterations in metabolic pathways may identify future therapies for TCE-exposed individuals.

## **7. Differential Effects of Uranium and Coal Mine Dust Exposure on Innate Immune Function *In Vitro* and In Humans**

**11:20 AM – 11:30 AM**

Mijung Oh<sup>1</sup>, Eunju Lim<sup>1</sup>, Onamma Edeh<sup>1</sup>, Sydnee Yazzie<sup>1</sup>, Jorge Moreno<sup>2</sup>, Alicia Bolt<sup>2</sup>, **Katherine E. Zychowski<sup>1</sup>**

<sup>1</sup> Department of Pathology, School of Medicine, University of New Mexico-Health Sciences

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**Introduction:** Former uranium (U) miners experience elevated risks of respiratory and systemic health effects, yet the biological mechanisms linking mine-dust exposure to chronic disease remain incompletely understood. We hypothesized that U-mine dust induces greater innate immune dysfunction than coal mine dust due to its unique physicochemical composition, resulting in altered inflammatory responses, impaired macrophage function, metabolic dysregulation, and possibly distinct extracellular vesicle (EV) signatures.

**Methods:** *In vitro* models were used to compare the effects of St. Anthony U mine dust and Colorado coal mine dust on innate immune responses. Endpoints included neutrophil extracellular trap (NET) formation, macrophage morphology, phagocytic function, cellular bioenergetics, and inflammatory gene expression following lipopolysaccharide (LPS) challenge. Human biospecimens were collected from former miners recruited from rural New Mexico communities, including U and non-U miners. Serum- and plasma-derived EVs were isolated and analyzed using untargeted proteomics to identify exposure-related protein and pathway signatures.

**Results:** U-mine dust exposure, *in vitro*, was associated with enhanced innate immune dysfunction compared with coal mine dust, based on increased neutrophil-extracellular trap (NET) formation. Experimental studies demonstrated altered NET formation and inflammatory responses following mine-dust exposure, impaired macrophage phagocytic activity, and significant metabolic dysfunction in macrophages exposed to U-mine dust. U-dust treated macrophages exhibited greater bioenergetic impairment than coal-dust-treated cells across mitochondrial stress and glycolytic assays. U-mine dust also modified LPS-induced inflammatory gene expression patterns. In a human cohort of former U, EV-associated proteomic profiles differentiated miners according to occupational tenure and identified enrichment of pathways related to extracellular matrix remodeling and inflammatory signaling. Extracellular-based analyses further suggested exposure-associated biological alterations that may serve as biomarkers of occupational exposure and immune dysfunction.

**Conclusions:** These findings support the hypothesis that U-mine dust produces greater innate immune and metabolic dysfunction than coal mine dust. Together, the *in vitro* and human findings support both direct effects of mine dust on first line (lung) immune cells and indirect effects on systemic macrophage function through circulating mediators such as EVs.

## **8. Inhaled Agricultural Dust Exposure Precedes Proximal Tubular Transporter Dysregulation and Immune Cell Depletion in the Kidney: Relevance to CKDu**

**11:35 AM – 11:45 AM**

**Matthew Gibb**, Lauren Rutt, Stephen Brindley, Laura Saba, Katherine James, Troy Schedin, Nichole Reisdorph, Richard Reisdorph, Rebecca McCullough, Alison K. Bauer, Jared M. Brown

University of Colorado Anschutz Medical Campus, Department of Pharmaceutical Sciences

Chronic kidney disease of unknown etiology (CKDu) disproportionately affects agricultural communities worldwide, including the San Luis Valley (SLV) of southern Colorado, where elevated CKD rates occur in the absence of conventional risk factors. While heavy metal contamination of water and soil has been implicated in SLV kidney disease burden, the contribution of inhaled metal-laden agricultural dust as an independent nephrotoxic exposure route has not been experimentally characterized. The San Luis Valley experiences frequent, severe dust events generating PM10 concentrations exceeding WHO guideline thresholds at more than six times the rate of urban Colorado reference sites, and ICP-MS analysis of collected SLV dust confirmed the presence of 10 of 11 detected metals with nephrotoxic or emerging nephrotoxic evidence, including manganese, arsenic, cadmium, lead, uranium, nickel, and tungsten. To investigate the pulmonary and renal consequences of this exposure, C57BL/6 mice (n=6 per group) received oropharyngeal aspiration of 100µg SLV agricultural dust or saline vehicle, Monday through Friday for 8 consecutive weeks. Dust-exposed animals demonstrated robust pulmonary immune activation, with significant increases in alveolar macrophages, interstitial macrophages, cDC1 and cDC2 dendritic cells, CD8+ and CD4+ T cells, and neutrophils by flow cytometry, alongside significantly elevated total bronchoalveolar lavage fluid cell counts and systemic lipid mediator changes by plasma lipidomics. In contrast, renal flow cytometry revealed broad immune cell depletion in dust-exposed kidneys, with near-complete loss of CD8+ T cells (35-fold,  $p<0.0001$ ), patrolling monocytes (4-fold,  $p<0.0001$ ), and cDC2 dendritic cells (220-fold,  $p<0.0001$ ), a divergent organ-level immune phenotype consistent with metal-induced immunosuppression and vascular remodeling-driven impairment of renal immune trafficking. Kidney transcriptomic profiling identified 584 significantly differentially expressed genes (321 upregulated, 263 downregulated,  $q<0.05$ ), with pathway enrichment analysis revealing disruption of membrane transport, Rap1 signaling, protein stability, and IgSF CAM pathways. Manual curation identified a coherent metal and ion homeostasis gene signature spanning lysosomal (Clcn3, Clcn7), mitochondrial (Nadk, Slc25a22, Nlrx1, Bcat2), nuclear (Irf9, Mapk14, Grb2), and basement membrane (Pxdn) compartments. Immunohistochemical analysis confirmed protein-level changes consistent with early proximal tubular injury, including decreased MATE1 and CD31 expression alongside upregulated OCT2, a pattern of transporter dysregulation and peritubular vascular remodeling characteristic of early-stage CKDu pathology. Taken together, these findings demonstrate that subchronic inhalation of metal-laden SLV agricultural dust is sufficient to drive coordinated pulmonary immune activation and renal molecular, immunological, and structural changes recapitulating the earliest features of CKDu-type proximal tubular nephropathy. These results establish dust inhalation as a previously underappreciated nephrotoxic exposure route in agricultural communities and provide experimental support for inhaled metal particulates as a contributor to CKDu pathogenesis in the San Luis Valley and potentially in other metal-contaminated agricultural regions worldwide.

## **9. Wildfire Smoke as a Driver of Neurological Aging and Injury**

**11:50 AM – 12:00 PM**

**Ember Suh**<sup>1</sup>, Jessica Begay<sup>1</sup>, Ting Jiang<sup>1</sup>, Zach Villaseñor<sup>2,3</sup>, Edward Barr<sup>1</sup>, Selita Lucas<sup>1</sup>, Guy Herbert<sup>1</sup>, Lingjun Li<sup>4</sup>, Ximeng Liu<sup>4</sup>, Shiquan Cui<sup>4</sup>, Kiran Bhaskar<sup>2,3</sup>, Haiwei Gu<sup>4</sup>, Shahani Noor<sup>5</sup>, Matthew Campen<sup>1</sup>

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Owing to the increasing severity of wildfires in the US, millions of people are routinely exposed to particulate matter from these events that may be harmful to the lungs and the brain. Previously, wildfire smoke (WFS) exposure was found to be associated with infiltrations of macrophages, neutrophils, and CD4<sup>+</sup> T cells, such as



Th17 and Treg, in the brain. WFS exposure also increased A $\beta$ 42 along the cerebrovasculature. However, factors, such as aging, can determine the severity and response of the neuroinflammatory response. In addition, the role of WFS on Alzheimer's disease and related dementias (ADRD) development is understudied and not well understood.

For neurometabolomics, 15-, 18-, and 21-month-old female C57BL/6 mice were exposed to either filtered air (FA) or simulated WFS (500  $\mu\text{g}/\text{m}^3$ ) for 4 hours every other day for 14 days and sacrificed 30-days post-exposure. Untargeted metabolomics were performed on brain hemispheres. To assess the role of WFS on ADRD, 8-month-old female and male Late-Onset Alzheimer's Disease 3 (LOAD3) mice that express human microtubule-associated protein tau (H1 haplotype), humanized ApoE4, and amyloid beta precursor protein (*A $\beta$* ) alleles with humanized A $\beta$ 1-42 region were exposed to either FA or simulated WFS (500  $\mu\text{g}/\text{m}^3$ ) for 4 hours every other day for 14 days and sacrificed 1-day post-exposure. To assess levels of proteins associated with ADRD phenotype in the dementia model, western blot was used to measure phospho-tau in the hippocampus. In addition, flow cytometry was used on brain hemispheres to measure neuroinflammation.

Untargeted metabolomics revealed neurometabolic alterations from WFS and overlap in affected metabolic pathways and metabolites from WFS and aging. Levels of phospho-tau were not affected by WFS exposure or by sex differences. Percentages of endothelial cells and macrophages in the brain did not change, but the percentages of the cells expressing activation markers (ICAM and MHC II on endothelial cells, ICAM on macrophages) increased in WFS-exposed LOAD3 male mice. Metabolomics data suggests that the effect of WFS is similar to the effect of aging in terms of neurometabolism and that while the levels of phospho-tau were not affected, endothelial cells and macrophages increased their expressions of activation markers. Collectively, these findings suggest potential vulnerabilities of dementia-prone mice.

## **10. Juvenile manganese exposure potentiates dopaminergic neurodegeneration resulting from encephalitic arbovirus infection via astrocyte-mediated inflammatory signaling**

**12:05 PM – 12:15 PM**

**Aidan M. Briggs<sup>1,2</sup>**, Adam J. Schuller<sup>1</sup>, Abigail M. Bibb<sup>1</sup>, Megan R. Hager<sup>3</sup>, Collin M. Bantle<sup>3</sup>, and Ronald B. Tjalkens<sup>1,2</sup>

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by selective nigrostriatal dopaminergic denervation resulting in motor dysfunction. Although the etiology of PD is not fully understood, there is mounting evidence associating risk of this disease with cumulative exposure to environmental agents, including industrial solvents, pesticides, air pollution, heavy metals, and infectious pathogens. Viral infections, in particular, are linked with PD risk through neuroinflammatory activation of glial cells that may represent a critical early mechanism in the etiology of this disorder. Our group has demonstrated that infection with the neurotropic alphavirus, Western equine encephalitis virus (WEEV), results in significant astrocytosis preceding dopaminergic neuron loss and PD-like motor deficits in mice. We have also shown that overexposure to the heavy metal manganese (Mn<sup>2+</sup>) during juvenile development potentiates nigrostriatal inflammation following infection with a non-neurotropic strain of Influenza virus H1N1. Accordingly, we postulated that astrocytic NF- $\kappa$ B signaling in Mn<sup>2+</sup>-primed mice is central to a heightened neuroinflammatory response to WEEV infection and subsequent dopaminergic neurotoxicity. To test this hypothesis, we treated juvenile wildtype or astrocyte-specific NF- $\kappa$ B knockout mice with Mn<sup>2+</sup> via the drinking water, followed by adult infection with WEEV. We then assessed histopathologic changes in PD-relevant brain regions using high content imaging and AI-based image analysis. Compared to vehicle treated, mice exposed to Mn<sup>2+</sup> during juvenile development followed by WEEV infection developed more viremic infection and mortality, increased astrogliosis, and disease-associated changes in microglial morphometry. Dopaminergic neurodegeneration was similarly amplified in Mn-primed mice compared to mice infected with WEEV alone. These phenomena were all dramatically attenuated in astrocyte-specific NF- $\kappa$ B knockout mice, despite an increase IBA1+ cell number in the substantia nigra.

Together, these findings suggest a critical role for astrocyte-mediated neuroinflammation in the context of an environmentally relevant viral model of PD.

**SESSION III - NEUROTOXICOLOGY**  
**Student Union Memorial Center | Kachina Room**  
**Wednesday, August 12 | 1:35 PM – 3:00 PM**

**INVITED SPEAKER**

**11. Manganese as a modulator of innate immunity in the brain**

**1:40 PM – 2:00 PM**

**Ronald Tjalkens**

Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA

Abstract not available.

**12. Glyphosate at the Human-Equivalent EPA Chronic Reference Dose Alters the Gut–Brain Axis and Exacerbates Alzheimer's Disease Pathogenesis in mice**

**2:05 PM – 2:15 PM**

**William Gendron<sup>1</sup>**, W. Winslow<sup>1</sup>, S. Bartholomew<sup>2</sup>, K. Pathak<sup>3</sup>, J. Paredes<sup>4</sup>, P. Pirrotte<sup>5</sup>, R. Velazquez<sup>2</sup>

<sup>1</sup> Arizona State University, ASU-Banner Neurodegenerative Disease Research Center at the Biodesign Institute, Tempe, United States

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<sup>4</sup> City of Hope Comprehensive Cancer Center, Department of Hematology, Beckham Research Institute, Duarte, United States

<sup>5</sup> Translational Genomics Research Institute, Early Detection & Prevention Division and Integrated Mass Spectrometry Shared Resources, Phoenix, United States

Glyphosate (GLY) is the most widely used herbicide worldwide, resulting in pervasive environmental contamination and widespread human exposure. Although regulatory agencies have established exposure thresholds considered safe, the U.S. chronic reference dose (cRfD; 1.75 mg/kg/day) remains substantially higher than acceptable daily intake limits adopted in several other countries. Despite the detection of GLY in human biofluids, its effects on the aging brain and neurodegenerative disease risk remain poorly understood. Our laboratory was the first to demonstrate that GLY crosses the blood-brain barrier and induces neuroinflammation in young C57BL/6J mice following short-term exposure at the No Observed Adverse Effect Level (NOAEL; 500 mg/kg/day) and a 10-fold lower dose. We subsequently showed persistent accumulation of the GLY metabolite aminomethylphosphonic acid (AMPA) in brain tissue months after exposure cessation, accompanied by sustained neuroinflammation and exacerbated Alzheimer's disease (AD)-like pathology. Whether exposure at the regulatory-relevant cRfD elicits similar biological effects, however, remains unknown. To address this question, 3xTg-AD and non-transgenic (NonTg) mice were exposed to the mouse-equivalent cRfD of GLY for 30 days between 4.5 and 5.5 months of age. Plasma was analyzed for the blood-based neurodegeneration biomarkers glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and pro-inflammatory cytokines. Hippocampal tissue was assessed for cytokines and AD-related pathology, while cecal contents were analyzed for the short-chain fatty acids (SCFAs) propionate, isovalerate, butyrate, and hexanoate. Short-term GLY exposure at the mouse-equivalent cRfD significantly increased circulating GFAP, NfL, and pro-inflammatory cytokines in both genotypes. In 3xTg-AD mice, GLY further exacerbated amyloid- $\beta$  and phosphorylated tau pathology, which positively correlated with plasma GFAP and NfL levels. GLY also altered gut microbial metabolites, increasing propionate in NonTg mice and producing a distinct SCFA signature in 3xTg-AD mice characterized by elevated isovalerate and reduced butyrate and hexanoate. These findings demonstrate that regulatory-relevant GLY exposure is sufficient to trigger systemic inflammation, disrupt gut microbial metabolism, accelerate AD-related neuropathology, and elevate clinically relevant blood biomarkers of neurodegeneration. Collectively, these data raise important questions regarding the neurological safety of current regulatory exposure limits and identify NfL, GFAP, GLY, and AMPA as promising translational biomarkers for monitoring GLY-associated neurotoxicity in vulnerable aging populations.



### **13. Global STING knockout rescues male-specific gait and nigrostriatal neurochemical decrements in mice subjected to the juvenile Manganese model of Parkinson's disease**

**2:20 PM – 2:30 PM**

**Abigail Bibb<sup>1</sup>**, Adam Schuller<sup>1</sup>, Megan Hager<sup>2</sup>, Aidan Briggs<sup>1</sup>, Brenna Baird<sup>1</sup>, and Ronald Tjalkens<sup>1</sup>

<sup>1</sup> Department of Neurology, Barrow Neurological Institute, Phoenix, AZ

<sup>2</sup> Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO

Parkinson's disease (PD) is the fastest growing neurodegenerative disorder world-wide, with idiopathic etiology and no existing cures. Manganese, an essential heavy metal commonly found in the environment, has been demonstrated to elicit PD-like neurotoxicity in human workers overexposed to this toxicant in mines or battery production plants. This Mn-induced Parkinsonism can be recapitulated in laboratory rodents, although mixed reports exist regarding the timing of exposure and association with nigrostriatal dopaminergic denervation characteristic of PD given inherent limitations of techniques classically used to query these disease metrics. Mechanisms underlying this selective neurotoxicity are broadly thought to include mitochondrial dysfunction, oxidative stress, and glial-mediated inflammatory signaling, all of which have been previously shown by our lab to result from Mn overexposure in juveniles. This motivated the present interrogation of immune modulatory nucleic acid sensing pathways, like the cGAS-STING signaling cascade, in the context of this Mn-induced PD onset. Notably, Mn has been shown capable of direct catalytic activation of cGAS, suggesting a role of this activation to provoke innate immune modulation via downstream signal transduction. To this end, we sought to explore the effects of genetic STING ablation on motor function and nigrostriatal neurotransmitter levels in a juvenile Mn model of PD using highly sensitive automated gait analysis and neurochemical profiling. Male and female wildtype (WT) or STING<sup>goldenticket</sup> (GT) mice were orally administered 30 mg/kg/day Mn or vehicle from PND14-28 followed by a 7 day post-lesioning period. Longitudinal weight measurements were recorded to ensure no overt signs of toxicity and scores of dystonic reflex were recorded throughout the study period to monitor progressive motor decline. At the terminal timepoint, all animals were subjected to automated gait analysis via the NoldusXT Catwalk system which collects 97 parameters associated with normal murine movement. This revealed significant PD-like bradykinesia in Mn-treated male WT animals which was not present in GT animals or any female subjects. At the end of the 28-day experiment, animals were sacrificed and the dorsolateral striatum was collected for neurochemical analysis using HPLC-ECD. This demonstrated sex-, treatment-, and genotype-specific alterations in PD-relevant neurotransmitter levels, including a male-specific Mn-induced dopaminergic deficit that was rescued in GT animals. Together, these findings suggest an important role of cGAS-STING signaling in pathogenesis of the Mn model of PD. The male-specific effects observed here reflect marked sex differences in the clinical susceptibility to PD. Future work will aim to parse out cell-type specificity of STING signaling relevant to these neurodegenerative sequelae.

