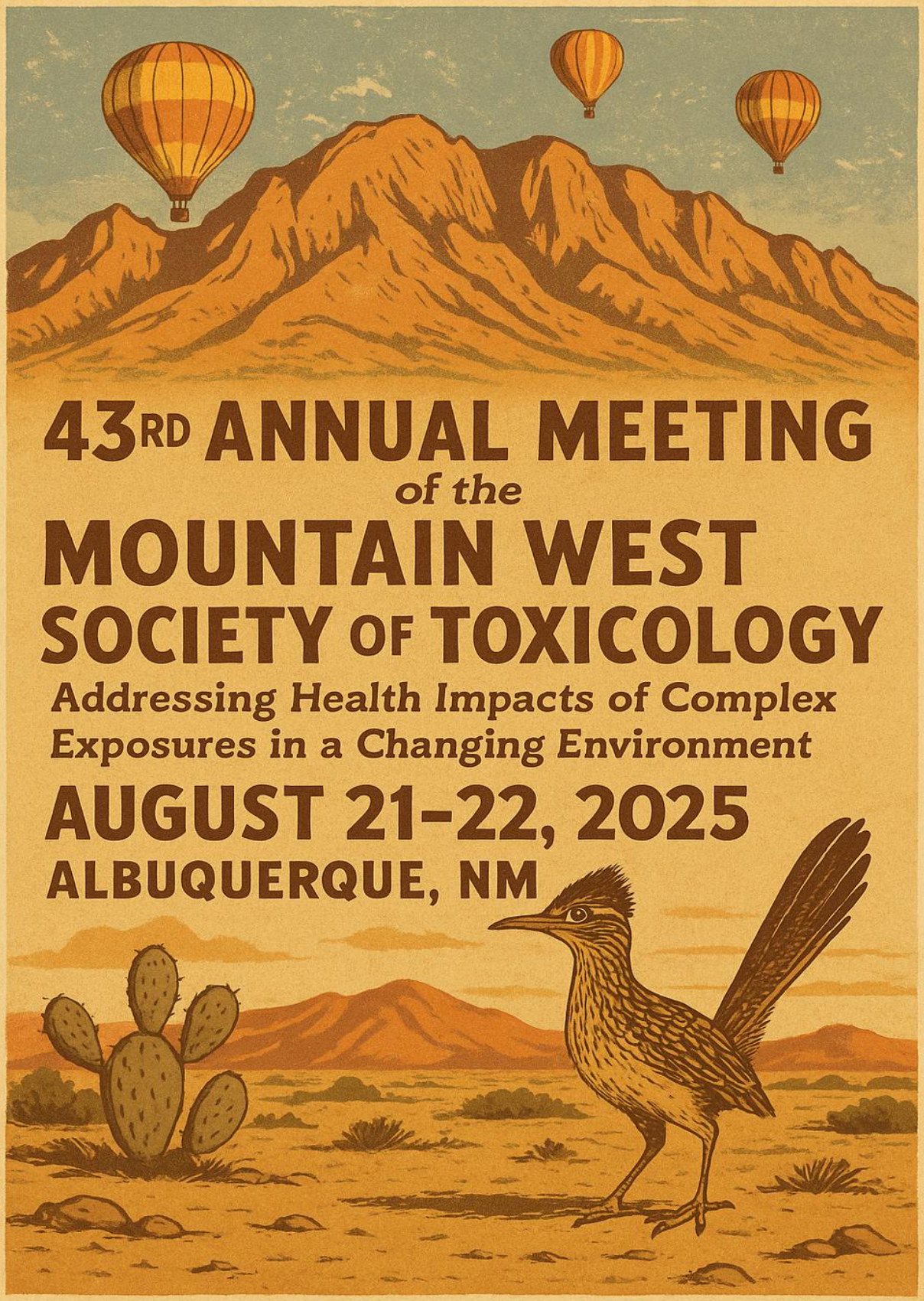

43RD ANNUAL MEETING
of the
MOUNTAIN WEST SOCIETY OF TOXICOLOGY

Addressing Health Impacts of Complex Exposures in a Changing Environment

AUGUST 21–22, 2025
ALBUQUERQUE, NM

PROGRAM BOOKLET

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WELCOME

Welcome to **Albuquerque, New Mexico** where **red and green chile** are loved! The city is known as the "Hot Air Ballooning Capital of the World" – more than 500 hot air balloons will take flight in October during the **53rd International Balloon Fiesta**! Albuquerque is also the home of the **Sandia Mountains**, meaning "watermelon" in Spanish because the mountains turn a watermelon pink color at sunset. Albuquerque is a city of rich history and culture; Albuquerque has more than a dozen museums, an Old Town area featuring more than 150 shops, restaurants and galleries, and a nostalgic stretch of **Route 66** that combines old and new for an exciting visitor experience. Many **films and TV shows** have been filmed in the city, including but not limited to *Breaking Bad*, *The Avengers*, *Transformers*, *Better Call Saul*, and Season 4 of *Stranger Things*.

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 programs from the Mountain West region attend and participate in MWSOT-related events and meetings: University of Arizona, Colorado State University, University of Colorado, Idaho State University, University of Nevada, University of New Mexico, University of Utah, Utah State University, and University of Wyoming.

University of New Mexico

It is an honor and pleasure for the **University of New Mexico (UNM) College of Pharmacy** to host the **43rd Annual Meeting of the Mountain West Society of Toxicology** featuring **"Addressing Health Impacts of Complex Exposures in a Changing Environment"**. At the UNM College of Pharmacy, undergraduate students, pharmacy (PharmD) students, and graduate (MS and PhD) students engage in exceptional opportunities in toxicology research to learn the art of scientific inquiry and discovery. The mission of the Department of Pharmaceutical Sciences is to advance pharmaceutical sciences through research and the education and training of our professional, graduate, and post-graduate students. The aims of the College of Pharmacy research projects are to develop cures and better treatments for cancers, to find better ways for vaccine delivery worldwide, to help babies exposed to alcohol before birth, to develop better treatments for infectious diseases, to prevent heart disease and heart failure, and to combat the effects of air pollutants, microplastics, pesticides, wildfire smoke, and heavy metals on our bodies.