### **14. Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson's disease**

**2:35 PM – 2:45 PM**

**Adam Schuller**, Omar Yanouri, Abigail Bibb, Aidan Briggs, Megan Hager, Nicole Yates, Brenna Baird, and Ron Tjalkens

<sup>1</sup> Department of Neurology, Barrow Neurological Institute, Phoenix, AZ

<sup>2</sup> Department of Environmental and Radiologic Health Sciences, Colorado State University, Fort Collins, CO

Parkinson's disease (PD) is the fastest growing neurodegenerative disorder, linked with exposure to environmental risk factors including: air pollution, heavy metals, viral infections, industrial solvents, and pesticides. Our group has consistently highlighted the key role of inflammatory astro-glial activation across toxicant-based models of this disorder. Most recently, the cGAS-STING pathway, which produces type-I interferons in response to mislocalized double stranded nuclear or mitochondrial DNA, has emerged as a potential disease-modifying therapeutic target. Efforts in this context have largely focused on microglial contributions to STING signaling; however, astrocytes are increasingly recognized as important contributors to parenchymal interferon levels. Here, we examined the effects of STING signaling on motor function and astrocyte reactivity using the rotenone model of PD in wild-type (WT) and STING<sup>goldenticket</sup> (GT) mice.

Primary astrocyte-enriched mixed glial cultures were employed to establish the  $IC_{50}[\text{Rotenone}] = 78.90\text{nM}$ , which was blunted by pharmacologic STING inhibition and genetic ablation. Oxidative mitochondrial DNA damage was significantly increased following acute rotenone treatment via quantification of 8-OHdG levels in fractionated nucleic acids. High-content immunocytochemical fluorescence microscopy and deep learning-based image analysis revealed a subsequent increase in perinuclear p-STING+ puncta in GFAP<sup>hi</sup>ALDH1L1<sup>hi</sup> astrocytes, and downstream STING-dependent nuclear p-IRF3+ translocation in the same dual-positive cell population. Notably, co-treatment with the VDAC inhibitor DIDS blunted rotenone-induced NF- $\kappa$ B activation and IFN- $\beta$  production, suggesting a role for release of damaged mitochondrial DNA in this inflammatory activation. Further mechanistic interrogation revealed a STING-dependent enrichment of MAPK signaling and ECM remodeling via transcriptomics, as well as enhanced astrocytic release of signaling factors TNF- $\alpha$ , VEGF, and IL-6, which were all blunted in GT cells. This resulted in an astrocyte-mediated neurotoxic effect on differentiated dopaminergic neuron-like cells treated with glial conditioned media in a STING-dependent manner. In vivo, automated gait assessment demonstrated progressive PD-like hypokinesia and widened base of support in male WT mice. Additionally, we observed progressive decreases in total distance traveled and rearing number, as well as an increase in total rest time in the open field test, together indicating a parkinsonian motor phenotype. Across this battery of motor functional assessment, we observed protection against aberrant gait in rotenone-treated GT males. Concordantly, HPLCECD neurochemical profiling of PD-relevant catecholamines revealed male-specific depletion of striatal dopamine following rotenone treatment and increased turnover of this metabolite, which was attenuated by genetic STING ablation. Together, these data demonstrate the importance of cGAS-STING signaling in inflammatory astrocyte reactivity and a potential role for this molecular transduction in the sequelae of PD-like neurotoxicity, dopaminergic denervation, and motor dysfunction. Future work will interrogate the effects of astrocyte-specific STING ablation on microstructural brain changes using advanced imaging techniques in vivo.

## **INVITED SPEAKER**

### **15. Neurological Signatures of PFAS in multi-OMIC platforms**

**2:50 PM – 3:00 PM**

**Melissa Furlong**

<sup>1</sup> Department of Environmental Health Sciences, Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

Abstract not available.

## SESSION IV – REPRODUCTIVE & METABOLIC TOXICOLOGY

Student Union Memorial Center | Kachina Room

Wednesday, August 12 | 3:30 PM – 4:45 PM

### INVITED SPEAKER

#### 16. Sex Differences in Phthalate Metabolism and Reproductive Toxicity

3:40 PM – 4:00 PM

Hovhannes M. Saribekyan<sup>1,4</sup>, Maile McSwain<sup>1,4</sup>, Carly Roberts<sup>3,4</sup>, Sarah White<sup>3,4</sup>, Valeria Ramirez<sup>1,4</sup>, Erica Sun<sup>3,4</sup>, Anaeli Guzman<sup>3,4</sup>, Shaina Duhra<sup>2,4</sup>, Dustin Rehnke<sup>3,4</sup>, Ashley Parker<sup>3,4</sup>, **Estela J. Jauregui**<sup>1,3,4</sup>

<sup>1</sup> College of Graduate Studies, Midwestern University, Glendale, AZ, 85308

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<sup>4</sup> Midwestern University, Glendale, AZ, 85308

Phthalates are widely used as plasticizers and solvents in consumer products, including food packaging, medical coatings, and medical device tubing. Although phthalate exposure has been associated with adverse reproductive outcomes in both men and women, little is known about whether environmentally relevant exposures affect male and female gonads differently. Using a CD-1 mouse model, we investigated sex-specific differences in DEHP metabolism by examining the expression of phthalate-metabolizing enzymes in the gonads and liver, as well as morphological changes in the ovaries and testes following short-term DEHP exposure. Baseline expression of DEHP-metabolizing enzymes was higher in the ovaries than in the testes, and additional sex-dependent differences were observed in hepatic enzyme expression. Short-term exposure (10-14 days) to environmentally relevant doses of DEHP (20 and 200 µg/kg/day), as well as a toxicological dose (1000 mg/kg/day), induced testicular damage in males compared with corn oil-treated controls. Mice exposed to 1000 mg/kg/day exhibited significantly more abnormal seminiferous tubules and increased pyknosis, while all DEHP-treated groups showed increased vacuolization and caspase-3-positive tubules, indicating germ cell damage and apoptosis, even at environmentally relevant exposure levels. In contrast, no detectable morphological changes were observed in the ovaries of DEHP-exposed females compared with corn oil-treated controls. In addition, DEHP exposure produced sex-specific differences in hepatic toxicity, further supporting differential responses between males and females. Together, these findings demonstrate that identical DEHP exposures produce sex-specific metabolic and toxicological responses in the gonads and liver. This work highlights the importance of considering biological sex in studies of phthalate toxicity, advances our understanding of how environmental toxicants contribute to reproductive dysfunction, and supports the need for sex-specific approaches to the prevention and treatment of endocrine and reproductive diseases.

Work supported by the Midwestern University Biomedical Sciences Program (VR), the Boehringer Ingelheim Stipend (SD), the Midwestern University Kenneth A. Suarez Research Fellowship (CR, ES), and NIH grant R15ES037124 (EJ).

#### 17. Lipid Dysregulation in Mouse Ovarian Antral Follicles After Oral Exposure to a Human Relevant Mixture of Three Phthalates

4:05 PM – 4:15 PM

**Kara L. Miller**<sup>1</sup>, Taylor Massey<sup>2</sup>, Vivianna Metzler<sup>2</sup>, Amanda Adams<sup>3</sup>, Xiaosong Liu<sup>1</sup>, Kimberlie Burns<sup>1</sup>, Lydia R. Porter<sup>4</sup>, Justin Snider<sup>4,5</sup>, Zeliann R. Craig<sup>1,5,6</sup>

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<sup>3</sup> Department of Molecular and Cellular Biology, The University of Arizona

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<sup>6</sup> Southwest Environmental Health Sciences Center, The University of Arizona

Dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), and di-2-ethylhexyl phthalates (DEHP) leach from consumer and medical products, leading to chronic daily exposure in women. Phthalates are associated with negative reproductive outcomes, ovarian dysfunction, and metabolic syndrome in women. In mice, exposure



to a human relevant mixture of DBP, BBP, and DEHP caused dysregulation of the antral follicle proteome mainly on lipid metabolism proteins. Therefore, a mouse model was utilized to establish the consequences of such alterations on follicular and systemic lipid profiles. Adult CD-1 female mice were pipet fed vehicle or the phthalate mixture (32µg/kg/day) for 10 days. Antral follicles were isolated and subjected to targeted lipid profiling, neutral lipid and triglyceride quantification, and analyses of key lipid metabolism proteins. Liver and serum samples were tested for systemic effects. Phthalate exposure increased follicular free fatty acid (FFA), acylcarnitine, and lysophospholipid content with fewer systemic changes. Neutral lipid content was unaffected by phthalate exposure, but follicle and hepatic triglyceride content were altered. Increased follicular fatty acid synthase, decreased carnitine o-palmitoyltransferase 2, and altered triglyceride hydrolysis enzymes were also observed. These findings strongly suggest that phthalate mixture exposure leads to molecular changes indicative of increased intrafollicular FFA synthesis, impaired beta oxidation, and decreased triglyceride abundance. Our results add key mechanistic information to our understanding of the associations between phthalates, antral follicles, and metabolic dysfunction in women.

## **18. Integrating Toxicokinetic, Mechanistic, and Epidemiologic Evidence to Evaluate the Estrogenic Potential of Methylparaben and Propylparaben**

**4:20 PM – 4:30 PM**

**Kylie Jones** and Christy A. Barlow

Aetia Scientific Collaborative, Boulder, CO

**Background:** Methylparaben (MeP) and propylparaben (PP) are widely used preservatives in cosmetics, personal care products, pharmaceuticals, and foods. Although these compounds exhibit estrogen receptor activity under experimental conditions, the biological relevance of these findings at typical consumer exposure levels remains an area of scientific and regulatory interest.

**Methods:** This review evaluates current evidence on the dermal absorption, metabolism, systemic distribution, and bioavailability of MeP and PP. Additionally, experimental studies assessing estrogenic potential were examined, including receptor binding affinity and reported biological effects.

**Results:** The available evidence demonstrates that MeP and PP exhibit weak estrogen receptor activity relative to endogenous estradiol, undergo rapid metabolism following absorption, and have limited systemic bioavailability under typical conditions of consumer use. Experimental estrogenic responses generally occur at exposure levels substantially exceeding those encountered through routine product use, while epidemiologic studies have not consistently demonstrated associations between paraben exposure and breast or gynecologic cancers.

**Conclusions:** Overall, the toxicokinetic, mechanistic, and epidemiologic evidence collectively suggest that MeP and PP are unlikely to produce clinically relevant endocrine effects or increase the risk of hormone -sensitive cancers at typical exposure concentrations.

## **19. Hepatic Transporter Dysfunction as an Early Indicator of Metabolic Dysfunction and Alcohol-Associated Liver Disease Progression**

**4:35 PM – 4:45 PM**

**Alexis B. Cruickshank-Taylor<sup>1</sup>**, Dominique O. Farrera<sup>1</sup>, Paxton A. Sample<sup>1</sup>, Peter S. Harris<sup>2</sup>, Kristofer S. Fritz<sup>2</sup>, Stephen H. Wright<sup>3</sup>, Nathan J. Cherrington<sup>1</sup>

<sup>1</sup> Department of Pharmacology and Toxicology, University of Arizona, Tucson, AZ, USA

<sup>2</sup> Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

<sup>3</sup> Department of Physiology, University of Arizona, Tucson, AZ, USA

Metabolic dysfunction and alcohol-associated liver disease (MetALD) results from the combined effects of the two leading causes of steatotic liver disease (SLD): cardiometabolic risk factors and alcohol consumption. Because SLD affects more than 30% of adults worldwide, MetALD is an increasingly prevalent, yet understudied disease. MetALD shares key histopathological features with metabolic dysfunction-associated steatohepatitis

(MASH), the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD). In MASH, hepatic transporter alterations are well-characterized and include decreased OATP1B3-mediated basolateral uptake, increased MRP3 efflux, and MRP2 mislocalization, reducing biliary excretion. This project aims to determine whether MRP2 mislocalization and basolateral transporter alterations occur during MetALD progression. Transporter expression and localization were determined using LC-MS/MS and immunohistochemistry approaches. Mice were fed a chronic high-fat, alcohol-containing diet for six weeks to model early MetALD. Preliminary immunohistochemical analysis shows Mrp2 mislocalization away from the canalicular membrane, suggesting decreased biliary efflux. To address the need for objective quantification of Mrp2 mislocalization across animal models in future studies, we developed a novel AI-based bile canalicular protein localization image analysis pipeline using Nikon NIS-Elements AR (v6.10) with General Analysis 3. The pipeline is currently undergoing evaluation and is expected to provide a foundation for objective assessment of bile canalicular protein localization, as demonstrated by Mrp2, and to support future comparative studies across experimental models. Subsequent studies will quantify the extent of mislocalization, examine its relationship with disease progression, and evaluate concordance between animal models and human tissue. Defining how transporters change throughout MetALD progression may enable early disease diagnosis through the development of mechanistically-informed drug probes targeting alterations in transporter function.

## SESSION V – COMMUNITY ENGAGED RESEARCH

Student Union Memorial Center | Kachina Room

Thursday, August 13 | 8:30 AM – 10:00 AM

### *INVITED SPEAKERS*

#### **20. Community-Engaged Research with Firefighters**

**8:35 AM – 9:10 AM**

**Jeff Burgess<sup>1</sup>, John Gulotta<sup>2,3</sup>**

<sup>1</sup> Department of Community, Environment & Policy, The University of Arizona, Tucson, AZ, USA

<sup>2</sup> Tucson Fire Department, Tucson, AZ, USA

<sup>3</sup> First Responders Center for Excellence (FRCE), Emmitsburg, MD, USA

The Fire Fighter Cancer Cohort Study (FFCCS) is a community-engaged research project with firefighters focused on the evaluation and prevention of risks for cancer, reproductive harm, and neurodegenerative disease in firefighters. FFCCS research questions originate from the fire service and fire department research liaisons are involved in all phases of the research, including scheduling enrollment of firefighter participants, collection of biological samples, and interpretation and dissemination of the study results. Given their deep involvement in the research, the liaisons and other fire service partners are also able to translate the study findings into actions by the firefighters and fire departments. This presentation will share some important FFCCS outcomes including exposure reduction and mitigation of toxic effects.

### *INVITED SPEAKER*

#### **21. Building resilience together: Community science for understanding co-exposures and compounding environmental threats**

**9:35 AM – 9:45 AM**

**Mónica Ramírez-Andreotta**

Soil/Water and Environmental Science, Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

Abstract not available.

### *INVITED SPEAKER*

#### **22. From data to action: Co-producing water quality research with a rural, Indigenous Arizona community**

**9:50 AM – 10:00 AM**

**Anupama Sethuraman**

Department of Environmental Science, University of Arizona, Tucson, AZ, USA

Abstract not available.

## SESSION VI – SYSTEMS & MECHANISTIC TOXICOLOGY

Student Union Memorial Center | Kachina Room

Thursday, August 13 | 10:25 AM – 11:55 AM

### INVITED SPEAKER

#### 23. PFAS inhibition of retinoic acid metabolism and signaling: a novel mechanism for developmental toxicity

10:35 AM – 10:55 AM

##### Jed Lampe

University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences

Craniofacial anomalies represent nearly one-third of congenital birth defects, and per- and polyfluoroalkyl substances (PFAS) have been identified as teratogens that produce these types of defects in humans and animal models. PFAS structurally mimic the Vitamin A hormone all-trans-retinoic acid (*atRA*), a morphogen regulating over 500 genes in craniofacial development. Due to the fact that the fetus cannot synthesize *atRA* de novo or clear excess maternal *atRA*, maternal hepatic *atRA* homeostasis is critical for normal fetal development. A primary determinant of this homeostasis is metabolic clearance of *atRA* by cytochrome P450 CYP26A1. We hypothesized that PFAS may disrupt this homeostasis by inhibiting CYP26-mediated *atRA* clearance, contributing to PFAS-associated birth defects. *In vitro* screening of 13 common PFAS for inhibition of CYP26A1 and CYP26B1 metabolism of *atRA* identified PFDA as the most potent CYP26A1 inhibitor ( $IC_{50} = 49.5 \mu M$  for 4-hydroxy-retinoic acid and  $51.3 \mu M$  for 4-oxo-retinoic acid formation), with no significant CYP26B1 inhibition observed for any compound. PFDA also disrupted *atRA* metabolism and RAR/RXR mediated signaling in primary female human hepatocytes after 48-hour semistatic exposure. These findings identify both CYP26A1-mediated *atRA* clearance and RAR/RXR signaling as molecular targets of PFDA, suggesting a mechanism by which prenatal PFAS exposure could irreversibly disrupt fetal and neonatal development.