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.

HISTORY

History of Mountain West Regional Chapter of the Society of Toxicology

The Birth of MWSOT

Michael R. Franklin, *PhD*, University of Utah

So where were you in 1982? Ronald Reagan is 71 and has been President for one year, the UK and Argentina are skirmishing over the Falkland Islands, Italy wins the Soccer World Cup in Spain, Michael Jackson sells over 20 million "Thriller" albums, and the first permanently implanted artificial heart is transplanted into a human in Salt Lake City. Unperturbed by all this other activity, an initiative to form a regional organization for anyone interested in the broadly defined field of toxicology was quietly gaining momentum. This initiative was largely spearheaded by the faculty, particularly Drs. Raghubir Sharma and Joseph Street, in the Toxicology degree program at Utah State University. A letter circulated in the region yielded over 100 expressions of interest; a number sufficient to indicate a viable organization could be formed. To put that number into perspective, the joint meeting of two national societies, ASPET and SOT that year listed just eight times that number of abstracts (816). The "Intermountain Society of Toxicology" was proposed and an initial slate of officers, in reality a steering committee, was proposed, circulated, and voted on. Perhaps surprising given the current boundaries and major sources of MWSOT members, these "officers" hailed from just two states, Idaho and Utah. They were from Moscow (Dr. Robert Krieger-VP [and future (1986) SOT Education Awardee]), Pocatello (Dr. Garland Garner – Councilor), Logan (Dr. Raghu Sharma, VP-Elect; Dr. Lynn James, Secretary-treasurer; Jeffery Hincks – student representative) and Salt Lake City (Dr. Michael Franklin, President; Dr. Bryan Finkle – Councilor; Patrick Iversen – student representative). Among the first orders of business was changing the name to a more encompassing "Mountain West Association of Toxicologists", the writing of By-Laws, organizing a meeting and soon thereafter, applying to become a regional chapter of SOT. In October of 1982, the fledgling organization hosted SOT President (and 1972 SOT Achievement Award Winner) Dr. Robert Dixon at Utah State University for an inaugural address and received an encouraging "go for regional status" recommendation.

The organization became an official Regional Chapter (its birthday?) in a letter signed by Dr. James Gibson on March 28th, 1984, the president of SOT at the time. By then, the organization had had its first annual meeting (October 28, 1983) held at the University of Utah. Membership listed at that time (numbers obtained from the payment of the princely sum of $4) totaled 68, with the majority resident in Utah, but with 8 from Washington, 8 from Idaho, 3 from Oregon, 3 from New Mexico and a lonely 1 from Arizona. By the time of the 2nd annual meeting, where, following the success of a Northwest Regional American Chemical Society "Molecular Toxicology" symposium in June, the Palouse region (Pullman-Moscow) was being considered a venue, formation of a Pacific Northwest regional chapter of SOT was forcing reevaluation of the geographical area to be served by the MWSOT and the viability of the chapter. Consequently, the 2nd annual meeting was held at Utah State University hosted by Dr. Lynn James. Meanwhile, steering committee discussions were resulting in significant expressions of interest in being part of a Mountain West chapter from toxicologists in Arizona, New Mexico, and Colorado. This interest provided a degree of reassurance of the viability of a geographically-challenged organization (to this day MWSOT covers the greatest amount of real estate of any regional chapter), and the center of gravity of MWSOT shifted towards the Four Corners area. In the Spring of 1985, the SOT Annual Meeting was held in Salt Lake City and MWSOT was able to hold a special "satellite" meeting, that included presentations from Dr. Philip Watanabe (a former Utah State University Graduate and 1980 SOT Achievement Awardee) and Dr. Jerry Hook (SOT President in 1987-8). At that time Dr. Raghu Sharma, Dr. Phil Watanabe's graduate student mentor, was serving as MWSOT president. Dr. Rogene Henderson as its Vice President and

Dr. Wesley Clayton as its Vice-President-elect. From this lineup started the rotating annual meeting system we are familiar with today. The 1985 meeting was held in Albuquerque and the 1986 meeting in Tucson. By the 5th annual meeting, Colorado toxicologists were heavily committed to the MWSOT and the 1987 meeting was held in Boulder. Abstract numbers had steadily risen from 22 to 26 for the 1st and 2nd annual meetings to 45 and 60 respectively at the 4th and 5th. From this it was evident that the formative first five years had produced a firm foundation for MWSOT, and the organization as well as the geographical boundary and the camaraderie, has endured to this day. As the founding MWSOT toxicologists fade (or have faded) into the admittedly awesome sunsets we have in the Mountain West, it might be instructive for younger generations to contemplate MWSOT's humble beginnings and how "mighty oaks from little acorns grow."

The above was assembled over 25 years later from the saved documents of the MWSOT Founding "packrat" President, Mike Franklin, with his apologies to any who have been slighted by his absence of total recall, or his inadequate collection of memorabilia.

****Thank you, Mike! From MWSOT!!!****

Years	MWSOT President
1982-85	Michael Franklin
1985-86	Rogene Henderson
1986-87	(John) Wesley Clayton
1987-88	Lynn James
1988-89	Janet Benson
1989-90	Dean Carter
1990-91	William Hadley
1991-92	James (Jim) Halpert
1992-93	David Ross
1993-94	Steven Aust
1994-95	Alan Dahl
1995-96	Daniel Liebler
1996-97	Ruth Billings
1997-98	Garold Yost
1998-99	Craig Marcus
1999-00	Patricia Hoyer
2000-01	Dennis Petersen
2001-02	Anne Aust
2002-03	Mary Walker
2003-04	Clark Lantz
2004-05	Linda Quattrochi
2005-06	Christopher Reilly
2006-07	Matthew Campen
2007-08	Richard Vaillancourt
2008-09	Vasilis Vasiliou
2009-10	Philip Moos
2010-11	Matthew Reed
2011-12	Donna Zhang
2012-13	Cynthia Ju
2013-14	Greg Lamb
2014-15	Todd Thompson
2015-16	Yin Chen
2016-17	Jared Brown
2017-18	Cassandra Rice
2018-19	Debra MacKenzie
2019-20	Ting Wang
2020-21	Ronald Tjalkens
2021-22	Mirella Meyer-Ficca
2022-23	Alicia Bolt
2023-24	Aikseng Ooi
2024-25	Kristofer Fritz
2025-26	Alessandro Venosa

2025 MWSOT LEGACY AWARD

It is our honor and pleasure to announce that the **2025 Mountain West Society of Toxicology Legacy Award** is awarded to **Dr. William H. Hadley**.

Dr. William (Bill) Hadley, the seventh President of the Mountain West Society of Toxicology (1990–1991), has dedicated his career to advancing toxicology in the Mountain West. He earned his Bachelor of Science in Pharmacy, followed by a Master's and PhD in Pharmacology/Toxicology from Purdue University.

In 1972, Dr. Hadley joined the University of New Mexico College of Pharmacy, where he rose through the academic ranks from Assistant to Full Professor. Over the course of his career, he became a tireless advocate for toxicology, fostering collaborations both within UNM and with the Inhalation Toxicology Research Institute (later the Lovelace Respiratory Research Institute). His research contributions were wide-ranging and impactful, with significant scholarly work in inhalation toxicology and metals toxicology.

Beyond his scientific achievements, Dr. Hadley was deeply committed to toxicology education and mentorship, inspiring countless students and colleagues throughout his career. His leadership, scholarship, and dedication helped establish and strengthen the toxicology community across the region.

The MWSOT recognizes Dr. William M. Hadley with the inaugural MWSOT Legacy Award as an outstanding supporter to the field of toxicology in the Mountain West for his exceptional contributions in toxicology education, research, and mentorship.

KEYNOTE SPEAKERS

COLLEGE OF PHARMACY

MW SOT

43RD ANNUAL MEETING OF MOUNTAIN WEST SOCIETY OF TOXICOLOGY
KEYNOTE SPEAKERS

Thursday, August 21 | 9:10 AM – 10:00 AM

Dr. Susan Bailey
Colorado State University
Professor and Radiation Cancer Biologist in Department of Environmental & Radiological Health Sciences

"Twins, Telomeres & Tourists – in SPACE!"

Friday, August 22 | 9:00 AM – 9:50 AM

Dr. Jared Brown
University of Colorado Anschutz Medical Campus
Professor in Department of Pharmaceutical Sciences, Toxicology Graduate Program Director

"Chronic Kidney Disease of Unknown Etiology: A Hidden Epidemic Driven by Multifactorial Occupational and Environmental Risk Factors"

KEYNOTE SPEAKERS

Thursday, August 21 | 9:10 AM – 10:00 AM

Dr. Susan Bailey

Colorado State University

Professor of Radiation and Cancer Biology in Department of Environmental & Radiological Health Sciences

"Twins, Telomeres & Tourists – in SPACE!"

NASA's first One Year Mission presented unique research opportunities for evaluating human health effects of long-duration spaceflight. Quite fortuitously, the astronaut selected for the One Year Mission, Scott Kelly, had an identical twin brother, Mark Kelly, also an astronaut and former Navy test pilot. Thus, the Twins Study was conceived – identical twin sons of similar nature and nurture, one spending a year in space onboard the International Space Station (ISS), while the other remained on Earth – and the most comprehensive study of the response of the human body to spaceflight ever conducted began. The Twins Study represented many firsts for the space program, including pioneering "multi-omics" investigations, and the first assessments of a biological marker of aging – telomeres.

Our investigations involved assessing telomere length dynamics (changes over time) and intimately related DNA damage responses (DDRs) in the twin astronauts, as well as in a cohort of 10 unrelated astronauts and their age/sex-matched ground controls. Most striking was the finding of significantly longer telomeres during spaceflight, irrespective of means of measurement or mission duration. Also unexpected was that telomere length shortened rapidly upon return to earth for all crewmembers. Of particular relevance to long-term health and aging trajectories, astronauts in general had many more short telomeres after spaceflight than they did before. Consistent with chronic exposure to the complex space radiation environment, signatures of persistent DDRs were also detected during and after spaceflight, which included telomeric and chromosomal DNA damage, as well as mitochondrial and oxidative stress. Additionally, radiation dose-dependent decreases in white blood cell counts post-spaceflight were observed. Together, findings provide mechanistic insight related to chronic space radiation exposure, and reveal differences in individual responses that have important implications for those on Earth, as well. Indeed, as the number and diversity of space travelers, and even space tourists, increases in the coming years, a better understanding of how spaceflight affects human health is essential to maintaining astronaut performance and health during, and improving disease and aging trajectories following, future long-duration exploration missions to the moon and beyond.

COLLEGE OF PHARMACY

MW SOT Mountain West Regional Chapter of the Society of Toxicology

KEYNOTE SPEAKERS

Friday, August 22 | 9:00 AM – 9:50 AM

Dr. Jared Brown

University of Colorado Anschutz Medical Campus

Professor in Department of Pharmaceutical Sciences, Toxicology Graduate Program Director, T32 Training Program in Molecular and Systems Toxicology Director, Colorado Center for Nanomedicine and Nanosafety Co-Director

"Chronic Kidney Disease of Unknown Etiology: A Hidden Epidemic Driven by Multifactorial Occupational and Environmental Risk Factors"

Chronic Kidney Disease (CKD) is a global health problem which has been increasing and is estimated to be the 5th leading cause of death worldwide by 2040. While diabetes and hypertension are common causes of end stage kidney disease (ESKD), in recent years epidemics of CKD of unknown etiologies (CKDu) have been identified in various agricultural communities around the world. One of the hardest hit regions is the Pacific Coast of Central America, where high frequencies of ESKD as a cause of death have been reported leading to 20,000 deaths or more. While minimal research explores the occurrence of CKDu in the United States, it may be more prevalent than recognized and has been documented in areas of the Southwest. Affected individuals are usually young men working manually outside. Subjects typically present with asymptomatic elevation in serum creatinine with minimal proteinuria, and progress over several years to ESKD. Biopsies consistently show chronic interstitial nephritis, often with glomerulosclerosis. Dialysis is often not available, resulting in early death. This has led to international efforts to identify the cause of this disease which continues to increase in prevalence. This presentation will discuss our current knowledge on the etiology of CKDu with a focus on environmental factors that contribute to disease. I will discuss our current research which supports the hypothesis that silica exposure from agricultural practices contributes to development of CKDu.