#### 24. Impacts of Heat Strain on ADME Function

11:00 AM – 11:10 AM

**Paxton Sample**, Vivian Pirro, Veronica Samala, Dominique Farrera, Alexis Cruickshank-Taylor, Nathan Cherrington

University of Arizona, College of Pharmacy, Department of Pharmacology and Toxicology

Environmental stressors are known to influence xenobiotic metabolism, but the impact of heat strain on xenobiotic absorption, distribution, metabolism, and elimination (ADME) remains largely unexplored. While previous studies have demonstrated altered toxicity due to high heat, mechanisms to describe these changes have not been investigated. Furthermore, the use of nonstandard heat stress conditions, which often do not consider nuances of environmental exposure, makes these models impractical for assessing real-world pharmacokinetics. This study examined the effect of heat strain on the expression and function of hepatic Cytochrome P450 enzymes (P450s) and transporters in a novel model of cyclically-induced, environmentally-relevant heat strain. Male Sprague-Dawley rats were exposed to cyclical heat stress (34°C/28°C, 12 hours/day for 7 days), and hepatic P450 and transporter expression/function were assessed using LC-MS/MS quantification of metabolite formation from isoform-specific probe substrates, total protein, and biliary elimination. Induction of heat strain was confirmed via body temperature measurements greater than 1 °C above baseline. Enzymatic activity of Cyp2e1 and 1a2 decreased significantly, alongside a trending decrease in Cyp3a1. Similarly, multiple hepatic transporters demonstrated decreased expression, including uptake transporters Ntcp, Oatp2b1, Oat2, and efflux transporters Bcrp and Bsep. Chlorzoxazone plasma AUC increased ~70%, consistent with reduced Cyp2e1-mediated metabolism. Furthermore, biliary elimination of pravastatin, a substrate of Oatp2b1 and Bsep, decreased significantly in heat strain, indicating decreased hepatic uptake and efflux. These data suggest that heat strain alters xenobiotic metabolism and disposition, providing a novel mechanism for increased susceptibility to chemical toxicity in heat. Taken together, these findings indicate that heat strain could be a major variable in individual susceptibility to toxicity and adverse drug reactions.



## 25. Mechanistic Evaluation of Ezetimibe-Glucuronide as a Functional Probe in Chronic Liver Disease

11:15 AM – 11:25 AM

**Dominique O. Farrera**, Alexis B. Cruickshank-Taylor, Paxton A. Sample, Stephen H. Wright, Geoffrey Block, Nathan J. Cherrington

University of Arizona, College of Pharmacy, Department of Pharmacology and Toxicology

Chronic liver diseases alter hepatic transporter function, leading to changes in drug disposition that may serve as indicators of hepatic health. We previously demonstrated that plasma ezetimibe-glucuronide (EZEG), a substrate of OATP1B3, MRP2, and MRP3, is a promising noninvasive functional probe for metabolic dysfunction-associated steatohepatitis (MASH). Following a 1 mg oral dose of ezetimibe, patients with biopsy-confirmed MASH exhibited ~4.5-fold higher plasma EZEG concentrations than non-MASH individuals, with excellent diagnostic performance at 60 minutes post-dose (AUROC = 0.92). While these findings establish proof-of-concept, the relationship between EZEG disposition and MASH pathogenesis remains unclear. Among the histopathologic features of MASH, plasma EZEG concentrations were most strongly associated with hepatocyte ballooning (AUROC = 0.97), prompting ongoing studies investigating how cytoskeletal remodeling disrupts MRP2 localization and transporter function. Because transporter dysregulation has been reported in alcohol-associated liver disease, metabolic and alcohol-associated liver disease, viral and autoimmune hepatitis, and primary biliary and primary sclerosing cholangitis, we are investigating whether EZEG serves as a broadly applicable functional assessment of hepatocyte dysfunction. This study evaluates how the etiologic features of MASH influence EZEG disposition and transporter regulation to establish EZEG as a mechanism-based functional liver test and provides new insight into transporter dysfunction across chronic liver diseases.

## 26. Investigating the Impact of Lithium Exposure on Gut Microbiota

11:30 AM – 11:40 AM

Daniella Hawley, Kelly Le, Caroline Ho, Liberty Li, Haiwei Gu

Arizona State University, College of Health Solutions, Phoenix, AZ, USA

A growing demand for lithium in technology has increased the environmental release of lithium cobalt oxide ( $\text{LiCoO}_2$ ) and raised concerns about the biological risks of lithium consumption. Another form of lithium,  $\text{Li}_2\text{CO}_3$  (lithium carbonate), is used pharmaceutically as a treatment for bipolar disorder and also prompts questions about the biological effects of lithium exposure. While human contact with lithium compounds is increasing both environmentally and pharmaceutically, their comparative effects on the gut microbiota remain largely unexplored. This study addresses this gap by evaluating how these specific chemical forms influence the growth of gut bacteria.

We assessed the effects of  $\text{Li}_2\text{CO}_3$  and  $\text{LiCoO}_2$  on three representative probiotic gut bacteria: *Lactocaseibacillus rhamnosus*, *Lactobacillus reuteri*, and *Bifidobacterium bifidum*, as well as a wild-type *Escherichia coli* strain. Bacteria were exposed to lithium concentrations ranging from 1 to 1,000  $\mu\text{g/mL}$  under anaerobic conditions, and growth was quantified using optical density at 600 nm ( $\text{OD}_{600}$ ) with viability confirmed through colony-forming unit (CFU) assays.

Across probiotic strains,  $\text{Li}_2\text{CO}_3$  did not significantly alter growth at 24 hours, whereas  $\text{LiCoO}_2$  consistently reduced  $\text{OD}_{600}$  values by 48–59%. However, this inhibition reached statistical significance only in *L. rhamnosus* ( $p = 0.0012$ ), with *L. reuteri* and *B. bifidum* showing non-significant reductions due to higher trial-to-trial variability. CFU assays supported these findings, suggesting that cobalt, rather than lithium, might be the primary driver of toxicity in these probiotic species. In contrast, wild-type *E. coli* displayed a divergent response:  $\text{Li}_2\text{CO}_3$  caused a highly significant reduction in  $\text{OD}_{600}$  at 24 hours ( $p < 0.0003$ ), while  $\text{LiCoO}_2$  significantly increased growth ( $p = 0.017$ ), suggesting a possible cobalt-associated growth advantage in this strain.

Overall, this study illustrates that battery derived  $\text{LiCoO}_2$  disrupts probiotic gut bacteria, while pharmaceutical  $\text{Li}_2\text{CO}_3$  remains biologically inert toward these strains at comparable concentrations. The opposing response

of wild-type *E. coli* suggest that lithium-based compounds may reshape gut microbial communities in a species-specific and chemically distinct way.

## **27. Nuclear Receptor Coactivator 4 Restricts Mitochondrial Iron Signaling by Controlling Intracellular Iron Partitioning**

**11:45 AM – 11:55 AM**

Hyeoncheol Kim<sup>1</sup>, Luke B. Villareal<sup>1</sup>, Naiara Santana-Codina<sup>2</sup>, Christian V. Cabanlong<sup>1</sup>, Lavanya Goodla<sup>1</sup>, Eric R. Prossnitz<sup>3</sup>, David R. Martin<sup>4</sup>, Joseph D. Mancias<sup>2</sup>, **Xiang Xue**<sup>1</sup>

<sup>1</sup> Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Albuquerque, NM

<sup>2</sup> Department of Radiation Oncology, Harvard Medical School, Boston, MA

<sup>3</sup> Division of Molecular Medicine, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM

<sup>4</sup> Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM

Iron is essential for mitochondrial metabolism, yet the mechanisms that coordinate iron distribution between cellular compartments and couple iron homeostasis to signaling remain poorly understood. Here, we identify Nuclear Receptor Coactivator 4 (NCOA4) as a central regulator of intracellular iron partitioning that controls communication between cytosolic and mitochondrial iron pools. Using human colorectal cancer specimens, genetically engineered mouse models, quantitative proteomics, and mechanistic studies in tumor cells, we show that NCOA4 deficiency triggers a compensatory iron-acquisition program that expands cytosolic labile iron and promotes mitochondrial iron loading. Increased iron availability drives reactive oxygen species production and induces a signaling circuit involving AMPK-CREB-dependent upregulation of mitochondrial iron transport pathways, resulting in mitochondrial iron accumulation and mitochondrial oxidative signaling. Elevated mitochondrial iron activates STAT3-dependent transcriptional programs that promote cellular proliferation and tumor growth. Genetic or pharmacologic disruption of mitochondrial iron transport or iron-dependent signaling abolishes the oncogenic consequences of NCOA4 deficiency, whereas epithelial NCOA4 overexpression restores iron homeostasis and suppresses tumorigenesis. Together, these findings establish NCOA4 as an upstream iron-partitioning factor that coordinates subcellular iron allocation and reveal mitochondrial iron as a signaling hub linking metabolic homeostasis to cell-fate regulation.

**SESSION VII – RISK ASSESSMENT**  
**Student Union Memorial Center | Kachina Room**  
**Thursday, August 13 | 12:05 PM – 12:15 PM**

**28. Comparing US National Databases to Examine Health Risks Near Los Alamos National Laboratory**  
**12:05 PM – 12:15 PM**

**Chanese A. Forté**

Union of Concerned Scientists

Purpose: This project came about from nuclear materials exposed communities contacting the Union of Concerned Scientists and requesting a better understanding of what risks exists in their region. This work aims to use publicly available information to assess social vulnerability and cumulative burdens of people residing near a nuclear weapons facility in the United States Southwest.

Introduction: Los Alamos National Laboratory has a nuclear weapons history as old as the US' first attempts at wrangling splitting the atom—better known as the Manhattan project. Nuclear materials often contain ionizing radiation and can increase cancer health risk. There has not been enough investigation of increased health risks or vulnerability to cancer in areas further than a 50-mile radius drive (as is the legal requirement for federal environmental impact studies).

The purpose of this report is to quantify the social epidemiology, subpopulation vulnerability, and new cancer health outcomes in the Rio Arriba, Taos, Los Alamos, Sandoval, Mora, San Miguel, and Santa Fe.

Methods: Three national databases were accessed to better understand the environmental exposure and health risks in the surrounding counties of the Los Alamos National Laboratory. Specifically, the US Environmental Protection Agency Environmental Justice Index Tool was utilized to identify vulnerable populations within the selected county region.

United States Census data was collected to quantify the social epidemiology of the region, and there was a special focus on people residing on sovereign Indigenous nations as well. Finally, the Center for Disease and Control and Prevention Surveillance, Epidemiology, and End Results data was collected to understand the burden of new cancer diagnoses in the area, by county.

Results: Santa Fe and Sandoval counties had the highest count of burdened census tracts out of the examined counties. There is a very large Indigenous population in the region as well as multiple sovereign Indigenous nations. Over, 400,000 people residing in the area are represented in the region with an even split of male and females and an overrepresentation in certain subpopulations. Many groups on the edges of the captured region had increased economic vulnerability, while Los Alamos is one of the wealthiest counties/areas in the region.

Discussion: Although significance is not calculated for these results, it is possible folks residing within the range of more than one nuclear facility may have higher cancer incidence compared to those near one facility only. No regulatory science currently quantifies the cumulative impacts of more than one nuclear facility.



# POSTER PRESENTATIONS

**WEDNESDAY, AUGUST 12**  
**Bear Down Gym | Bear Down Court**

| Poster | Presenter           | Title                                                                                                                                                                | Institution                                    |
|--------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| 1      | Abigail Bibb        | Global STING knockout rescues male-specific gait and nigrostriatal neurochemical decrements in mice subjected to the juvenile Manganese model of Parkinson's disease | Barrow Neurological Institute                  |
| 2      | Adam Schuller       | Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson's disease                  | Barrow Neurological Institute                  |
| 3      | Aidan Briggs        | Juvenile manganese exposure potentiates dopaminergic neurodegeneration resulting from encephalitic arbovirus infection via astrocyte-mediated inflammatory signaling | Barrow Neurological Institute                  |
| 4      | Aref Barkhordari    | 2,8-DHA Crystal Deposition Activates HTR2B Signaling and Inhibits PGC1 $\alpha$ and Mitochondrial Function in the Renal Cortex                                       | University of Tehran                           |
| 5      | Beatrice Finch      | THC and Related Cannabinoids Inhibit Fetal/Neonatal P450 CYP3A7                                                                                                      | University of Colorado Anschutz Medical Campus |
| 6      | Benjamin Schumacher | Ambient Air Concentrations of Toxicants and Risk of Frontotemporal Dementia                                                                                          | Barrow Neurological Institute                  |
| 7      | Bianca Rodriguez    | Daily Ingestion of a Human Relevant Mixture of Phthalates Influences the Liver Proteome in Mice                                                                      | University of Arizona                          |
| 8      | Brandon Carman      | Airway Epithelial MARCKS Preserves Epithelial Cell Identity and Limits Influenza A-Induced Lung Injury                                                               | University of Arizona                          |
| 9      | Brenna Baird        | Fasudil Attenuates Wildfire Smoke-Induced BBB Dysfunction and Neuroinflammation                                                                                      | Barrow Neurological Institute                  |
| 10     | Charlotte McVeigh   | Analysis of potential drivers of tungsten-enhanced breast cancer metastasis: A longitudinal study of bone marrow adipocytes                                          | University of New Mexico                       |
| 11     | Chloe Flanigan      | Erionite-Induced Carcinogenicity: Mechanistic Insights and Comparative Potency with Asbestos                                                                         | Aetia Scientific Collaborative                 |
| 12     | Diksha Manhas       | Developmental age and sex dependent regulation of CYP2B10 activity in mouse brain                                                                                    | University of Arizona                          |
| 13     | Emily Mitchem       | Characterizing the Metabolic Impact of SIRT1 Overexpression on Alcohol-Associated Liver Disease                                                                      | University of Colorado Anschutz                |
| 14     | Felix Ayala-Fierro  | Process for the Review of the Potential Cancer Risk of Flavoring Substances                                                                                          | JUUL Labs, Inc                                 |
| 15     | Grace Picha         | The Effects of Arsenic and Alcohol on Behavior and the Microbiome                                                                                                    | University of New Mexico                       |
| 16     | Jocelyn Cuthbert    | Contributions of Aging, Pregnancy History, and Ozone Exposure to Ovarian Fibrosis in Mice.                                                                           | Fort Lewis College                             |





# POSTER PRESENTATIONS

**WEDNESDAY, AUGUST 12**  
**Bear Down Gym | Bear Down Court**

| Poster | Presenter                 | Title                                                                                                                                       | Institution                                                            |
|--------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| 17     | Kai McAlister             | 2,8-DHA Crystal Deposition Activates HTR2B Signaling and Inhibits PGC1 $\alpha$ and Mitochondrial Function in the Renal Cortex              | University of Arizona                                                  |
| 18     | Kaitlyn Andreoni          | Shared Mitochondrial and Metabolic Proteomic Responses in Ovarian and Cardiac Tissues Following Phthalate Exposure                          | University of Arizona                                                  |
| 19     | Kelly Le & Caroline Ho    | Investigating the Impact of Lithium Exposure on Gut Microbiota                                                                              | Arizona State University                                               |
| 20     | Kylie Jones               | Integrating Toxicokinetic, Mechanistic, and Epidemiologic Evidence to Evaluate the Estrogenic Potential of Methylparaben and Propylparaben  | Aetia Scientific Collaborative                                         |
| 21     | Mae Esquibel              | Disruption of Early Human Red Blood Cell Development by Arsenite and Its Primary Metabolite Monomethylarsonous Acid                         | University of New Mexico                                               |
| 22     | Michaela Hvizdak          | Per- and Polyfluoroalkyl Substances (PFAS) Antagonize Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) Activity                   | University of Colorado Anschutz                                        |
| 23     | Miely Suarez              | Stratifying mouse ovarian follicle growth dynamics to inform computational models of folliculogenesis and environmental toxicant disruption | University of Arizona                                                  |
| 24     | Milad MazloumiBakhshayesh | Micro- and Nanoplastic Exposure Drives Neurobehavioral, Metabolic, and Cardiovascular Alterations in dementia-prone mouse model.            | University of New Mexico                                               |
| 25     | Mina Alaaldin             | Chronic Low-Dose Arsenic Exposure Induces rDNA Instability in Human Bronchial Epithelial Cells                                              | University of Arizona                                                  |
| 26     | Nicholas Perpetua         | Reduction of Hexavalent Chromium Produces Stable Chromium-DNA Adducts <i>In Vitro</i>                                                       | University of Arizona                                                  |
| 27     | Nohi Leyva                | Integrating Environmental Aging and Cryomilling to Model Realistic Micro- and Nanoplastic Exposure Pathways                                 | University of New Mexico                                               |
| 28     | Sophia von Hippel         | Does bisphenol-A alter serotonin receptor gene expression in the descending trigeminal pain circuit?                                        | University of Arizona                                                  |
| 29     | Stephanie Bersie          | Particulate Transfer from Cell Corpses to Engulfing Macrophages Disrupts Phagocytosis and Drives Inflammation                               | University of Colorado Anschutz Medical Campus; National Jewish Health |
| 30     | Sumira Phatak             | The goldilocks zone of placentation: CXCR4 in overgrowth and restriction.                                                                   | University of New Mexico                                               |
| 31     | Sydnee Yazzie             | G Protein–Coupled Estrogen Receptor Regulates Pulmonary and Neuroinflammatory Responses to Acute Wood Smoke Exposure                        | University of New Mexico                                               |



# POSTER PRESENTATIONS

**WEDNESDAY, AUGUST 12**  
**Bear Down Gym | Bear Down Court**

| Poster | Presenter       | Title                                                                                                                                                                         | Institution              |
|--------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| 32     | Talia Owen      | A Multiscale Integration of <i>In Vitro</i> and <i>In Vivo</i> Ovarian and Endocrine Dynamics, via Computational Modeling, to Predict Toxicant Effects on Female Reproduction | University of Arizona    |
| 33     | William Gendron | Glyphosate at the Human-Equivalent EPA Chronic Reference Dose Alters the Gut–Brain Axis and Exacerbates Alzheimer's Disease Pathogenesis in mice                              | Arizona State University |
| 34     | Xiangdi Mao     | Environmental Fungal Exposure Reprograms Pulmonary Host Responses Through Distinct Inflammatory and Immune-Priming Pathways                                                   | University of Arizona    |



# POSTER PRESENTATION ABSTRACTS

## **1. Global STING knockout rescues male-specific gait and nigrostriatal neurochemical decrements in mice subjected to the juvenile Manganese model of Parkinson s disease**

### **Poster #1**

**Abigail Bibb<sup>1</sup>**, Adam Schuller<sup>1</sup>, Megan Hager<sup>2</sup>, Aidan Briggs<sup>1</sup>, Brenna Baird<sup>1</sup>, Ron Tjalkens<sup>1</sup>

<sup>1</sup> Department of Neurology, Barrow Neurological Institute, Phoenix, AZ

<sup>2</sup> Department of Environmental and Radiologic Health Sciences, Colorado State University, Fort Collins, CO

Parkinson s disease (PD) is the fastest growing neurodegenerative disorder world-wide, with idiopathic etiology and no existing cures. Manganese, an essential heavy metal commonly found in the environment, has been demonstrated to elicit PD-like neurotoxicity in human workers overexposed to this toxicant in mines or battery production plants. This Mn-induced Parkinsonism can be recapitulated in laboratory rodents, although mixed reports exist regarding the timing of exposure and association with nigrostriatal dopaminergic denervation characteristic of PD given inherent limitations of techniques classically used to query these disease metrics. Mechanisms underlying this selective neurotoxicity are broadly thought to include mitochondrial dysfunction, oxidative stress, and glial-mediated inflammatory signaling, all of which have been previously shown by our lab to result from Mn overexposure in juveniles. This motivated the present interrogation of immune modulatory nucleic acid sensing pathways, like the cGAS-STING signaling cascade, in the context of this Mn-induced PD onset. Notably, Mn has been shown capable of direct catalytic activation of cGAS, suggesting a role of this activation to provoke innate immune modulation via downstream signal transduction. To this end, we sought to explore the effects of genetic STING ablation on motor function and nigrostriatal neurotransmitter levels in a juvenile Mn model of PD using highly sensitive automated gait analysis and neurochemical profiling. Male and female wildtype (WT) or STING<sup>goldenticket</sup> (GT) mice were orally administered 30 mg/kg/day Mn or vehicle from PND14-28 followed by a 7 day post-lesioning period. Longitudinal weight measurements were recorded to ensure no overt signs of toxicity and scores of dystonic reflex were recorded throughout the study period to monitor progressive motor decline. At the terminal timepoint, all animals were subjected to automated gait analysis via the NoldusXT Catwalk system which collects 97 parameters associated with normal murine movement. This revealed significant PD-like bradykinesia in Mn-treated male WT animals which was not present in GT animals or any female subjects. At the end of the 28-day experiment, animals were sacrificed and the dorsolateral striatum was collected for neurochemical analysis using HPLC-ECD. This demonstrated sex-, treatment-, and genotype-specific alterations in PD-relevant neurotransmitter levels, including a male-specific Mn-induced dopaminergic deficit that was rescued in GT animals. Together, these findings suggest an important role of cGAS-STING signaling in pathogenesis of the Mn model of PD. The male-specific effects observed here reflect marked sex differences in the clinical susceptibility to PD. Future work will aim to parse out cell-type specificity of STING signaling relevant to these neurodegenerative sequelae.

## **2. Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson s disease**

### **Poster #2**

**Adam Schuller<sup>1</sup>**, Omar Yanouri<sup>2</sup>, Abigail Bibb<sup>1</sup>, Aidan Briggs<sup>1</sup>, Megan Hager<sup>2</sup>, Nicole Yates<sup>2</sup>, Brenna Baird<sup>1</sup>, Ron Tjalkens<sup>1</sup>

<sup>1</sup> Department of Neurology, Barrow Neurological Institute, Phoenix, AZ

<sup>2</sup> Department of Environmental and Radiologic Health Sciences, Colorado State University, Fort Collins, CO

Parkinson s disease (PD) is the fastest growing neurodegenerative disorder, linked with exposure to environmental risk factors including: air pollution, heavy metals, viral infections, industrial solvents, and

pesticides. Our group has consistently highlighted the key role of inflammatory astro-glial activation across toxicant-based models of this disorder. Most recently, the cGAS-STING pathway, which produces type-I-interferons in response to mislocalized double stranded nuclear or mitochondrial DNA, has emerged as a potential disease-modifying therapeutic target. Efforts in this context have largely focused on microglial contributions to STING signaling; however, astrocytes are increasingly recognized as important contributors to parenchymal interferon levels. Here, we examined the effects of STING signaling on motor function and astrocyte reactivity using the rotenone model of PD in wild-type (WT) and STING<sup>goldenticket</sup> (GT) mice. Primary astrocyte-enriched mixed glial cultures were employed to establish the IC<sub>50</sub>[Rotenone] = 78.90nM, which was blunted by pharmacologic STING inhibition and genetic ablation. Oxidative mitochondrial DNA damage was significantly increased following acute rotenone treatment via quantification of 8-OHdG levels in fractionated nucleic acids. High-content immunocytochemical fluorescence microscopy and deep learning-based image analysis revealed a subsequent increase in perinuclear p-STING<sup>+</sup> puncta in GFAP<sup>hi</sup>ALDH1L1<sup>hi</sup> astrocytes, and downstream STING-dependent nuclear p-IRF3<sup>+</sup> translocation in the same dual-positive cell population. Notably, co-treatment with the VDAC inhibitor DIDS blunted rotenone-induced NF-κB activation and IFN-β production, suggesting a role for release of damaged mitochondrial DNA in this inflammatory activation. Further mechanistic interrogation revealed a STING-dependent enrichment of MAPK signaling and ECM remodeling via transcriptomics, as well as enhanced astrocytic release of signaling factors TNF-α, VEGF, and IL-6, which were all blunted in GT cells. This resulted in an astrocyte-mediated neurotoxic effect on differentiated dopaminergic neuron-like cells treated with glial conditioned media in a STING-dependent manner. In vivo, automated gait assessment demonstrated progressive PD-like hypokinesia and widened base of support in male WT mice. Additionally, we observed progressive decreases in total distance traveled and rearing number, as well as an increase in total rest time in the open field test, together indicating a parkinsonian motor phenotype. Across this battery of motor functional assessment, we observed protection against aberrant gait in rotenone-treated GT males. Concordantly, HPLC-ECD neurochemical profiling of PD-relevant catecholamines revealed male-specific depletion of striatal dopamine following rotenone treatment and increased turnover of this metabolite, which was attenuated by genetic STING ablation. Together, these data demonstrate the importance of cGAS-STING signaling in inflammatory astrocyte reactivity and a potential role for this molecular transduction in the sequelae of PD-like neurotoxicity, dopaminergic denervation, and motor dysfunction. Future work will interrogate the effects of astrocyte-specific STING ablation on microstructural brain changes using advanced imaging techniques in vivo.

### **3. Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson s disease**

#### **Poster #3**

**Aidan M. Briggs**<sup>1,2</sup>, Adam J. Schuller<sup>1</sup>, Abigail M. Bibb<sup>1</sup>, Megan R. Hager<sup>3</sup>, Collin M. Bantle<sup>3</sup>, Ronald B. Tjalkens<sup>1</sup>

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Parkinson s disease (PD) is a progressive neurodegenerative disorder characterized by selective nigrostriatal dopaminergic denervation resulting in motor dysfunction. Although the etiology of PD is not fully understood, there is mounting evidence associating risk of this disease with cumulative exposure to environmental agents, including industrial solvents, pesticides, air pollution, heavy metals, and infectious pathogens. Viral infections, in particular, are linked with PD risk through neuroinflammatory activation of glial cells that may represent a critical early mechanism in the etiology of this disorder. Our group has demonstrated that infection with the neurotropic alphavirus, Western equine encephalitis virus (WEEV), results in significant astrogliosis preceding dopaminergic neuron loss and PD-like motor deficits in mice. We have also shown that overexposure to the heavy metal manganese (Mn<sup>2+</sup>) during juvenile development potentiates nigrostriatal inflammation following infection with a non-neurotropic strain of Influenza virus H1N1. Accordingly, we postulated that astrocytic NF-



kB signaling in Mn<sup>2+</sup>-primed mice is central to a heightened neuroinflammatory response to WEEV infection and subsequent dopaminergic neurotoxicity. To test this hypothesis, we treated juvenile wildtype or astrocyte-specific NF-kB knockout mice with Mn<sup>2+</sup> via the drinking water, followed by adult infection with WEEV. We then assessed histopathologic changes in PD-relevant brain regions using high content imaging and AI-based image analysis. Compared to vehicle treated, mice exposed to Mn<sup>2+</sup> during juvenile development followed by WEEV infection developed more viremic infection and mortality, increased astrogliosis, and disease-associated changes in microglial morphometry. Dopaminergic neurodegeneration was similarly amplified in Mn-primed mice compared to mice infected with WEEV alone. These phenomena were all dramatically attenuated in astrocyte-specific NF-kB knockout mice, despite an increase IBA1+ cell number in the substantia nigra. Together, these findings suggest a critical role for astrocyte-mediated neuroinflammation in the context of an environmentally relevant viral model of PD.

#### **4. Toxic Effects of Tributyltin, Triphenyltin, and SnCl<sub>2</sub> on the Development of Zebrafish (*Danio rerio*) Embryos**

##### **Poster #4**

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Tin (Sn) is one of the heavy metals to which various functions in biological development are attributed in small quantities, for example, a role in cell structure, enzyme activities, and protein and carbohydrate metabolism in fish. Tributyltin (TBT) and triphenyltin (TPT) are endocrine disrupting chemicals that are widely distributed in the aquatic environment. The aim of this study was to investigate the effects of TBT, TPT, and SnCl<sub>2</sub> on the embryonic development of zebrafish. In this study, zebrafish embryos were used to observe the acute toxicity of TBT, TPT, and SnCl<sub>2</sub>. Fish embryo toxicity analysis was performed for different TBT, TPT, and SnCl<sub>2</sub> concentrations (1, 5, 10, 15, and 20 ng/L). Fertilized eggs in 24-well plates (20 eggs in each concentration) were incubated at 26°C for 4 days, and embryo clotting, embryo heartbeat, and morphological abnormalities were recorded after 96 h. Coagulation increased significantly in a dose-dependent manner, and TBT was able to induce coagulation in zebrafish embryos. Heartbeat changes significantly decreased ( $p < 0.05$ ) in a dose-dependent manner at different TBT doses ( $p < 0.05$ ). The percentage of mortality was higher in embryos at trace levels of TBT, indicating that the embryos are more sensitive to the toxicity of TBT. TBT is therefore extremely toxic and can have fatal consequences for zebrafish embryos, ultimately leading to the extinction of species and a decline in biodiversity in the aquatic environment. After analyzing the images 96 h after fertilization and converting them to a teratogenic index score, it was found that the index for the two compounds TPT and TBT was 4.6 and 9.6 ng/L, respectively.

#### **5. THC and Related Cannabinoids Inhibit Fetal/Neonatal P450 CYP3A7**

##### **Poster #5**

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**Background:** Currently, few test systems exist to study drug toxicity and metabolism in pregnant people and neonates. The cytochrome P450 (CYP) sub-family CYP3A is crucial to the metabolism of over 50% of xenobiotics and drugs, with CYP3A4 as the primary adult isoform studied. However, in the fetus and neonate, the main CYP3A isoform is CYP3A7, which exhibits critical differences metabolic rate and regiospecificity. Assessment of CYP3A7 inhibition by drugs remains limited, leaving these populations susceptible to potential adverse events. Marijuana is one of the most widely abused drugs worldwide, and it has been shown that D9-tetrahydrocannabinol (D9-THC), cannabidiol (CBD) and cannabinol (CBN) inhibit CYP3A7 activity (Yamaori et

al. 2011 Life Sciences 88 730-736). However, little research has investigated whether cannabinoid precursors, breakdown products or metabolic derivatives can also inhibit CYP3A7 and cause harmful drug-drug interactions (DDIs).

**Objective:** Our goal was to utilize a fluorescence screening assay to assess a panel of THC derivatives for their ability to inhibit recombinant CYP3A7 activity. THC derivatives were chosen based on their prevalence in Cannabis sativa products and their structurally significant groups.

**Methods:** The inhibitory capabilities of our cannabinoid drug panel on CYP3A7 enzymatic activity were measured using a dibenzylfluorescein (DBF)-based assay previously developed in the Lampe Lab (Work et al. 2021 Sci Rep 11:19443). Incubations consisted of recombinant CYP3A7 bacosomes (10 pmol/mL), 200 nM DBF, 20 mM THC derivatives in 0.1 M phosphate buffer (pH 7.4). Reactions were started with 1 mM NADPH and ran for 10 min at 37 °C before being stopped with 2 M NaOH. After a 1 h contact with NaOH, fluorescence signal was measured on the i-Tecan plate reader. Methanol or acetonitrile solvent controls served as 100% activity. Several THC derivatives were also tested for their maximal inhibitory potency (IC<sub>50</sub>) by testing different concentration ranges. Non-linear regressions were performed in GraphPad Prism v11.0.2. Molecular docking was also employed to elucidate binding interactions between THC derivatives and CYP3A7 utilizing a CYP3A7 crystal structure with the endogenous substrate DHEA-S bound (8GK3; Lui et al. 2023, J. Biol. Chem. 299(8): 104993), and the docking software Autodock vina v1.2.7.

**Results:** An initial inhibition screening was run for 32 derivatives along with a known inhibitor and solvent controls. Each drug was tested at 20 mM. CBD, CBN, D9-THC and cannabigerolic acid (CBGA), the most prevalent substances in cannabinoid products, were further tested at varying concentrations to determine IC<sub>50</sub> values. CBD, CBN, D9-THC and CBGA have IC<sub>50</sub> values of 2.21 mM, 5.79 mM, 9.00 mM and 2.14 mM respectively, with R<sup>2</sup> values ≥0.970. Molecular docking results showed conserved contacts with residues F108, F213, F304 and T309 between CBD, CBN, D9-THC and CBGA.

**Discussion and Conclusions:** CBG showed the greatest inhibitory effects for the CYP3A7 recombinant enzyme, followed by CBGA, CBD, and CBN. Cannabinoids have been previously tested for their CYP3A7 inhibition potential (>50% inhibition at 50 mM) (Yamaori et al. 2011 Life Sciences 88 730-736), however in our tests, CBD, CBN and D9-THC yielded IC<sub>50</sub> values of 2.21 mM, 5.79 mM and 9.00 mM respectively. This has important implications for the fetus and neonate, as cannabis is the second-most common psychoactive substance used during pregnancy and breastfeeding, and it can readily transfer to the infant via breastmilk (Garry et al. 2009, Journal of Toxicology 596149). Furthermore, adverse birth and developmental events have been reported, such as low birth weight and attention deficits later in childhood. Interestingly, CBN is not reported to be a strong inhibitor of adult CYP3A4/5, showing some isoform differences. CYP3A7 has important endogenous and exogenous functions, and its inhibition should be assessed to inform safety profiles in these special populations.

## 6. Ambient Air Concentrations of Toxicants and Risk of Frontotemporal Dementia

### Poster #6

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**Background:** Frontotemporal dementia (FTD) is a neurodegenerative disease characterized by progressive behavioral, language, and executive dysfunction. While approximately 1/3 of cases have a genetic etiology, environmental exposures likely play a role in pathophysiology. Environmental exposures, including ambient air concentrations of neurotoxicants, likely promote key mechanisms implicated in FTD neurodegeneration.

**Methods:** This study utilized population-based United States Medicare data to identify incident FTD cases from 2016-2018. We calculated standardized incidence ratios (SIRs) by county. Exposure measurement was derived

from census-tract level ambient concentrations of 175 toxicants from the Environmental Protection Agency's 2014 National Air Toxics Assessment (NATA), a nationwide inventory of toxic air emissions, and were spatially joined to the beneficiaries ZIP+4. We applied spatial and statistical methods to explore each toxicant individually and employed generalized weighted quantile sum (gWQS) regression to evaluate the joint association of the correlated toxicants with the risk of FTD. We used logistic regression to calculate adjusted odds ratios (aOR) and corresponding confidence intervals (CI) for each toxicant and mixtures of toxicants, adjusting for age, sex, and race.

**Results:** This study included 47,625 incident cases of FTD and 188,193 controls. County-level SIRs ranged from 0.4 – 115.0 ( $p < 0.05$ ). Our three strongest individual associations were 2,2,4-trimethylpentane (aOR: 1.09, 95% CI: 1.08-1.10), toluene (aOR: 1.08, 95% CI: 1.07-1.09), and ethylbenzene (aOR: 1.08, 95% CI: 1.07-1.09). By census tract, each one-tertile increase in the gWQS mixture was associated with 42% higher risk of FTD, adjusting for age, sex, and race (aOR: 1.42, 95% CI: 1.25 - 2.07). Geographically weighted regression elucidated unique patterns for select toxicant and U.S. regions.

**Conclusion:** Exposure to ambient air concentrations of select toxicants may increase risk of FTD.

## **7. Daily Ingestion of a Human Relevant Mixture of Phthalates Influences the Liver Proteome in Mice**

### **Poster #7**

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Phthalates are endocrine disrupting chemicals used in hair products, perfumes, and nail polish. Increased exposure to phthalates is associated with negative reproductive health outcomes and metabolic dysfunction in women. Ingestion of a mixture of dibutylphthalate (DBP), di-2-ethylhexyl phthalate (DEHP), and benzyl butyl phthalate (BBP) has been shown to disrupt lipid metabolism proteins and various lipid types within the ovary in mice. However, the effects of this three-phthalate mixture on other key metabolic organs remain unknown. Therefore, this study was designed to examine the impact of this phthalate mixture on the liver. Adult CD-1 female mice were pipet fed daily with corn oil or the phthalate mixture (32 µg/kg/day) for ten days. Liver samples were subjected to proteome profiling. Of the 6,143 total liver proteins detected, 164 were significantly changed between vehicle and phthalate-treated livers. Gene ontology analysis showed that the 107 proteins significantly increased in response to phthalates mapped to mitochondria, metabolism, and ATP binding. Whereas the 57 proteins that were decreased mapped to protein binding, protein transport, and cytoplasmic translation. Alterations in mitochondrial function and integrity proteins, such as MICOS complex subunit Mic19 (MIC19), mitoguardin 2 (MIGA2), and mitochondrial import inner membrane translocase subunit (TIM9) were observed. Based on the enrichment of mitochondria relevant proteins, overall mitochondrial density was assessed via DNA copy number and citrate synthase activity. No significant changes in these parameters were observed. These findings provide insight into systemic effects of phthalate mixtures by revealing significant liver proteome changes while suggesting null effects on mitochondrial density. This work was funded by NIEHS grants R01ES037265 and R25ES34923.