ORAL PRESENTATIONS

Abstract	Time	Presenter	Title	Institution
1	Thursday, Aug 21 10:10 – 10:30 AM	Rama Gullapalli, MD, PhD	Environmental Pollutant Effects on Liver Pathophysiology: Leveraging Novel Optical Imaging Techniques and Approaches	University of New Mexico
2	Thursday, Aug 21 10:30 – 10:50 AM	Alessandro Venosa, PhD	Decoding Lung Cell Behavior with Spatial Transcriptomics	University of California, Davis
3	Thursday, Aug 21 10:50 – 11:10 AM	Laurissa Barela	Quantitative Analysis and Identification of Micro- and Nanoplastics in the Hemisphere of a Human Brain	University of New Mexico
4	Thursday, Aug 21 11:15 – 11:35 AM	Charlotte McVeigh	Longitudinal Study of Bone Marrow Adipocytes Throughout Tungsten-Enhanced Breast Cancer Metastasis	University of New Mexico
5	Thursday, Aug 21 11:35 – 11:55 AM	Aidan Briggs	Intranasal Infection with Western Equine Encephalitis Virus Induces Dynamic Temporal Gliosis and Progressive Neurodegeneration in the Hippocampus of C57Bl/6 Mice	Colorado State University
6	Thursday, Aug 21 11:55 – 12:15 PM	Gabriel P. López, PhD	Point-of-Use Technologies for Environmental Detection of Heavy Metals on Tribal Lands	University of New Mexico
7	Thursday, Aug 21 1:30 – 1:50 PM	Jorge Gonzalez-Estrella, PhD	Understanding Mechanisms of Microplastic Generation and Chemical Transformation from Thermal Oxidation, Ultraviolet Radiation, and Mechanical Abrasion	Oklahoma State University
8	Thursday, Aug 21 1:50 – 2:10 PM	Xiang Xue, PhD	Environmental Microplastics Promote Colon Tumorigenesis via Piezo1-Ca^{2+}-ROS Signaling and Hypoxia-Induced Metastatic Pathways	University of New Mexico
9	Thursday, Aug 21 2:10 – 2:30 PM	Michaela Hvizdak	*Per-* and Polyfluoroalkyl Substances Inhibit Human Neonatal Cytochrome P450 CYP3A7 Retinoic Acid Hydroxylase Activity	University of Colorado Anschutz Medical Campus
10	Thursday, Aug 21 2:35 – 2:55 PM	Emily Mitchem	Deacetylation of SOD3 by Sirtuins Restores Furin Cleavage	University of Colorado Anschutz Medical Campus

Abstract	Time	Presenter	Title	Institution
11	Thursday, Aug 21 2:55 – 3:15 PM	Brenna Baird	The Impacts of a Western Diet and Healthy Fatty Acids on Wildfire Smoke-Induced Neuroinflammation	University of New Mexico
12	Thursday, Aug 21 3:15 – 3:35 PM	Katie Zychowski, PhD	Wildfire-Induced Immunological Dysfunction and the Role of Ovarian Hormone Signaling	University of New Mexico
13	Thursday, Aug 21 3:45 – 4:05 PM	Adam J. Schuller, PhD	Astrocytic STING Signaling is Context-Dependent Across Environmental Insults	Colorado State University
14	Thursday, Aug 21 4:05 – 4:25 PM	Rahul Kumar	Chronic Low-Dose Exposures of Cadmium and Hyperglycemia Drive Dysfunctional Hepatic Mitochondrial Biogenesis and Dynamics	University of New Mexico
15	Thursday, Aug 21 4:25 – 4:45 PM	Julie Moreno, PhD	Pathological and Biomarker Profiles in Aging Dogs with Cognitive Decline	Colorado State University
16	Thursday, Aug 21 4:50 – 5:10 PM	Sean Boland	Aging-Associated Glial Activation and Blood-Brain-Barrier (BBB) Degradation in Canine Cognitive Decline Syndrome (CCDS)	Colorado State University
17	Thursday, Aug 21 5:10 – 5:30 PM	Matthew Gibb, PhD	Mast Cells Are Critical Initiators of Acute Pulmonary Inflammation from Chemical and Environmental Toxicants	University of Colorado Anschutz Medical Campus
18	Friday, Aug 22 10:00 – 10:20 AM	José Cerrato, PhD	Metals and Climate Health: Lessons Learned about Community Engagement	University of New Mexico
19	Friday, Aug 22 10:20 – 10:40 AM	Esther Erdei, PhD	How Can Immunotoxicology Research Support Community-Based Environmental Health Studies?	University of New Mexico
20	Friday, Aug 22 10:50 – 11:10 AM	Kathy James, PhD	The Association Between Chronic Drought Conditions and Metals Exposure in Drinking Water in the San Luis Valley, Colorado	University of Colorado Anschutz Medical Campus
21	Friday, Aug 22 11:10 – 11:30 AM	Zelieann Craig, PhD	Impact of Human-Relevant Di-n-Butyl Phthalate Exposure on Ovulation, Fertilization, and Early Embryo Development in a Mouse Model	University of Arizona

ORAL PRESENTATION ABSTRACTS

1. **Environmental Pollutant Effects on Liver Pathophysiology: Leveraging Novel Optical Imaging Techniques and Approaches**