## **8. Airway Epithelial MARCKS Preserves Epithelial Cell Identity and Limits Influenza A-Induced Lung Injury**

### **Poster #8**

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Myristoylated alanine-rich C-kinase substrate (MARCKS) is a highly conserved membrane-associated protein implicated in mucus production, airway inflammation, and tissue repair. However, in part because of the limited availability of airway epithelial cell-specific MARCKS knockout (KO) models, MARCKS mechanistic role in airway epithelial homeostasis and injury remains unclear. To address this gap, we have developed an airway epithelial cell-specific MARCKS KO mouse model. Under baseline conditions, MARCKS KO airways

appear largely functional and exhibited no significant changes in the expression of mucociliary clearance-associated genes. However, MARCKS deficiency affected serous cell biology as indicated by altered expression and secretion of BPIFA1 (also known as SPLUNC1), a secreted protein involved in innate immune defense and antimicrobial activity. Given these findings and MARCKS implication in injury repair, wild-type (WT) and MARCKS KO mice were infected with influenza A virus to investigate the role of MARCKS in airway epithelial cell injury. Histological analysis by H&E staining revealed significantly greater lung injury in MARCKS KO mice than in WT controls. Furthermore, MARCKS KO mice exhibited marked reductions—and, in some cases, near-complete loss—of mature airway epithelial cell markers, including the club cell marker SCGB3A1, mucous cell markers MUC5AC and MUC5B, the ciliated cell marker FOXJ1, and the serous cell-associated protein SPLUNC1. Together, these findings support a previously unrecognized role for MARCKS in maintaining airway epithelial identity and resilience following viral injury.

## 9. Fasudil Attenuates Wildfire Smoke-Induced BBB Dysfunction and Neuroinflammation

### Poster #9

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**Background and Purpose:** Wildfires across the United States have steadily increased over the past 40 years. Smoke from wildfires can cause cardiovascular and respiratory diseases, with new studies highlighting potential neurological outcomes<sup>1</sup>. The purpose of the following studies are to delineate the dynamics of peripheral immune populations in response to woodsmoke, the mechanism of infiltration into the brain, and the treatment options available. This study is the first to deliver a comprehensive timeline of neuroinflammation following wildfire smoke inhalation, collecting tissue from animals 1, 14, and 28 days after exposure. Air pollution has previously shown to impact the blood-brain barrier which serves an essential role in mitigating neuroinflammation. Therefore, we introduced the Rho-kinase inhibitor fasudil to strengthen this barrier and demonstrate an endothelial- dependent mechanism of peripheral immune infiltration.

**Methods:** Fasudil was administered via osmotic mini pumps which provide a consistent dose over 21 days. Mice are exposed to either filtered air or a woodsmoke exposure (0.5mg/m<sup>3</sup> every other day for 14 days, 4hr/day). Timeline studies will follow these mice over the course of exposure, and extend past 1, 14, and 28 days after exposure. Left hemispheres will be collected for high dimensional flow cytometry analysis using the Aurora Cytex. Markers for peripheral immune infiltration included T cells (CD3, CD4, CD8), adhesion molecules (VCAM, ICAM) resident immune cells (CD11b, TMEM119, ACSA-2) and other inflammation-dependent markers.

**Results:** Results demonstrate the presence of CD4 T cells in response to woodsmoke inhalation and the decrease of this population over time. VCAM and ICAM expression also showed similar trends, peaking 1 day after our 14 day exposure paradigm. Treatment with fasudil demonstrates the depletion of VCAM expression which indicates the endothelial-dependent nature of woodsmoke-induced neuroinflammation. Results were conferred with immunofluorescent imaging of the hippocampus with analysis of astrocytes, microglia, and presence of albumin. Albumin levels were elevated with woodsmoke exposure, indicating a leaky blood-brain barrier. Activated astrocytes, quantified via GFAP, and microglia, quantified via Iba-1, were also elevated after exposures. Fasudil lowered levels of albumin in the brain as well as levels of activated astrocytes and microglia. Overall, we demonstrate the ability of woodsmoke to cause indirect neuroinflammation through the recruitment of peripheral immune populations. With this knowledge, we will continue our investigation of a blood-brain barrier dependent mechanism of neuroinflammation through imaging of the right hemisphere for



albumin leakage, glial activation, and presence of CD4 T cells. Further research detailing the mitigation of toxicity could lead to public health-based recommendations following air pollution events.

## **10. Analysis of potential drivers of tungsten-enhanced breast cancer metastasis: A longitudinal study of bone marrow adipocytes**

### **Poster #10**

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**Background and Purpose:** Tungsten (W) is classified as an emerging environmental toxicant due to increased human exposure and a lack of knowledge of the health risks. Epidemiological and in vivo studies demonstrate that exposure to W contributes to the carcinogenic process, but the molecular mechanisms are poorly defined. Due to a cohort of breast cancer patients accidentally exposed to W during intraoperative radiotherapy, our lab is investigating the effects of W on breast cancer progression and metastasis. W is known to accumulate in the bone, creating a site for long-term exposure and toxicity. Previous research in our lab has shown that in multiple triple-negative breast cancer orthotopic models, W enhances breast cancer metastasis to the bone niche. These findings suggest that W deposition in the bone creates a favorable microenvironment to promote metastasis. Bone marrow adipocytes (BMA) play an important role in breast cancer metastasis to the bone through the secretion of adipokines/cytokines that drive tumor cells homing, colonization, and growth by changing the microenvironment. Understanding weekly changes throughout metastasis in BMA is critical to uncover adipokines/cytokines that could drive colonization and proliferation of tumor cells in the bone niche following W exposure. We aim to understand changes in BMA throughout the metastatic process to identify W mediated changes that could enhance breast cancer metastasis to the bone.

**Methods:** 6-8 week old female BALB/c and C57BL/6 mice were exposed to 15ppm W in their drinking water or tap water for 4 weeks. After 4 weeks of exposure, mice underwent orthotopic injections of 4T1 (BALB/c) or E0771-Luc (C57BL/6) cells into the 4th mammary fat pad. Longitudinal time points were conducted to track changes after 4 weeks of exposure to W with no tumor cell injection (0 week; 0W), 2 weeks post-tumor cell injection (2 week; 2W), and 3 weeks post-tumor cell injection (3 week; 3W). At the end, bones were collected for multiple parameters. Femurs were used for immunohistochemistry staining of Perilipin-1+ (Plin1+) adipocytes in the bone marrow. Bone marrow from tibiae was cultured to select for mesenchymal stromal cells (MSCs), which were differentiated into BMA through media selection. Cell supernatant and RNA were collected from both MSCs and BMA to profile changes in adipokines/cytokines throughout the metastatic process.

**Results:** While both models have increased metastasis to the bone following W exposure, 4T1 induced greater systemic inflammation compared to E0771-Luc. RANK L expression was significantly increased at 0W and trending at 3W in 4T1, but only a trending increase in E0771-Luc. This supports previous data showing increased osteolysis in 4T1 following W exposure at the final tumor endpoint whereas in E0771-Luc, W does not. Adiponectin levels remained unchanged in E0771-Luc, but significantly increased following W exposure at 2W and 3W in 4T1. CXCL2 expression was significantly increased following W exposure at 0W and 2W and trending at 3W in 4T1 and was significantly increased at 3W in E0771-Luc. Previous data from our research group also showed increased gene expression of CXCL2 at final tumor endpoint in 4T1. Plin-1+ staining revealed that E0771-Luc has more adipocytes compared to 4T1, regardless of exposure.

**Conclusions:** Some analytes did not have changes either with W exposure or by week, suggesting that perhaps they are not the main drivers of metastasis. Analytes such as RANK L and Adiponectin showed changes following W exposure, but they were dependent upon the model used. These data suggest that there are inherent differences between models and W could be doing slightly different things in each model, including a systemic inflammation component that we observed more in the 4T1 compared to the E0771-Luc. CXCL2 was

increased in both models, suggesting a common key player in enhanced metastasis to the bone. CXCL2 is known to play a role in tumorigenesis and immune escape of tumor cells. CXCL2 might be a key mediator that could be further studied in this context to provide insights. This study provides insights into adipokine/cytokines that might be critical players in W enhanced breast cancer metastasis to the bone.

## **11. Erionite-Induced Carcinogenicity: Mechanistic Insights and Comparative Potency with Asbestos**

### **Poster #11**

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Erionite (CAS No. 66733-21-9) is a naturally occurring fibrous zeolite with mesotheliogenic potency greater than that of asbestos minerals. However, unlike asbestos, erionite has rarely been used for commercial purposes, and as a result, information on exposure pathways remains limited. Numerous experimental animal studies evaluating the carcinogenic potential of erionite have produced a high incidence of mesotheliomas across routes of administration, and epidemiological studies have demonstrated elevated mesothelioma mortality in populations exposed to erionite. Although the carcinogenicity of erionite is well established, the underlying mechanisms remain poorly defined. The purpose of this analysis is to synthesize and critically evaluate the experimental, mechanistic, and epidemiological evidence on the human health hazards associated with erionite exposure, with emphasis on biological mechanisms driving its mesotheliogenic potency. Across experimental systems, erionite has demonstrated equal or greater potency than asbestos in inducing mesothelioma. It produces concentration-dependent cytotoxicity in human and rodent cell types, along with genotoxic and cell-transforming effects indicative of DNA damage and mutagenic stress. Persistent macrophage activation, generation of reactive oxygen and nitrogen species, and sustained inflammatory signaling have been identified as key mediators of chronic tissue injury and tumorigenesis. These responses are further modulated by structural iron and other physicochemical characteristics, including redox cycling and enhanced surface reactivity. Erionite's fibrous morphology, high aspect ratio, and remarkable biopersistence collectively underpin its pronounced mesotheliogenic potential relative to asbestos. Collectively, these interrelated processes position erionite among the most potent mineral fibers known, inducing mesothelioma through convergent pathways involving inflammation, oxidative stress, and genotoxic damage.

## **12. Developmental age and sex dependent regulation of CYP2B10 activity in mouse brain**

### **Poster #12**

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CYP2B10 is a cytochrome P450 monooxygenase highly inducible in the liver by drugs and environmental chemicals. CYP2B10 is also expressed in the brain, where it may be regulated differently from the liver and contribute to drug metabolism or toxicity within the CNS. This work aims to characterize CYP2B10 basal activity and inducibility to better understand its capacity for xenobiotic bioactivation in the brain. Male and female mice aged 1 and 3 months were treated with PCB-11 (500 µmol/kg, oral gavage) or vehicle for three consecutive days. Mice were sacrificed 24 hours after the final dose, and brain and liver microsomes were prepared. CYP2B10 activity was detected using bupropion as a probe substrate. Basal CYP2B10 activity in the brain varied with both age and sex, and the extent of PCB-11 induction also varied among these groups. Interestingly, the trends of developmental changes differed between males and females, with basal CYP2B10 activity declining with age in females but increasing in males. In addition, PCB-11 caused greater induction in juvenile mice of

both sexes, with stronger induction in females. These findings suggest that brain CYP2B10 activity may be regulated by sex hormones, a novel hypothesis to be tested more directly in future studies.

### **13. Characterizing the Metabolic Impact of SIRT1 Overexpression on Alcohol-Associated Liver Disease**

#### **Poster #13**

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Greater than 90% of individuals who chronically misuse alcohol will develop hepatic steatosis, an early pathology of alcohol-associated liver disease (ALD), which is characterized by lipid accumulation and metabolic dysregulation. The long-term overconsumption of alcohol can result in late-stage cirrhosis and hepatocellular carcinoma, as well as acute alcohol-associated hepatitis. Indeed, ALD is a leading cause of liver cirrhosis and the most common indication for liver transplant in the US, yet there are currently no FDA approved drugs for the treatment of ALD. Acetate and downstream acetyl-CoA produced by the metabolism of alcohol can induce changes in protein post-translational modifications (PTMs), including lysine acetylation. This PTM regulates protein localization and function, including the activation of enzymes involved in lipid accumulation and synthesis, and downregulation of proteins involved in fatty acid oxidation. Moreover, the oxidative metabolism of ethanol metabolism leads to a decrease in NAD<sup>+</sup> concentrations and exacerbating metabolic dysfunction. Sirtuins: a class of lysine deacetylases that regulate apoptosis, inflammation, and lipid metabolism use NAD<sup>+</sup> as a cofactor. Our studies utilized transgenic sirtuin 1 overexpressing (SIRT1<sup>super</sup>) mice exposed to a 10-day ethanol regimen to explore the role of SIRT1 in ALD pathogenesis. We found metabolic disruption in cytosolic and mitochondrial metabolic pathways as well as altered energy flux regulation from SIRT1 overexpression. This included differences in isocitrate dehydrogenase (IDH2) and fatty acid synthase (FASN) abundance with both SIRT1 overexpression and EtOH consumption. Utilizing metabolomics and proteomics we detected changes in numerous central hepatic metabolites, including acetyl-CoA and other TCA cycle metabolites (glucose-6-phosphate, NADH and NADP<sup>+</sup>). Key differences were observed in male versus female mice, specifically in mitochondrial metabolism and proteostasis networks. Overall, numerous hepatic pathways were found to be enriched due to SIRT1 overexpression and ethanol metabolism, providing a link between the effects of the oxidative metabolism of ethanol, the regulation of sirtuin function, and the early onset of hepatic dysregulation.

### **14. Process for the Review of the Potential Cancer Risk of Flavoring Substances**

#### **Poster #14**

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JUUL Labs Inc

Flavoring substances are used in many consumer products including e- liquids for electronic nicotine delivery systems (ENDS). Health hazard characterization, including the potential for cancer effects, is critical in the risk assessment of any ingredient. The inhalation risk assessment for non-carcinogenic effects follows the nonlinear dose response model based on a threshold, below which there is no effect, resulting in the estimate of the reference concentration (RfC). For carcinogenic effects it follows the linear model (no threshold) assuming a mutagenic mode of action (MoA) (e.g. direct interaction with DNA). For cancer effects attributed to a non-mutagenic mode of action (MoA), the no-threshold linear model has been adopted as the default approach as it is considered health-protective. The linearity of the model allows the calculation of the cancer slope factor (CSF). CSFs are estimated using the benchmark dose level (BMDL) associated with a 10% response (BMDL10) (i.e., 10% extra risk of carcinogenic effect in exposed test animals) to serve as the point-of-departure (PoD). The excess lifetime cancer risk (ELCR) characterization relies on cancer potency factors (CPFs) for each ingredient which are inhalation unit risk (IUR) values, adjusted to daily exposure levels corresponding with a cancer risk of 1 in 100,000, over 52-year exposures. The ELCR characterization is used by the U.S. Food and

Drug Administration's Center for Tobacco Products (USFDA CTP) to support Premarket Tobacco Product Applications (PMTA) for ENDS. The CPF is similar to the non-significant-risk-level (NSRL), established by California's Office of Environmental Health Hazard Assessment (OEHHA), for cancer-causing chemicals listed under Proposition 65. The NSRL is a threshold of daily intake that is considered to pose no more than a 1 in 100,000 lifetime cancer risk. This procedure was used to determine the potential contribution, if any, of five flavoring substances to the overall cancer risk assessment. The CPF estimates were compared to NSRL estimates to demonstrate validity in this approach. Additionally, for non-mutagenic substances the CPF was compared to the RfD to determine the presence of a buffer for potential non-mutagenic health hazards.

## **15.The Effects of Arsenic and Alcohol on Behavior and the Microbiome**

### **Poster #15**

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Arsenic (As) exposure through contaminated drinking water remains a major global health concern. Chronic As exposure has been associated with a range of neurobiological and behavioral abnormalities, including anxiety-like behaviors, impaired learning, and disruptions in dopaminergic (DA) signaling. Similarly, excessive alcohol consumption is a major public health issue that also alters DA transmission, stress pathways, and neurocircuitry related to reward and anxiety. While both As and alcohol independently induce adverse neurobehavioral outcomes, the potential for co-exposure to exacerbate these effects remains poorly understood. Given the overlap in their neural targets, combined exposure to As and ethanol (EtOH) may produce additive or synergistic effects on behavior and neurochemistry. The current study aimed to (1) determine whether chronic low-dose As exposure increases binge-like EtOH intake, (2) assess whether As and EtOH co-exposure exacerbates anxiety-like behaviors, and (3) identify exposure-related changes in behavioral and neural biomarkers associated with DA function and stress regulation. Male and female C57BL/6J mice ( $n = 39$ ) were randomly assigned to one of four exposure conditions in a  $2 \times 2$  design: arsenic (in the form of arsenite, AsIII) exposure (0 ppm or 1 ppm)  $\times$  EtOH exposure (tap water or 20% EtOH). AsIII exposure was delivered continuously in drinking water, while EtOH exposure was administered using a Drinking-in-the-Dark paradigm to model binge-like self-administration. During daily, 3-week DID procedure, mice had 2-hour access to 20% EtOH or tap water beginning 3 hours into the dark cycle. Behavioral assays were conducted to assess locomotor activity and anxiety-like behavior following exposure. Locomotor activity was quantified by total distance traveled in the open field test (OFT), while anxiety-like behavior was assessed by time spent in the center zone of the OFT. Various tissues, including the brain, were collected for ongoing analyses of As accumulation and neurochemical biomarkers related to DA and stress systems. Significant sex-dependent effects of AsIII exposure were observed in locomotor behavior. AsIII exposure decreased locomotor activity in males and increased activity in females, suggesting a sexually dimorphic response to chronic low-dose arsenic. However, co-exposure to AsIII and EtOH did not produce additional alterations in locomotor behavior. Additionally, there were no significant differences in ethanol or water consumption between groups, indicating that AsIII exposure did not enhance binge-like drinking behavior under the conditions tested. Anxiety-like behavior was not significantly affected by co-exposure; however, a main effect of sex was detected, with males spending more time in the center zone than females. This pattern suggests greater anxiety-like behavior in females across exposure conditions. Co-exposure to AsIII and EtOH did not exacerbate behavioral phenotypes relative to individual exposures. Nevertheless, the observed sex-specific effects of AsIII on locomotor activity highlight the potential for differential vulnerability to environmental neurotoxins across sexes. Ongoing analyses are quantifying As accumulation in peripheral and neural tissues and assessing alterations in DA and stress-related markers within the striatum and hippocampus. These data will provide critical mechanistic insight into how chronic low-dose arsenic exposure interacts with alcohol to influence brain function and behavior. Collectively, this work advances understanding of combined environmental and substance-based neurotoxicity. Funding: This work was supported by NIH-NIAAA grant R00 AA027835, NIH/NIGMS grant



K12GM088021, the NIEHS Core Center Grant P30ES032755; the UNM Center for Metals in Biology and Medicine through NIGMS Grant P20 GM130422; the NIEHS UNM METALS Superfund Research Program Grant P42 ES025589; the UNM Comprehensive Cancer Center Grant NCI P30CA118100; and the UNM College of Pharmacy.