Thursday, August 21 | 10:10 – 10:30 AM

Rama R. Gullapalli[1,2,3], Rahul Kumar[1,2], Ashwin Chinala[1,2], Eliane El Hayek[4], Marcus A. Garcia[4], Matthew J. Campen[4]

[1]Department of Pathology, [2]Department of Biomedical Engineering, [3]Centre for Metals in Biology and Medicine, [4]Department of Pharmaceutical Sciences University of New Mexico, Albuquerque, NM, 87131

Metabolic (Dysfunction) Associated Fatty Liver Disease (MAFLD) is an emerging liver disease of global concern. MAFLD is implicated in the rapidly rising trend of hepatic morbidity and mortality across the globe. Chronic liver disease (CLD; including MAFLD) rates are highest in the southwestern United States, including in the state of New Mexico (NM). NM has the highest rate of CLD in the US (36.4/100,000 in 2022), mainly among Hispanic and Native American populations. We hypothesize environmental exposures (e.g., chemical pollutants, heavy metals and plastic pollution) can accelerate hepatic metabolic dysfunction in conjunction with established risk factors like type II diabetes and obesity. Our lab is currently developing an array of optical imaging techniques to understand the effects of toxicological pollutants such as heavy metals and nano- and microplastic (NMP) pollution. Our initial optical technique study established the use of a high-throughput optical imaging platform, Cellomics CX7 (ThermoFisher, Waltham, MA), to quantitatively measure reactive oxygen species (ROS) levels in human liver cell models. Cellular ROS levels were quantitated in Cd exposed cells using the high-throughput Cellomics platform using superoxide relevant dihydroethidium (DHE) labeling. In a second optical technique project, we evaluated nano- and microplastic (NMP) uptake in decedent human liver tissues for the first time using polarized light approaches in brain, liver and kidney tissues. This novel optical approach was titled polarization wave microscopy (PWM). Subsequently, we have extended this optical imaging technique by studying an additional thirty-two human liver samples (M=19; F=13) to determine the NMP accumulative patterns in New Mexican residents. In addition to polarization wave microscopy (PWM), we conducted detailed histopathological analyses delineating the NMP cellular distribution patterns in the hepatic tissue architecture. Additional orthogonal assessment using pyrolysis-gas chromatography-mass spectrometry, multi-spectral fluorescence and transmission electron microscopy (TEM) and scanning electron microscopy (SEM) imaging approaches were used to confirm the refractile bodies detected using PWM imaging. We are currently developing newer optical imaging-based techniques such as fluorescence lifetime imaging microscopy (FLIM) and confocal Raman spectroscopy. Preferential accumulation of NMPs in steatotic hepatic cells is a finding of major concern in light of the rapidly increasing global incidence of hepatic fatty liver diseases. Many of our findings were enabled by establishing novel optical techniques in the lab, highlighting the usefulness of light-based approaches to understand toxicological impacts of pollutants in the liver. Our studies underscore the need to develop novel imaging techniques to understand and characterize the precise biological effects of environmental pollutants in the human liver tissues. Novel approaches are needed to understand the role of chronic pollutants as emerging environmental risk factors driving global chronic liver dysfunction patterns observed among humans.

2. Decoding Lung Cell Behavior with Spatial Transcriptomics

Thursday, August 21 | 10:30 – 10:50 AM

Alessandro Venosa[1], Qiuming Wang[1], Claire Montgomery[1]
[1]University of California, Davis

Genetic mutations, environmental and occupation exposure, and aging represent co-factors influencing pulmonary function and disease onset and progression. The heterogenous nature of the injury phenotype warrants further examination. We therefore utilized spatial transcriptomics and proteomics technologies to examine the distribution of cellular activation in models of aging, acute exposure, fibrosis, and cancer. To study genetic predisposition in aging and fibrosis, we developed a murine line expressing the disease-linked isoleucine to threonine missense mutation at position 73 [I73T] in the alveolar type-2 cell-restricted Surfactant Protein-C [SP-C] gene [SFTPC]. In parallel, we utilized SP-C mutant mice to model acute exposure to the ubiquitous air pollutant ozone (O_3), which is known to produce immediate, reversible, and spatially heterogeneous epithelial damage and myeloid dominant inflammation in the lung. Using the GeoMx spatial sequencer we show spatial distribution of cellular senescence in the aging lung, with epithelial cells in the peri-injured regions driving signals related to histone and chromatin remodeling and p21 expression. This technology applied to examination of kinase activity show O_3 signals, regardless of the sampling region. In the context of SP-C mutant driven fibrosis, we found that Cd68+ macrophages found in the remodeled lung display a globally hypoactive transcriptional profile. This heterogenous response was also seen in the tumor center of lung adenocarcinomas, compared to the outer boundaries of the mass. Cell annotation also revealed a reduced cellular diversity in the interior of large tumors. While further phenotypic characterization is necessary, this work highlights heterogeneity in the cellular activity across the spectrum of lung injury, which may be key in the development of effective therapies for at-risk populations.

3. **Quantitative Analysis and Identification of Micro- and Nanoplastics in the Hemisphere of a Human Brain**

Thursday, August 21 | 10:50 – 11:10 AM

Laurissa Barela[1], Emily Phan[1], Aerlin Decker[1], Rui Liu[1], Eliane El Hayek[1], Josiah Kingston[1], Barry Bleske[2], Natalie Adolphi[4], Daniel F Gallego[4], Rama R. Gullapalli[3], Matthew J. Campen[1], Marcus A. Garcia[1]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of New Mexico Health Sciences; [2]Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico Health Sciences, Albuquerque, NM, USA; [3]Department of Pathology, University Of New Mexico Health Sciences, Albuquerque, NM, USA; [4]Office of the Medical Investigator, University of New Mexico, Albuquerque, NM, USA