## **16. Contributions of Aging, Pregnancy History, and Ozone Exposure to Ovarian Fibrosis in Mice**

### **Poster #16**

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Ovarian cancer is often referred to as the “silent killer” because ineffective screening tools and lack of symptoms early in disease result in many cases being diagnosed at advanced stages, contributing to a low 5-year survival rate comparative to other cancers. Improving our understanding of the driving mechanisms underlying ovarian cancer may lead to advances in screening and treatment. The ovary is one of the first organs to exhibit signs of aging, including reduced folliculogenesis, increased expression of genes associated with inflammation, and changes in the abundance and activity of Macrophages, T-cells, and B-cells. This study examined ovarian activity, fibrosis, and macrophage presence in mouse ovaries to examine aging of the reproductive tract, and the impact of age, pregnancy history, I73T mutations, and ozone exposure. Reproductive tract sections were stained with Pico-Sirus Red to visualize collagen networks, and Immunohistochemistry using CD68 was performed to identify macrophages. Images were acquired using the Discover ECHO microscope with fixed imaging settings. Fibrosis was quantified by measuring 100 um sections of ovarian stroma, with no active structures, with Image J utilized to quantify red pigmentation as a measure of fibrosis. Neither age nor pregnancy history was associated with a significant differences in ovarian fibrosis, and did not have a significant interaction. The I73T mutation also had no effect on ovarian fibrosis. In contrast, ozone exposure was associated with a significant increase in fibrosis in young mice. Additional samples are needed to determine whether this effect is also seen in older mice. Although aging was not associated with increased collagen deposition, age-related changes may instead reflect alterations in collagen organization rather than overall abundance. Future studies will quantify macrophage abundance in the same stromal regions to better characterize the relationship between fibrosis and immune cell infiltration. A better understanding of the mechanisms by which ozone exposure promotes ovarian fibrosis may provide additional insight into environmental factors that contribute to ovarian aging and potentially influence ovarian cancer risk.

## **17. 2,8-DHA Crystal Deposition Activates HTR2B Signaling and Inhibits PGC1 $\alpha$ and Mitochondrial Function in the Renal Cortex**

### **Poster #17**

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**Background:** Adenine phosphoribosyltransferase (APRT) deficiency is a genetic condition, which impairs the body's natural ability to metabolize exogenous adenine, resulting in the generation 2,8 dihydroxyadenine, a toxic metabolite that forms highly insoluble crystals capable of depositing in the tubular lumen of the kidney and provoking profound kidney damage. APRT deficiency often results in the development of chronic kidney disease (CKD). Utilizing a rat model of adenine-induced CKD, we evaluated the mechanisms of 2,8-DHA toxicology in the renal cortex. Specifically, we hypothesized that 2,8-DHA crystal deposition would result in profound mitochondrial impairment as a result of activation of 5-hydroxytryptamine receptor 2B (HTR2B)

signaling, a known driver of fibrosis and mitochondrial dysfunction.

**Methods:** Rats were divided into three groups: 1) rats receiving a control diet (regular chow), 2) rats receiving a 0.2% adenine-supplemented diet with daily vehicle [saline + 0.1% DMSO] injection, and 3) rats receiving 0.2% adenine-supplemented diet with daily administration of an HTR2B antagonist, MARY1 [0.3 mg/kg] (n=8/group). Rats were exposed to adenine diet and treated for 4 weeks. Following treatment, kidneys were harvested, and cortical tissue was analyzed via immunoblotting and histological staining analysis.

**Results:** Our results confirmed that 0.2% adenine-supplemented was sufficient to induce CKD in rats as measured by urinary albumin-creatinine ratio (ACR), Masson's trichrome histology, and kidney injury molecule 1 (KIM1) expression. Adenine-supplementation resulted in profound mitochondrial dysfunction as evidenced by a ~70% reduction in cellular concentration of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and a ~60% reduction in peroxisomal proliferator-activated receptor gamma coactivator 1-alpha (PGC1 $\alpha$ ) expression. Moreover, all 5 of the complexes of the electron transport chain (ETC) exhibited reduced expression in adenine-exposed groups. Treatment with an HTR2B inhibitor fully prevented these reductions.

**Conclusion:** These results suggest that 2,8-DHA nephrotoxicity is partly mediated by HTR2B. It also indicates that pharmacological antagonism of HTR2B may be a promising new target for the treatment of APRT-induced nephropathy and/or CKD. Future studies will aim to further define the mechanism underlying HTR2B-mediated mitochondrial dysfunction.

## **18. Shared Mitochondrial and Metabolic Proteomic Responses in Ovarian and Cardiac Tissues Following Phthalate Exposure**

### **Poster #18**

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Dibutyl phthalate (DBP), di-2-ethylhexyl phthalate (DEHP), and benzyl butyl phthalate (BBP) are endocrine-disrupting chemicals (EDCs) with substantial risk of daily exposure due to their widespread use as plasticizers in manufacturing and product packaging. Phthalates are found ubiquitously in household goods, food packaging, medicinal coatings, however their use in personal care products places women at particularly high-risk for exposure. Phthalate exposure has been linked to female reproductive dysfunction, infertility-associated disorders, cardiometabolic disease, and mitochondrial dysfunction. Previous work using a unique mouse model examined the reproductive effects of a biologically relevant mixture of DBP, DEHP, and BBP, with dosing based on phthalate levels detected in follicular fluid from reproductive-aged women. Antral follicles from mice exposed to this mixture (32PHT; 32  $\mu$ g/kg/d) for 10 days showed strong enrichment of mitochondrial proteins and significant changes in proteins linked to lipid metabolism, phosphorylation, cell cycle regulation, and mRNA processing. Specifically, phthalate exposure increased follicular proteins involved in fatty acid synthesis and decreased proteins involved in fatty acid oxidation. Extending this model to examine the cardiometabolic effects of 32PHT exposure after 30 days of dosing, proteomic analysis of heart tissue identified 3,848 proteins, 188 of which were significantly altered (P<0.05). Compared to vehicle controls, 32PHT-treated mice exhibited upregulation of 132 proteins and downregulation of 56 proteins. Bioinformatic analysis revealed enrichment of pathways associated with mitochondrial function, lipid homeostasis, fatty acid beta-oxidation, membrane integrity, oxidative stress responses, transcriptional regulation, and protein degradation, suggesting altered lipid metabolic balance, stress adaptation, and mitochondrial-associated functioning. In contrast, pathways involved in angiogenesis, cytoskeletal protein binding, N-glycan processing, and cellular signaling were depleted, indicating reduced signal transduction, intercellular communication, cell structure integrity, and cellular remodeling. Collectively, these proteomic changes suggest shared mechanisms of 32PHT toxicity in ovarian and cardiac tissues, particularly involving mitochondrial function, fatty acid processing, lipid metabolism, cellular signaling, oxidative stress, and cell membrane integrity.

## 19. Investigating the Impact of Lithium Exposure on Gut Microbiota

### Poster #19

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A growing demand for lithium in technology has increased the environmental release of lithium cobalt oxide ( $\text{LiCoO}_2$ ) and raised concerns about the biological risks of lithium consumption. Another form of lithium,  $\text{Li}_2\text{CO}_3$  (lithium carbonate), is used pharmaceutically as a treatment for bipolar disorder and also prompts questions about the biological effects of lithium exposure. While human contact with lithium compounds is increasing both environmentally and pharmaceutically, their comparative effects on the gut microbiota remain largely unexplored. This study addresses this gap by evaluating how these specific chemical forms influence the growth of gut bacteria. We assessed the effects of  $\text{Li}_2\text{CO}_3$  and  $\text{LiCoO}_2$  on three representative probiotic gut bacteria: *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, and *Bifidobacterium bifidum*, as well as a wild-type *Escherichia coli* strain. Bacteria were exposed to lithium concentrations ranging from 1 to 1,000  $\mu\text{g/mL}$  under anaerobic conditions, and growth was quantified using optical density at 600 nm ( $\text{OD}_{600}$ ) with viability confirmed through colony-forming unit (CFU) assays. Across probiotic strains,  $\text{Li}_2\text{CO}_3$  did not significantly alter growth at 24 hours, whereas  $\text{LiCoO}_2$  consistently reduced  $\text{OD}_{600}$  values by 48–59%. However, this inhibition reached statistical significance only in *L. rhamnosus* ( $p = 0.0012$ ), with *L. reuteri* and *B. bifidum* showing non-significant reductions due to higher trial-to-trial variability. CFU assays supported these findings, suggesting that cobalt, rather than lithium, might be the primary driver of toxicity in these probiotic species. In contrast, wild-type *E. coli* displayed a divergent response:  $\text{Li}_2\text{CO}_3$  caused a highly significant reduction in  $\text{OD}_{600}$  at 24 hours ( $p < 0.0003$ ), while  $\text{LiCoO}_2$  significantly increased growth ( $p = 0.017$ ), suggesting a possible cobalt-associated growth advantage in this strain. Overall, this study illustrates that battery derived  $\text{LiCoO}_2$  disrupts probiotic gut bacteria, while pharmaceutical  $\text{Li}_2\text{CO}_3$  remains biologically inert toward these strains at comparable concentrations. The opposing response of wild-type *E. coli* suggest that lithium-based compounds may reshape gut microbial communities in a species-specific and chemically distinct way.

## 20. Integrating Toxicokinetic, Mechanistic, and Epidemiologic Evidence to Evaluate the Estrogenic Potential of Methylparaben and Propylparaben

### Poster #20

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**Background:** Methylparaben (MeP) and propylparaben (PP) are widely used preservatives in cosmetics, personal care products, pharmaceuticals, and foods. Although these compounds exhibit estrogen receptor activity under experimental conditions, the biological relevance of these findings at typical consumer exposure levels remains an area of scientific and regulatory interest.

**Methods:** This review evaluates current evidence on the dermal absorption, metabolism, systemic distribution, and bioavailability of MeP and PP. Additionally, experimental studies assessing estrogenic potential were examined, including receptor binding affinity and reported biological effects.

**Results:** The available evidence demonstrates that MeP and PP exhibit weak estrogen receptor activity relative to endogenous estradiol, undergo rapid metabolism following absorption, and have limited systemic bioavailability under typical conditions of consumer use. Experimental estrogenic responses generally occur at exposure levels substantially exceeding those encountered through routine product use, while epidemiologic studies have not consistently demonstrated associations between paraben exposure and breast or gynecologic cancers.

**Conclusions:** Overall, the toxicokinetic, mechanistic, and epidemiologic evidence collectively suggest that MeP and PP are unlikely to produce clinically relevant endocrine effects or increase the risk of hormone-sensitive cancers at typical exposure concentrations.

## 21. Disruption of Early Human Red Blood Cell Development by Arsenite and Its Primary Metabolite Monomethylarsonous Acid

### Poster #21

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Chronic exposure to heavy metals is linked to adverse health outcomes, such as anemia. Arsenite (the trivalent inorganic form of arsenic, AsIII), specifically, causes hematotoxicity in both *in vivo* and *in vitro* models. However, little is known about the relative hematotoxicity of the AsIII methylated metabolites. Preliminary *in vitro* studies indicate that the major trivalent AsIII metabolite, monomethylarsonous acid (MMAIII), is more toxic than its parent inorganic arsenical. Therefore, this study investigated the differential hematotoxicity of AsIII and MMAIII in primary human bone marrow CD34+ hematopoietic progenitor cells (HPCs) from male and female donors with varied backgrounds. To evaluate effects on growth and differentiation mediated by AsIII and MMAIII, CD34+ cells obtained commercially from STEMCELL Technologies were cultured in two parallel systems. The first system utilized HemaTox Erythroid medium which is selective for erythroid development, and the second system comprised of H4330 MethoCult medium which supports both erythroid and myeloid progenitors. HPCs cultured in both conditions were exposed to low concentrations of AsIII or MMAIII. At 3- and 7-day timepoints, viability and growth of early RBCs was assessed using acridine orange/propidium iodide staining. Erythroid differentiation at these same timepoints was assessed using flow cytometry by comparing CD71+ and CD235a+ marker expression. AsIII and MMAIII reduced the growth and differentiation of early human RBCs in a dose-dependent manner at the 7-day timepoint. Flow cytometry revealed impaired erythroid differentiation following MMAIII treatment, with early RBCs failing to mature into CD235a+ cells. Impacts on hematopoietic differentiation were further evaluated via colony formation in H4330 MethoCult medium after 14 days. Colony-forming assays demonstrated significant reductions in erythroid colony forming units (BFU-E and CFU-E) following exposure AsIII and MMAIII in a dose-dependent manner. In summary, these findings indicated that early stages of human RBC development are highly susceptible to hematotoxicity from AsIII and MMAIII, with MMAIII eliciting greater toxicity than its parent arsenical. Future work aims to understand how arsenic biotransformation plays a role in impaired erythropoiesis. Funding: This work was supported by the NIGMS of the NIH Grant 1R16 GM146669; the NIEHS Core Center Grant P30ES032755; the UNM Center for Metals in Biology and Medicine through NIGMS Grant P20 GM130422; the NIEHS UNM METALS Superfund Research Program Grant P42 ES025589; and the UNM Comprehensive Cancer Center Grant NCI P30CA118100.

## 22. Per- and Polyfluoroalkyl Substances (PFAS) Antagonize Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) Activity

### Poster #22

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**Background and Purpose:** Defects of the head and face account for approximately one-third of all congenital abnormalities worldwide and are a significant threat to neonatal and infant mortality. Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) is associated with significant birth defects in humans and rodents. PFASs are highly dependent on retinoic acid homeostasis and signaling, which regulates the expression of 500 genes through agonism of the retinoic acid receptor (RAR) and retinoid X receptor (RXR). RAR/RXR binding to RXR yielding synergistic effects on transcription. Throughout pregnancy, systemic concentrations



of the predominant RAR agonist, all-trans-retinoic acid (*atRA*) are tightly maintained at approximately 5 nM. This homeostasis is achieved through an autoregulatory feedback loop in which excess *atRA* drives the transcription of genes encoding members of the cytochrome P450 (CYP) 26 and 3A families, which actively metabolize retinoic acid. PFAS share many structural similarities with *atRA*, affording them an increased capacity for ligand recognition in other biological pathways mediated by retinoid gradients. We have previously demonstrated the ability for PFAS to inhibit the homeostatic oxidative activities of CYP26A1 and fetal/neonatal CYP3A7. Additionally, we found that perfluorodecanoic acid (PFDA) significantly downregulates transcription of retinoid target genes in female primary human hepatocytes. We therefore hypothesize that PFAS antagonize RAR and RXR activity, thereby contributing to the craniofacial defects associated with prenatal exposure.

**Methods:** Twelve PFAS (FBSA, PFBS, PFPeA, GenX, FHxSA, PFHxS, 4:2 FTS, PFOA, PFOS, PFNA, PFDA, and PFUnDA) were tested at 10 and 100  $\mu$ M for their capacity to antagonize RAR $\alpha$ / $\beta$ / $\gamma$  and RXR $\alpha$ / $\beta$ / $\gamma$  activity based on their widespread use and/or presence in fetal or maternal tissues. Screenings were conducted using the INDIGO Biosciences cell-based luciferase reporter assay for each isoform (State College, PA). Briefly, incubations were performed in the presence of *atRA* or 9-*cis*-RA agonist at the EC<sub>50-80</sub> for each respective receptor. Reference compounds (RAR $\alpha$ , BMS 195614; RAR $\beta$ / $\gamma$ , CD 2665; and RXR $\alpha$ / $\beta$ / $\gamma$ , UVI 3003) were included as positive controls for antagonism. Following a 22-24 h incubation period (37°C, 5% CO<sub>2</sub>), media was removed, and luciferase detection reagent was added. After 5 min, luminescence was quantified with a microplate reader (TECAN; Männedorf, Switzerland) at 500 mSec per well. The log<sub>2</sub>(FoldChange) of each treatment was quantified against the vehicle control, and statistical significance was calculated using a two-way ANOVA with Dunnett's post hoc test for multiple comparisons. Experiments were performed in triplicate.

**Results:** Our results indicate that FBSA, PFBS, PFPeA, GenX, FHxSA, 4:2 FTS, PFNA, PFDA, and PFUnDA significantly antagonized RAR and RXR activity (*p*<sub>adj</sub> < 0.05). An inverted U-shaped relationship was observed between carbon chain length and receptor activity, in which the shorter ( $\leq$  C<sub>6</sub>) and longer PFAS ( $\geq$  C<sub>9</sub>) were more potent antagonists compared to mid-length PFAS (e.g., PFOA and PFOS). The 11-carbon PFUnDA demonstrated the highest potency for receptor antagonism across all six isoforms. PFUnDA (100  $\mu$ M) significantly antagonized RAR activity with log<sub>2</sub>(FCs) of -4.62 ( $\alpha$ ), -1.35 ( $\beta$ ), and -4.52 ( $\gamma$ ) (*p*<sub>adj</sub> < 0.001). PFUnDA (100  $\mu$ M) also inhibited RXR activity with log<sub>2</sub>(FCs) of -0.52 ( $\alpha$ ), -1.39 ( $\beta$ ), and -2.31 ( $\gamma$ ) (*p*<sub>adj</sub> < 0.05). In addition to PFUnDA, FHxSA and PFDA both significantly antagonized all six RAR and RXR isoforms (*p*<sub>adj</sub> < 0.01).