The ubiquitous presence of micro- and nanoplastics (MNPs) brings concern for environmental and human health conditions. While MNPs have been observed and categorized throughout the body, no studies have successfully mapped and quantified the specific accumulation and distribution of MNPs within singular organs. This study focuses on MNPs found in the human brain, specifically the right cerebral hemisphere's white and grey matter. This area includes the olfactory, optic, cranial nerves, cerebral artery, corpus colosseum, basal ganglia, hippocampus, occipital cortex, medulla, pons, cerebellum, and brainstem. For analysis, autopsy samples were obtained in 2024 from the Office of the Medical Investigator in Albuquerque, New Mexico. Using a digestion protocol and Pyrolysis Gas Chromatography/Mass Spectrometry (Py-GC/MS), results showed the highest average concentration of MNPs in the white matter (WM) (3605 ug/g). In contrast, the grey matter (GM) (1,485ug/g), arteries, and nerves (2,501ug/g) showed a significantly lower concentration. Of the 12 polymers screened for, polyethylene (PE) showed the highest prevalence (WM:1178ug/g, GM:512ug/g), followed by polypropylene (PP) (WM:1079ug/g, GM:344ug/g) polyethylene terephthalate (PET) (WM:225ug/g, GM:86ug/g), and polyvinyl chloride (PVC) (WM:216ug/g, GM:87ug/g), in the basilar artery (PE: 2111µg/g, PP: 781.37µg/g), pituitary (PE: 44.54ug/g, PP: 56µg/g), and cranial nerves (PE: 2413ug/g, PP: 290ug/g).

These findings highlight the potential implications of MNP accumulation on brain function and overall health. By enhancing the detection sensitivity for 12 distinct polymers in brain tissue, this research contributes to a more comprehensive understanding and map of MNP accumulation on brain function and overall health. As we further investigate MNPs in other organs, such research could reveal critical links between MNP accumulation and specific diseases. Additionally, it opens up new avenues for exploring environmental and health policies to mitigate the effects of MNPs on human health. Future studies may examine correlations between MNP buildup and disease, helping to uncover possible connections between plastic accumulation and a wide range of health conditions.

4. **Longitudinal Study of Bone Marrow Adipocytes Throughout Tungsten-Enhanced Breast Cancer Metastasis**

Thursday, August 21 | 11:15 – 11:35 AM

Charlotte M. McVeigh[1], Jennifer A. Tjung[1], Jorge L. Moreno[1], Sydnee J. Yazzie[1], Lauren K. Heine[1], Grace A. Picha[1], Serena C. Helewicz[1], Guy W. Herbert[1], Sebastian Medina[1] and Alicia M. Bolt[1]

[1]The University of New Mexico, College of Pharmacy, Department of Pharmaceutical Sciences, Albuquerque, NM 87131; [2]The University of New Mexico, Department of Pathology, Albuquerque, NM 87131

Background and Purpose: Tungsten is classified as an emerging environmental toxicant due to increased human exposure and lack of knowledge of the health risks. Epidemiological and in vivo studies demonstrate that exposure to tungsten contributes to the carcinogenic process, but the molecular mechanisms remain unclear. Due to a cohort of breast cancer patients accidentally exposed to tungsten during intraoperative radiotherapy, our lab is investigating the effects of tungsten exposure on breast cancer progression and metastasis. Tungsten is known to accumulate in the bone, creating a site for long-term exposure and toxicity. Breast cancer is also known to metastasize to the bone. Previous research in our lab has shown that in multiple triple-negative breast cancer orthotopic models, tungsten enhances breast cancer metastasis to the bone using in vivo imaging of bioluminescent-tagged cancer cells. These findings suggest that tungsten 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 that drive tumor cells homing, colonization, and growth by changing the microenvironment. Research also suggests that breast cancer cells arrive in the bone in as little as 10 days in murine models, starting the colonization and remodeling process. Triple-negative breast cancer is a devastating disease, known for being aggressive and highly metastatic. Understanding weekly changes throughout metastasis in bone marrow adipocytes is critical to uncover cytokines that could be driving colonization and proliferation of tumor cells in the bone niche following tungsten exposure. We aim to understand the changes in bone marrow adipocytes throughout the metastatic process to inform the effect tungsten plays in changing these adipocytes, to enhance breast cancer metastasis to the bone.

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

Results: Comparisons will be drawn between time points and orthotopic models to understand differences in adipocyte populations in the bone niche throughout metastatic progression in response to tungsten exposure. While both models have increased metastasis to the bone following tungsten exposure, the 4T1 model induces greater systemic inflammation compared to the E0771-Luc model. We will quantify the number of Plin1+ adipocytes within the bone marrow throughout metastatic progression to see how the population numbers change. Analysis of secreted adipokines/cytokines from MSCs and adipocytes will inform which ones may be playing a role in metastatic progression by week in response to tungsten exposure.

Conclusions: This study will provide critical information on the molecular effects of tungsten exposure that occur throughout metastatic progression in the bone. Understanding adipokine/cytokine expression and their influence on the bone microenvironment will help narrow down possible key players that tungsten influences. These insights could prove to be valuable in better elucidating how tungsten targets the bone niche to drive breast cancer metastasis.

5. **Intranasal Infection with Western Equine Encephalitis Virus Induces Dynamic Temporal Gliosis and Progressive Neurodegeneration in the Hippocampus of C57BL/6 Mice**

Thursday, August 21 | 11:35 – 11:55 AM

Aidan Briggs[1], Adam Schuller[1], Omar Yanouri[1], Savannah Rocha[1], Abigail Bibb[1], Megan Hager[1], and Ronald Tjalkens[1]

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Arboviruses, including encephalitic alphaviruses such as Western equine encephalitis virus (WEEV), are increasingly emerging in human and animal populations as a result of climate change-induced warmer temperatures and increased rainfall. This expansion of mosquito-occupied territories has increased infectious risk for previously invulnerable groups and presents the possibility for large-scale outbreaks capable of drastically altering the health of these populations. Encephalitic alphaviruses have been characterized to possess neurotropic capacity, associated with longitudinal central nervous system dysfunction. Following viral-induced encephalitis, lingering effects such as chronic neuroinflammation and glial-mediated immune modulation are strongly correlated with the onset and progression of neurodegenerative disorders, including Parkinson's disease and related dementias. These age-related conditions are well characterized in their hallmark features of neuronal loss and protein aggregation; however, the temporal involvement of glial subpopulations in viral-induced inflammatory signaling and subsequent neurodegeneration remain elusive, especially in the context of brain regions involved in learning and memory. Our lab has previously demonstrated that sub-lethal WEEV infection is sufficient to elicit a robust astrocyte-mediated complement response associated with gait aberrancies, dopaminergic neurodegeneration, and pathologic protein aggregation in the substantia nigra of outbred CD-1 mice and wild-type, inbred C57Bl/6 mice. This is associated with the capacity for persistence of viral replication in the brain parenchyma, including within the hippocampus, long after peripheral clearance. Together, these data motivated the longitudinal assessment of hippocampal glial dynamics and neurodegeneration following WEEV infection. Eight-week-old C57Bl/6 mice were intranasally administered 20 µL of 1×10^4 PFU/mL McMillan WEEV under anesthesia. Mice were subsequently sacrificed at one-, two-, four-, and eight-week timepoints (n = 6-10 mice/timepoint/group). Hippocampal sections were labeled using automated multiplex immunofluorescence, high-content batch scanned, and objectively quantified via deep learning-based analysis pipelines trained to at least 100,000 iterations across the extent of the dataset. A substantial increase in % $GFAP^+$ area was observed 1 week post infection (WPI) in the dentate gyrus (DG) and CA1 hippocampal subregion, which resolved in the DG by 4 WPI, but progressively increased in the CA1, CA2, and CA3 regions over the remaining timepoints. Slight elevation in the density of $IBA1^+$ cells/mm^2 in the CA1, CA2, CA3, and DG were initially observed 1WPI, but peaked at 2WPI. Interestingly, this suggests a similar trend of viral-induced microgliosis subsequent to initial astrocyte activation, reflecting the pattern of cellular reactivity observed in the basal midbrain. Additionally, a significant interaction effect accounting for time and infection status was evidenced by progressive decrease in the number of $NeuN^+$ cells/mm^2 in the CA1 region. We further applied spatial phenomics to integrate the complex temporal relationship between glial and neuronal cell number, morphology, infection status, and location, to assess for disease-associated states in infected animals compared to controls. Together, these data highlight the dynamic nature of gliosis and progressive neurodegeneration following WEEV infection in the hippocampus. Future work will aim to investigate the significance of these histologic changes on cognition and executive function and examine the effects of modulating glial inflammatory signaling on the progression of this pathologic sequelae.

6. Point-of-Use Technologies for Environmental Detection of Heavy Metals on Tribal Lands

Thursday, August 21 | 11:55 – 12:15 PM

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Uranium extraction in the United States has left a toxic legacy of heavy metal contamination in water sources on Tribal Nations. Due to the necessity for clean water in traditional communities of the arid Southwest, there is an urgent need for field-deployable technologies that rapidly detect toxicants. Through funding from the National Science Foundation's Using the Rules of Life to Address Societal Challenges program, the University of New Mexico and Navajo Technical University are developing bioinspired approaches to address this critical societal challenge. We provide updates on efforts to (1) compare field-deployable methods with recognized gold-standard laboratory methods, (2) pre-concentrate heavy metals for improving measurements of environmental water samples, and (3) characterize the binding properties of DNA aptamers and proteins that bind to heavy metals. We present our progress on the development of accurate, affordable, and simple-to-use methods for detection of heavy metal contamination through collaboration with environmental personnel of the Pueblo of Laguna.

7. **Understanding Mechanisms of Microplastic Generation and Chemical Transformation from Thermal Oxidation, Ultraviolet Radiation, and Mechanical Abrasion**

Thursday, August 21 | 1:30 – 1:50 PM

Andrea Arredondo-Navarro[1*], Dulce Gallardo-Owens[1], Justin Scott[1], Sabrina Farias[1], Xuewen Wang[1], Wesley Cochran[1], Eliane El Hayek[2], Matteo Minghetti[3], Jose M. Cerrato[4], Jorge Gonzalez-Estrella[1*]

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This study compares the generation of microplastics (MPs) from plastics exposed to oxidation, ultraviolet (UV) radiation, combined with mechanical abrasion – all of them, environmentally relevant weathering processes. Our research has shown that open-pit waste burning contributes to MP generation, yielding chemical fingerprints related to thermal and UV-oxidation. It is well established that mechanical abrasion fragments plastics; however, the combined effects of mechanical abrasion with oxidation processes are not well understood yet. To address this, we selected consumer-derived plastics and exposed them to thermal, UV, and non-oxidative conditions, followed by mechanical abrasion, to evaluate fragmentation rates and functional chemical changes. Attenuated Total Reflectance–Fourier Transform Infrared (ATR-FTIR) analyses spectroscopy indicated that abrasion introduced vinyl/oxidized products in LDPE, EPS, and PP (1000–1300 cm^{-1}); UV and thermal treatments induced carbonyl stretches (~1710 cm^{-1}) in LDPE, PP, and EPS; in contrast, PET was not affected by the thermal treatment, while UV exposure led to a general reduction in the area of its characteristic peaks. Fluorescence microscopy and pyrolysis gas chromatography/mass spectrometry (py-GC-MS) results indicated that UV oxidation with abrasion increased MP generation for LDPE (2.8x by fluorescence, 65x by pyrolysis) and for PP (1.9x and 2.9x, respectively). On the other hand, non-oxidized PS with abrasion yielded higher particle counts (1.5x more than UV treatment and 3.5x more than thermal treatment). Finally, PET showed no significant differences across treatments. These findings underscore the importance of the polymer structure in MP generation and transformation under combined environmental weathering processes.