**Conclusion:** Nine of the twelve PFAS tested (FBSA, PFBS, PFPeA, GenX, FHxSA, 4:2 FTS, PFNA, PFDA, and PFUnDA) significantly antagonized retinoid receptor activity *in vitro*. Potency was dependent on chain length, in which shorter and longer compounds displayed more antagonism compared to mid-length PFAS. Interference with retinoid signaling during human development leads to severe congenital defects and malformations of the head and face. Biomarkers of PFAS teratogenicity largely overlap with those implicated in altered retinoid signaling during development. We therefore offer our findings as further mechanistic evidence for PFAS teratogenicity through altered retinoid signaling via RAR and RXR antagonism.

## 23. Stratifying mouse ovarian follicle growth dynamics to inform computational models of folliculogenesis and environmental toxicant disruption

### Poster #23

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Ovarian follicles are the functional units of the ovary as they support oocyte development and reproductive hormone synthesis. Folliculogenesis, the process of ovarian follicle development toward ovulation, is required

for reproductive function and overall premenopausal health in women. Unfortunately, due to its complexity and need for tight regulation, follicle development is highly susceptible to toxicity by endocrine disrupting chemicals (EDCs). There is a growing need for new approach methodologies (NAMs) to facilitate the characterization of toxicant-induced reproductive disruption while reducing the number of whole animal studies required. Key steps towards the development of NAMs for ovarian toxicity include developing highly predictive computational models that are informed by detailed biological data derived from *in vitro* follicle maturation assays. Therefore, the objective of this study was to generate time course data corresponding to ovarian follicle diameter, cellular compartment sizes, antrum formation, and hormone outputs using follicles with distinct growth and survival trajectories. Additionally, dibutyl phthalate (DBP), a known EDC, was used as a model chemical to characterize how known toxicant exposure alters these parameters. To achieve our objective, secondary and multi-layer follicles (100-250  $\mu\text{m}$ ) were mechanically isolated from 21-day old female CD-1 mice, encapsulated in alginate beads (0.5%) and cultured individually for up to 240 hours. Follicles were treated with vehicle control (0.075% DMSO), three concentrations of DBP (0.001, 0.1, and 10  $\mu\text{g}/\text{mL}$ ), or a cell death control (7600  $\mu\text{g}/\text{mL}$  hydroxyurea). Follicle diameter and brightfield images were obtained every 24 hours to assess daily growth, compartment-specific morphology and area, and antrum formation. Culture media samples were collected to measure 17 $\beta$ -estradiol (E2) and testosterone (T4) concentrations over time. Follicles were stratified into three distinct growth groups based on the diameter percent change of DMSO controls at 144 hours relative to baseline. Using these criteria, individual follicles from all treatments were classified as non-growing ( $\leq 0\%$ ), slow growing (0 – 51.85%), or fast growing ( $\geq 51.85\%$ ). Finally, these growth patterns were used to compare changes in compartment morphology and hormone production between treatments. Our results show that follicles can be stratified into biologically meaningful categories based on growth dynamics. Specifically, fast-growing vehicle control follicles secrete significantly more estradiol and have greater growth in the granulosa cell compartment compared to DBP-exposed follicles. Vehicle control fast-growing follicles are also much more likely to form an antrum compared to their counterparts. When these growth patterns are applied to DBP-treated follicles, we see a decrease in the percentage of fast-growing follicles as DBP exposure concentration increases. Fast- and slow-growing follicles exposed to high concentrations of DBP also show decreased diameter over time compared to their DMSO counterparts. This work provides experimentally derived parameters that will inform predictive computational models about different follicle populations and their responses to DBP. This will ultimately help improve predictions of disrupted follicle development in response to EDCs, contributing to improved risk assessment for female reproductive health.

## **24. Micro- and Nanoplastic Exposure Drives Dose-, Sex-, and Time-Dependent Neurobehavioral, Metabolic, and Cardiovascular Remodeling in LOAD3 Mice**

### **Poster #24**

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**Background:** Micro- and nanoplastics (MNPs) are emerging environmental contaminants capable of accumulating in tissues and potentially disrupting multiple organ systems. However, the effects of prolonged MNP exposure on neurological, metabolic, behavioral, and cardiovascular outcomes remain poorly understood. This study investigated dose-, sex-, and

exposure-duration-dependent effects of MNP exposure in the LOAD3 mouse model of genetic susceptibility to late-onset Alzheimer's disease.

**Methods:** Six-month-old male and female LOAD3 mice were assigned to control, low-plastic, or high-plastic diets for either 4 or 13 weeks (n = 10/group). Behavioral testing was followed by blood and tissue collection for biochemical, histological, metabolomic, lipidomic, neurological, reproductive, and echocardiographic analyses.

**Results:** Body weight increased over time across experimental groups, whereas high-plastic exposure reduced relative testis weight in males, suggesting potential reproductive effects. Brain analyses demonstrated increasing trends in phosphorylated tau, A $\beta$ 40, and A $\beta$ 42, with the highest levels generally observed in high-plastic-exposed mice. Brain metabolomics revealed dose- and sex-dependent metabolic remodeling following MNP exposure. High-plastic exposure produced the strongest changes, particularly increasing proline, GABA, nicotinamide, choline, and glutamic acid, with more pronounced responses in males. Brain lipidomics revealed sex-dependent responses to MNP exposure, with more pronounced changes in males. In males, lipidomic alterations increased with exposure level, with the high-plastic group showing the greatest changes, suggesting a dose-dependent response. Behavioral findings suggested increased locomotor activity and altered novelty-directed exploration. Echocardiography further demonstrated sex-, dose-, and duration-dependent changes in cardiac structure and function.

**Conclusions:** Chronic MNP exposure produced multi-organ effects that varied according to dose, sex, and exposure duration. High-plastic exposure generally produced the strongest changes, including trends toward increased Alzheimer's disease-associated biomarkers, early metabolic and lipidomic remodeling, altered behavior, reproductive effects, and progressive cardiac remodeling. These findings suggest that long-term MNP exposure may accelerate neurocardiovascular dysfunction in genetically susceptible populations.

## **25. Chronic Low-Dose Arsenic Exposure Induces rDNA Instability in Human Bronchial Epithelial Cells**

### **Poster #25**

**Mina Alaaldin**, Stephen Smith, Bernardo Lemos

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Arsenic is a Group 1 human carcinogen that promotes genomic instability, but its effects on ribosomal DNA (rDNA) remain largely unknown. rDNA is highly transcribed, repetitive, and structurally vulnerable, and its dysregulation is increasingly linked to aging and cancer. We hypothesized that chronic low-dose arsenic exposure disrupts rDNA regulation and nucleolar organization in human bronchial epithelial cells. BEAS-2B cells were continuously exposed to 0.5 or 1.0  $\mu$ M arsenic for up to 12 months with routine passaging. Chronic arsenic exposure shifted the distribution toward a greater number of nucleoli per cell, consistent with nucleolar fragmentation. At 12 months, arsenic-exposed cells had significantly more nucleoli per cell than controls (4.83  $\pm$  1.62 vs. 4.29  $\pm$  1.80; p < 0.01) and a greater total nucleolin-positive area (35.43  $\pm$  9.72 vs. 26.99  $\pm$  8.75; p < 0.0001), demonstrating progressive disruption of nucleolar architecture. Nanopore sequencing identified more than 50 significantly hypomethylated CpG sites within rDNA. All detected differentially methylated sites were hypomethylated, with effects varying across rDNA regions, revealing a consistent but region-specific epigenetic response to arsenic. Despite these abnormalities,  $\gamma$ H2AX puncta per cell were significantly reduced in arsenic-exposed cells relative to controls at 12 months (3.03  $\pm$  6.13 vs. 8.77  $\pm$  7.41; p < 0.0001), as was  $\gamma$ H2AX colocalization with nucleoli (1.15  $\pm$  3.03 vs. 2.14  $\pm$  2.91; p = 0.004). This paradoxical reduction in  $\gamma$ H2AX signaling may reflect adaptation or attenuation of the DNA damage response rather than resolution of genotoxic stress. Together, these findings define a coordinated arsenic-induced phenotype characterized by nucleolar disorganization, region-specific rDNA hypomethylation, and reduced DNA damage signaling. We propose that chronic arsenic exposure remodels the rDNA-nucleolar axis while weakening the cellular response to persistent genomic stress, potentially allowing rDNA dysfunction to accumulate and contribute to arsenic-induced carcinogenesis.

## 26. Reduction of Hexavalent Chromium Produces Stable Chromium-DNA Adducts *In Vitro*

### Poster #26

**Nicholas Perpetua**, Aayla Ritchie, Stephen Smith, Bernardo Lemos

Department of Pharmacology & Toxicology, R. Ken Coit College of Pharmacy, University of Arizona, Tucson

Hexavalent chromium [Cr(VI)] is a potent environmental carcinogen produced by industrial processes that has been linked to lung, sinus, and stomach cancers. Cr(VI) undergoes intracellular reduction by ascorbate, with additional contributions from glutathione and cysteine to form more reactive chromium species, some of which, trivalent chromium [Cr(III)], are presumed to have the capacity to generate DNA adducts. However, literature surrounding the formation of chromium-DNA adducts remains uncertain with some studies suggesting that chromium does not form adducts under cellular conditions. Here we show that *in vitro* Cr(VI) reduction induces chromium-DNA adducts under physiologically relevant reducing conditions. PCR amplified DNA regions were exposed to increasing concentrations of potassium dichromate at near-physiological pH in the presence of a cell-relevant concentration of ascorbate to model physiologically relevant reducing conditions. Agarose gel electrophoresis revealed dose-dependent decreases in DNA mobility and band intensity, consistent with structural modifications associated with DNA adduct formation following Cr(VI) reduction. DNA was subsequently purified and analyzed for bound chromium by inductively coupled plasma mass spectrometry (ICP-MS), confirming dose-dependent increases in DNA-associated chromium. DNA samples treated with Cr(VI) but without the reducing agent ascorbate, exhibited no detectable DNA-bound chromium, supporting the notion that reduction of Cr(VI) is necessary for the formation of reactive chromium species. Further studies suggest the composition of the DNA sequence influences adduct-associated electrophoretic changes. Additional studies show that Cr(III)-mediated adduct formation induces similar modifications to agarose gel mobility and ICP-MS of DNA post Cr(III) exposure. Together, these findings demonstrate that Cr(VI) reduction forms chromium-DNA adducts under physiologically relevant reducing conditions, establishing a robust platform for investigating chromium-DNA adducts and informing future environmental health research into Cr(VI)-mediated genomic instability and carcinogenesis.

## 27. Integrating Environmental Aging and Cryomilling to Model Realistic Micro- and Nanoplastic Exposure Pathways

### Poster #27

**Nohi Leyva**<sup>1</sup>, Laurissa Barela<sup>2</sup>, Emily Phan<sup>1</sup>, Milad MazloumiBakhshayesh<sup>1</sup>, Eve Rowland<sup>2</sup>, Sakshi Patil<sup>1</sup>, Sumira Phatak<sup>1</sup>, Jessica Begay<sup>1</sup>, Eliane EL Hayek<sup>1</sup>, Matthew J. Campen<sup>1</sup>, Marcus A. Garcia<sup>2</sup>

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<sup>2</sup> Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico Health Sciences

Plastic pollution has emerged as a global environmental and public health concern as larger plastic debris undergoes weathering, fragmenting into micro- and nanoplastics (MNPs) capable of entering biological systems. However, many toxicological studies continue to rely on pristine, laboratory-generated plastics that fail to replicate the chemical and physical characteristics of environmentally aged particles, limiting the ability to accurately model real-world exposures. To address this challenge, we developed a workflow for generating MNPs from naturally weathered marine plastics. Approximately 50 pounds of plastic debris were collected from Kamilo Beach, Kona, Hawaii, in collaboration with the Hawaii Wildlife Fund. Located within the North Pacific Gyre, Kamilo Beach receives marine debris transported across the Pacific Ocean, providing a diverse source of naturally weathered plastics. Following collection, materials underwent controlled UV aging before cryogenic milling to generate particles for biological studies, primarily measuring 63 µm and smaller. Collected materials were characterized using pyrolysis gas chromatography-mass spectrometry (Py-GC/MS) and complementary analytical techniques to identify dominant polymer compositions and evaluate molecular changes associated with environmental weathering. Compared with pristine laboratory-grade polymers, aged plastics exhibited altered chemical signatures, including reductions in long-chain carbon fragments and increased brittleness that promoted fragmentation into biologically relevant particle sizes. These MNPs are



being incorporated into controlled vivo exposure studies through specially formulated rodent chow. Experimental groups consist of control, low-dose, and high-dose MNP diets, with animals evaluated at 4- and 12-week time points to investigate dose-dependent effects on particle uptake, biodistribution, tissue accumulation, and toxicological outcomes across multiple organ systems. This model provides a platform for examining chronic dietary exposure using environmentally aged particles rather than pristine laboratory materials. By integrating environmental sampling, chemical characterization, particle generation, and controlled biological exposure models, this work provides a more representative platform for investigating chronic MNP exposure. Together, these methods bridge the gap between environmental contamination and laboratory toxicology, improving our understanding of the biological consequences of realistic MNP exposure, and informing future risk assessment.

## **28. Does bisphenol-A alter serotonin receptor gene expression in the descending trigeminal pain circuit?**

### **Poster #28**

**Sophia von Hippel**, Tally Largent-Milnes

Department of Pharmacology, University of Arizona

Exposure to the endocrine disrupting compound bisphenol-a (BPA) alters behaviors associated with headache<sup>1</sup>, fear<sup>2</sup>, and anxiety<sup>3-8</sup>, and can disrupt neurodevelopment of serotonergic systems<sup>2,9-11</sup>. BPA acts on hormone receptors to scramble gene expression, eliciting many adverse health effects<sup>12</sup>. In a dose-response curve study of oral BPA exposure, 0.5 µg/kg BW/day BPA diminished gene expression of estrogen receptor alpha in the rostral ventral medulla (RVM), a key nucleus of the descending trigeminal pain circuit. Besides the RVM, this circuit is composed of multiple other nuclei, including the periaqueductal grey (PAG) and spinal trigeminal nucleus caudalis (Vc) [unpublished data]. Serotonin (5HT) mediates headache, fear, and anxiety via this circuit<sup>13</sup>, and the serotonin receptor density is regulated in part by estrogen receptors<sup>14</sup>. In this study, we hypothesized that low-dose oral BPA would significantly alter gene expression of serotonin receptors 5HT1B, 5HT1D, 5HT1F, 5HT2A, and 5HT2C in the descending trigeminal pain circuit. We exposed female naïve Sprague Dawley rats to 0.5 µg/kg BW/day BPA via daily treats for two weeks, then conducted qPCR for 5HTRs in the PAG, RVM, and Vc. BPA significantly reduced 5HT2C gene expression in the PAG and increased 5HT1F gene expression in the RVM and Vc. BPA did not affect gene expression of 5HT1B or 5HT2A in any of the three nuclei but did show a non-significant ( $p = 0.0601$ ) trend towards decreased 5HT1D gene expression in the Vc. Notably, 5HT2C in the PAG has been implicated in anxiety, pain, and aversive behaviors<sup>15-17</sup>. This study is the first to examine endocrine disruption of serotonin receptors in the descending trigeminal pain circuit, and future work will examine whether these changes in gene expression are reflected in susceptibility to 5HTR-modulated behaviors, such as medication overuse headache from triptan medications.

## **29. Particulate Transfer from Cell Corpses to Engulfing Macrophages Disrupts Phagocytosis and Drives Inflammation**

### **Poster #29**

**Stephanie Bersie**<sup>1,2</sup>, Shannon Hott<sup>1,2</sup>, Alexandra McCubbrey<sup>1,2</sup>

<sup>1</sup> Department of Medicine, National Jewish Health

<sup>2</sup> University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy & Pharmaceutical Sciences

**Background:** The human lungs are constantly exposed to inhaled particulate matter (PM). Approximately 15% of inhaled PM reaches the lower respiratory tract where it is engulfed by alveolar macrophages (AM). This study explores the fate of PM contained within macrophages following cell death, testing the hypothesis that 1) non-degradable PM remains within dead cells and transfers to new, living macrophages during cell clearance, 2) the nature of cell death (i.e. apoptosis, necrosis) determines the mode of PM transfer, and 3) macrophage engulfment of PM-laden cell corpses alters immunometabolic programming.

**Methods & Results:** PM-loaded cell corpses were first generated *in vitro*. Imaging confirmed that intracellular 1µm beads, amorphous silica, and PM2.5 remained within apoptotic (AC) and necrotic (NC) cells after death. PM-loaded AC or NC were then co-cultured with live bone marrow-derived macrophages (BMDM). Analyses showed that plasma membrane from AC was easily detected in BMDM containing PM, indicating that PM in AC transfers to BMDM via engulfment of whole AC or AC blebs and bodies. PM transfer was also observed *in vivo* from apoptotic resident AM (RAM) to living recruited AM (RecAM). Intriguingly, when co-culture experiments were performed with NC, BMDM obtained PM not only via whole corpse engulfment, but also by pulling intracellular PM from NC corpses in the absence of NC-derived plasma membrane. Further examination using an intracellular/extracellular co-staining model revealed that BMDM pull intracellular materials from NC even in the absence of PM. Studies are ongoing to understand if the PM “slurping” phenomenon is part of broad removal of NC organelles exposed during plasma membrane rupture. Finally, RT-PCR was performed to understand how PM-laden cell corpses impact the macrophage inflammatory response. BMDM engulfing PM-laden cell corpses exhibited increased expression of *Tnfa*. *In vivo*, the RAM transcriptional response to engulfment of PM-laden AC was also assessed using a chimera mouse model. Transcriptomics identified a highly modified gene response between clean RAM engulfing clean AC versus PM-laden RAM engulfing PM-laden AC. Preliminary analysis revealed an observable downregulation in gene transcription as a whole in PM-exposed RAM. This observation is supported by *in vitro* co-culture assays, where BMDM pre-exposure to PM prior to co-culture displayed both a significant impairment to phagocytic capacity as well as muted *Tnfa* transcription.

**Conclusions:** This work shows that non-degradable PM contained within cell corpses is transferred to new, living macrophages during corpse clearance, where it perturbs normal programming and functions. These data also demonstrate a novel “slurping” phenomenon, where macrophages clear intracellular material from NC without true corpse engulfment. *In vivo*, corpse clearance may be an important factor driving PM persistence within phagocytic cell pools. Understanding the fate of non-degradable PM will advance understanding of how environmental exposures drive inflammation and the development of pulmonary disease.

### **30. The goldilocks zone of placentation: CXCR4 in overgrowth and restriction**

#### **Poster #30**

**Sumira Phatak**, Matthew Campen

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Preeclampsia and gestational diabetes are common pregnancy complications associated with major short- and long-term health risks for both mother and offspring, including hypertension, cardiovascular disease, obesity, and diabetes. CXCR4 is a key regulator of placental development, trophoblast invasion, vascularization, and immune tolerance at the maternal-fetal interface. To define the role of CXCR4 signaling in early placentation, ewes were assigned to control, inhibition (AMD3100), or enhancement (CXCL12) from GD5-12, spanning the period of attachment and vascularization. Single-nucleus RNA sequencing of GD12 placentas revealed cell type-specific transcriptional changes linked to placental dysfunction. Across treatment groups, fibroblast and epithelial clusters showed pathways related to autophagy or oxidative stress, suggesting shared stress responses in the placental microenvironment. In AMD3100- treated placentas, MMP16 was commonly downregulated and, together with IFI6 and GRP in binucleate trophoblasts, indicated impaired extracellular matrix remodeling, reduced survival in the maternal immune environment, and disrupted proliferative and endocrine signaling, consistent with compromised invasion and maturation. In contrast, CXCL12 treatment induced upregulation of MMP16 in binucleate trophoblasts, consistent with enhanced extracellular matrix remodeling and increased trophoblast migration and invasion, alongside transcriptional signatures of disorganized vascularization, oxidative stress, and maladaptive placental responses. Both treatments also affected genes associated with structural insufficiency, metabolic stress, and disrupted maternal-fetal interface function. Together, these findings define CXCR4-dependent placental pathways that shape trophoblast invasion, vascular remodeling, and cellular stress responses in a large-animal model, highlighting candidate

biomarkers and mechanistic targets for early detection and translational interventions aimed at improving placental function and reducing maternal-fetal metabolic and hypertensive disease risk.

### **31. G Protein–Coupled Estrogen Receptor Regulates Pulmonary and Neuroinflammatory Responses to Acute Wood Smoke Exposure**

#### **Poster #31**

**Sydney Yazzie<sup>1</sup>**, Eunju Lim<sup>1</sup>, Mijung Oh<sup>1</sup>, Kelvin Chepkwony<sup>1</sup>, Luca Tatro<sup>1</sup>, Edward Barr<sup>2</sup>, Tou Yia Vue<sup>3</sup>, Eric Prossnitz<sup>5</sup>, Brandon Phinney<sup>5</sup>, Shuguang Leng<sup>4</sup>, Jennifer Gillette<sup>1</sup> and Katherine Zychowski<sup>1</sup>

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Wood smoke (WS) exposure is an emerging environmental health concern linked to systemic and neurological inflammation. Estrogen signaling, particularly through the G protein–coupled estrogen receptor (GPER), has been implicated in modulating immune responses, yet its role in neuroinflammation following WS exposure remains unclear. To address this, we investigated how GPER signaling influences neuroinflammatory outcomes following acute WS exposure. 10-12wk old GPER knockout (KO) and wild-type (WT) mice were exposed to either filtered air (FA) or WS (4h/d for 2d, ~0.575mg/m<sup>3</sup>) (n=8 per group/exposure). Brain and lung tissue as well as bronchoalveolar lavage fluid (BALF) were collected to evaluate cytokine immune responses. In a separate cohort (n=5 per group/exposure), cerebral blood flow dynamics were assessed within 24h of the last exposure using laser speckle imaging. Laser Speckle Imaging revealed that WS significantly increased cerebral blood flow in WT mice but not in GPER KO mice (20.99 ± 9.553 SEM, p=0.0335, Welch's t test). Flow cytometry analysis of BALF revealed decreased resident alveolar macrophages in WT mice after WS exposure (p=0.0309, Nonparametric T test), accompanied by increased monocyte-derived macrophages in GPER KO/WS versus WT/FA (mean diff. = -0.388 ± 0.137, p=0.0243, two-way ANOVA). We also observed elevated monocyte-derived macrophages in GPER KO/WS versus WT/FA (p=0.0128, Nonparametric T test). Additionally, T cell abundance was reduced in GPER KO mice compared to WT FA controls (p=0.0070, Nonparametric T test). Cytokine gene expression RT-qPCR analysis on cerebellum tissue showed statistically significant increase in IL-6 gene expression in KO/FA compared to WT/FA (p=0.0169) and KO/WS (p=0.0256, two-way ANOVA). Together, preliminary results demonstrate that GPER signaling influences immune responses and cerebrovascular adaptation following acute WS exposure. Future work will include evaluating mRNA cytokine gene expression in lung tissue as well as brain regions such as the hippocampus and cortex.

### **32. A Multiscale Integration of *In Vitro* and *In Vivo* Ovarian and Endocrine Dynamics, via Computational Modeling, to Predict Toxicant Effects on Female Reproduction**

#### **Poster #32**

Zelieann R. Craig<sup>1</sup>, Miely A. Suarez<sup>1</sup>, Viviana A. Romero<sup>1</sup>, **Talia N. Owen<sup>1</sup>**, James P. Sluka<sup>2</sup>, Karen Watanabe<sup>3</sup>, Israel Chagolla<sup>3</sup>, Qiang Zhang<sup>4</sup>, Adam J. Krieg<sup>5,6</sup>, Mary Zelinski<sup>5,6</sup>

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Most knowledge of ovarian toxicology comes from rodent studies, though rodent responses do not always predict human risk. While nonhuman primates are perhaps the best animal model for humans, studies are constrained by cost, shortages, and complex welfare requirements. To address these limitations, our NIEHS-funded project, *In Vitro* to *In Vivo* Extrapolation of Toxicant Effects on Ovarian Function, advances New

Approach Methodologies (NAMs) by developing *in vitro* assays and *in silico*, computational models to predict *in vivo* effects from *in vitro* data. Ultimately, we aim to enable robust *in vitro* to *in vivo* extrapolation (IVIVE) and cross-species extrapolation, though we currently require *in vivo* data for model development and evaluation. This NAM framework leverages mechanistic biology and predictive modeling to generate human-relevant ovarian toxicity insights while reducing our reliance on animal experimentation.

We are developing biologically based, multiscale computational models using harmonized *in vitro* and *in vivo* data from CD-1 mice (*Mus musculus*) and rhesus macaques (*Macaca mulatta*) exposed to a representative toxicant, dibutyl phthalate (DBP), which has known human exposure and reproductive effects. By aligning endpoints across species and experimental systems, these models will simulate follicle maturation under normal and chemically perturbed conditions. Initial efforts focus on proof-of-concept IVIVE and cross-species extrapolation models, establishing a scalable framework for predicting ovarian toxicity and ultimately informing human fertility risk assessment.

This presentation highlights our progress toward this NAM framework. Experimental data include *in vitro* mouse follicle cultures that quantify follicle growth dynamics and functional endpoints across folliculogenesis stages. This data is used to calibrate a tissue-scale computational model describing follicle development from the multilayer stage through the antral stage, enabling simulation of growth trajectories and cell type-specific steroid hormone synthesis under normal conditions. In parallel, we developed a whole-body physiologically based kinetic model that includes the ovary and key reproductive hormones in the hypothalamic-pituitary-ovarian axis providing a systems-level representation of DBP and hormone distribution and regulation. Together, these components establish the foundation for integrating follicle-scale biology with organism-level hormonal dynamics and advances this integrated computational platform as an *in silico* NAM tool to support IVIVE, cross-species extrapolation, and reduced reliance on traditional animal testing. (Supported by NIEHS Grant R01ES034690-02)

### **33. Glyphosate at the Human-Equivalent EPA Chronic Reference Dose Alters the Gut–Brain Axis and Exacerbates Alzheimer's Disease Pathogenesis in mice.**

#### **Poster #33**

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Glyphosate (GLY) is the most widely used herbicide worldwide, resulting in pervasive environmental contamination and widespread human exposure. Although regulatory agencies have established exposure thresholds considered safe, the U.S. chronic reference dose (cRfD; 1.75 mg/kg/day) remains substantially higher than acceptable daily intake limits adopted in several other countries. Despite the detection of GLY in human biofluids, its effects on the aging brain and neurodegenerative disease risk remain poorly understood. Our laboratory was the first to demonstrate that GLY crosses the blood-brain barrier and induces neuroinflammation in young C57BL/6J mice following short-term exposure at the No Observed Adverse Effect Level (NOAEL; 500 mg/kg/day) and a 10-fold lower dose. We subsequently showed persistent accumulation of the GLY metabolite aminomethylphosphonic acid (AMPA) in brain tissue months after exposure cessation, accompanied by sustained neuroinflammation and exacerbated Alzheimer's disease (AD)-like pathology. Whether exposure at the regulatory-relevant cRfD elicits similar biological effects, however, remains unknown. To address this question, 3xTg-AD and non-transgenic (NonTg) mice were exposed to the mouse-equivalent cRfD of GLY for 30 days between 4.5 and 5.5 months of age. Plasma was analyzed for the blood-based neurodegeneration biomarkers glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and pro-



inflammatory cytokines. Hippocampal tissue was assessed for cytokines and AD-related pathology, while cecal contents were analyzed for the short-chain fatty acids (SCFAs) propionate, isovalerate, butyrate, and hexanoate. Short-term GLY exposure at the mouse-equivalent cRfD significantly increased circulating GFAP, NfL, and pro-inflammatory cytokines in both genotypes. In 3xTg-AD mice, GLY further exacerbated amyloid- $\beta$  and phosphorylated tau pathology, which positively correlated with plasma GFAP and NfL levels. GLY also altered gut microbial metabolites, increasing propionate in NonTg mice and producing a distinct SCFA signature in 3xTg-AD mice characterized by elevated isovalerate and reduced butyrate and hexanoate. These findings demonstrate that regulatory-relevant GLY exposure is sufficient to trigger systemic inflammation, disrupt gut microbial metabolism, accelerate AD-related neuropathology, and elevate clinically relevant blood biomarkers of neurodegeneration. Collectively, these data raise important questions regarding the neurological safety of current regulatory exposure limits and identify NfL, GFAP, GLY, and AMPA as promising translational biomarkers for monitoring GLY-associated neurotoxicity in vulnerable aging populations.

### **34. Environmental Fungal Exposure Reprograms Pulmonary Host Responses Through Distinct Inflammatory and Immune-Priming Pathways**

#### **Poster #34**

**Xiangdi Mao**, Venesa Romero, Melisa Smith, Lingxiang Zhu, Yin Chen

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**Background:** *Coccidioides* is an environmentally acquired airborne fungal pathogen whose expanding geographic distribution is increasing the risk of inhalation exposure and Valley fever. However, the early pulmonary responses that distinguish pathogenic fungal exposure from nonpathogenic or vaccine-like exposure remain poorly understood.

**Methods:** We compared pulmonary responses following intranasal exposure to wild-type (WT) and live-attenuated  $\Delta cps1$  *Coccidioides* arthroconidia using murine lung RNA sequencing, pathway enrichment, immune-cell deconvolution, bronchoalveolar lavage cytokine profiling, and airway epithelial-cell transcriptomic analysis.

**Results:** WT exposure induced a progressive pulmonary response characterized by early epithelial ciliary remodeling followed by robust inflammatory activation, including IL-17, TNF, NF- $\kappa$ B, complement, and chemokine signaling, together with neutrophil recruitment and matrix remodeling. In contrast,  $\Delta cps1$  exposure activated conserved antifungal recognition pathways while preferentially inducing interferon-regulated defense, cell-cycle, DNA replication, and DNA-repair programs. Immune-cell deconvolution demonstrated reduced granulocyte and neutrophil signatures but relatively enhanced natural killer cell-associated features following  $\Delta cps1$  exposure. Consistent with these findings, airway epithelial cells exposed to WT arthroconidia exhibited inflammatory, hypoxic, and metabolic stress responses, whereas  $\Delta cps1$  exposure elicited a markedly stronger interferon-mediated innate defense program.

**Conclusions:** These findings demonstrate that fungal developmental capacity profoundly influences pulmonary responses following environmental inhalation exposure. While pathogenic WT *Coccidioides* promotes inflammatory lung remodeling, attenuated  $\Delta cps1$  exposure elicits a controlled immune-priming state characterized by enhanced interferon signaling and reduced neutrophilic inflammation. This work provides new insights into the mechanisms underlying environmentally induced lung injury and host adaptation and identifies early pulmonary response pathways that may serve as biomarkers or therapeutic targets for environmentally acquired fungal disease

# Tucson Eats

## UNIVERSITY BOULEVARD

*Easy walk from The Graduate Hotel*

### No Anchovies

Unique pizza flavors by the slice

Recommendation: Teriyaki Chicken, Hot Wing Pizza

### Scented Leaf

Delicious and refreshing tea

Recommendation: Fruit Gusher, Pink Starburst, Mojito Blanco

### Jimmy's Pita and Poke

Recommendation: The Hercules pita, build your own poke bowl with aloha tuna

### Gentle Ben's

Recommendation: The Western, The Diane

### HeeMee Coffee + Bakery

Recommendation: Matcha, Bulgogi Bowl, Katsu Sandwich

### Time Market

Fresh pastries and pizza

Recommendation: Fig and Proscuitto Pizza, Hummus Plate, Pepperoni Slice

Jimmy's Pita & Poke



Time Market



Kukai



## SUN LINK

*Hop on the Sun Link and visit restaurants along 4<sup>th</sup> ave, downtown, and Mercado San Augustin*

### Boxyard

Large outdoor patio, bar, and various food stands

### La Yaquesita Mexican Cuisine

Recommendation: Horchata, Yaquesita tacos

### Corbett's

Pickleball, food and drinks

### Kukai

Japanese kitchen at the MSA Annex

Recommendation: Takana Onigiri, Katsu Curry, Gyu Don

### Bōs Burger

Wagyu smash burgers and fries



# LOCAL TUCSON RESTAURANTS

*5-10 minute drive from  
The University of Arizona*

## La Indita

Native cuisine

Recommendation: Chicken Enchiladas with Green sauce, Number 3 Combination Plate

## El Güero Canelo

Home of the Sonoran Hot Dog



## Locale

Italian cuisine with beautiful outdoor patio

Recommendation: Fried calamari, Fusilli

## Rocco's Little Chicago

Recommendation: Chicken Wings, Kitchen Sink thin crust pizza

## El Charro Café

The Nation's Oldest Mexican Restaurant

Recommendation: The Carne Seca platter, The Bandera Enchiladas



## Zemam's Ethiopian Cuisine

Recommendation: Mixed Veggie & Meat Sampler, Yemisir Kay Wat, Lega Tibs

## Barrio Brewing Co.

Recommendation: The Western burger with beer battered fries, Pub Fried Fish Tacos, Southwest Eggrolls

## Postino

Enjoy a bottle of wine and Bruchetta board

## Tumerico

Vegetarian-Vegan LatinAmerican cuisine.

The Nation's #1 Rated Restaurant on Yelp!

Recommendation: Cuban Tacos



El Güero Canelo

El Charro Café

Tumerico

## Coffee and Tea Lovers!

Tucson is home to many small businesses! We have incredible coffee shops and local roasters.  
In order from closest to farthest from The Graduate Hotel:

SCENTED LEAF

CAFE LUCE

PRESTA

CAFE PASSE

TRANSIT TEA

TALEGA COFFEE CO.

BARISTA DEL BARRIO

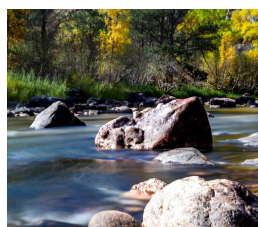
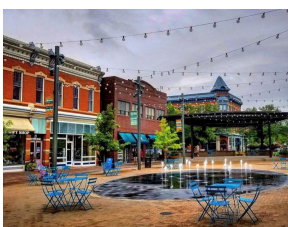
REN COFFEEHOUSE



# ACKNOWLEDGMENTS

The **University of Arizona** and the **Mountain West Regional Chapter of the Society of Toxicology** would like to thank all invited speakers, presenters, judges, and attendees for making the 44th Annual Meeting of the Mountain West Society of Toxicology at Tucson, Arizona a success!

We look forward to seeing you all again at the **Society of Toxicology 66th Annual Meeting and ToxExpo** from **Sunday, March 14 to Wednesday, March 17, 2027!** See you soon at **San Antonio, TX**, world-renowned for the Alamo and the iconic River Walk! Don't forget to join our MWSOT reception night!



MWSOT is excited to announce that the **45th Annual Meeting of the Mountain West Society of Toxicology** will be held at **Colorado State University** in **Fort Collins, CO!** Please join MWSOT next year at the Craft Beer Capital of Colorado and the home of the Horsetooth Reservoir, the Cache la Poudre River, and the historic Old Town that inspired Disneyland's Main Street!

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