8. **Environmental Microplastics Promote Colon Tumorigenesis via Piezo1–Ca^{2+}–ROS Signaling and Hypoxia-Induced Metastatic Pathways**

Thursday, August 21 | 1:50 – 2:10 PM

Xiang Xue[1], Lavanya Goodla[1], Eliane Hayek[1], Marcus Garcia[1], Siem Goitom[1], Xiangxiang Wu[1], Tae-Hyung Kim[1], Laura V Gonzalez Bosc[1], Matthew Campen[1]

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Key Words: Microplastics, colorectal cancer, mechanosensing, liver metastasis, hypoxia

Plastic production continues to rise exponentially despite increasing environmental concerns. Recent studies have detected microplastics in human blood, feces, brain, liver, and colon tissues; however, their impact on colon tumorigenesis remains unclear. Given projections that colorectal cancer (CRC) will become the most common cancer globally by 2040, it is critical to investigate novel environmental risk factors such as microplastic exposure. In this study, we explored whether microplastics promote CRC progression. Analysis of human colon tumor samples revealed polyethylene as the most abundant microplastic. In murine MC38 colon cancer cells, treatment with polystyrene microplastics (1 and 5 μm) and ocean-derived microplastics significantly increased reactive oxygen species (ROS) production. Liver metastases from microplastic-treated MC38 cells exhibited elevated oxidative stress, increased hypoxia-inducible factors (HIF-1α, HIF-2α, HIF-3α), and upregulation of mesenchymal markers ZEB2 and Vimentin. In vitro, microplastic exposure disrupted mitochondrial membrane potential and enhanced pro-metastatic signaling. Mechanistic studies using atomic force microscopy revealed activation of a PIEZO1–Ca^{2+}–ROS axis by microplastics, suggesting a role for mechanotransduction in CRC progression. Pharmacologic inhibition of HIFs (Acriflavin) and MMP9 (Minocycline) suppressed microplastic-induced signaling and metastasis. Antioxidants Carnosine and Tempol also reversed oxidative damage and key molecular changes. These findings uncover a previously unrecognized link between environmental microplastic exposure and colon tumor progression and highlight oxidative stress and mechanosensitive pathways as key mediators. This work underscores the importance of addressing environmental pollutants in cancer prevention strategies.

9. *Per-* and Polyfluoroalkyl Substances Inhibit Human Neonatal Cytochrome P450 CYP3A7 Retinoic Acid Hydroxylase Activity

Thursday, August 21 | 2:10 – 2:30 PM

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Craniofacial abnormalities account for nearly one-third of all congenital defects[1]. Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) has been associated with significant birth defects, including craniofacial abnormalities, in both humans and laboratory animals[2-3]. PFAS structurally resemble the native short-chain fatty acid substrates of cytochrome P450 (CYP) enzymes involved in maintaining homeostasis during development. A major pathway involved in regulating formation of the head and face surrounds retinoic acid signaling and metabolism in chordates. The Vitamin A1 derivative and morphogen, all-*trans*-retinoic acid (*at*RA), regulates over 500 target genes throughout embryogenesis, including those involved in eye development and hindbrain patterning[4-5]. Interference with *at*RA gradients at key points during gestation may lead to adverse downstream phenotypes consistent with that following prenatal PFAS exposure[6]. Human neonatal CYP3A7 is the primary retinoic acid hydroxylase in the fetal liver[7]. We have previously demonstrated the capacity for PFAS to inhibit CYP3A7 metabolism of the steroid, dehydroepiandrosterone-sulfate (DHEA-S), *in vitro*[8]. We hypothesize that PFAS inhibit homeostatic CYP3A7 metabolism of *at*RA, resulting in the adverse downstream phenotypes observed in affected neonates, including craniofacial abnormalities. To test this hypothesis, we screened 14 prominent PFAS for their capacity to inhibit CYP3A7 oxidation of *at*RA at 10 and 100 µM via LC-MS/MS. IC_{50} values were obtained for PFAS inhibiting more than 50% of 4-hydroxy-retinoic acid (4-OH-RA) and 4-oxo-retinoic acid (4-oxo-RA) product formation. Based on our screening data, PFUnDA, PFDA, PFOS, and FHxSA were significant inhibitors of CYP3A7-mediated *at*RA metabolism *in vitro*. Of the PFAS tested, PFUnDA achieved the lowest half-maximal inhibitory concentrations of 20.9 µM (R^2=0.964) and 17.9 µM (R^2=0.964) for the 4-OH and 4-oxo-RA metabolites, respectively. Our findings support a novel mechanism of PFAS teratogenicity on the fetal axis of retinoic acid homeostasis during human development.

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10. Deacetylation of SOD3 by Sirtuins Restores Furin Cleavage

Thursday, August 21 | 2:35 – 2:55 PM

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The environmental toxicant cadmium (Cd) results in oxidative damage through the disruption of redox signaling and the increase in production of reactive oxygen species. Additionally, previous research demonstrates that Cd downregulates the expression and activity of SIRT1 and SIRT3, members of the sirtuin family of lysine deacetylases which control cellular stress resistance. SIRT1 and SIRT3 regulate oxidative stress responses in part through the deacetylation of superoxide dismutase 1 (SOD1) and SOD2, respectively. The extracellular isoform of superoxide dismutase (SOD3) is a critical enzyme in the maintenance of antioxidant status through the scavenging of superoxide radicals. Yet, no reports have described the effect of acetylation on SOD3. SOD3 distribution to the extracellular matrix is determined by the presence of a C-terminal heparin binding domain (HBD). This region can be removed through intracellular proteolytic processing by furin. Here, immunoblotting and mass spectrometry were used to quantify the global and site-specific acetylation of recombinant human SOD3. Acetylation was found to prevent furin cleavage with no impact on SOD3 activity. Importantly, our results reveal that SOD3 is robustly deacetylated by SIRT1 and SIRT3, with moderate activity against K220 and high activity against K211 and K212 in the HBD furin cleavage region. Overall, our findings reveal that sirtuin-directed deacetylation of SOD3 restored furin cleavage, defining a potential means of cadmium disruption of redox signaling and control.

11. The Impacts of a Western Diet and Healthy Fatty Acids on Wildfire Smoke-Induced Neuroinflammation

Thursday, August 21 | 2:55 – 3:15 PM

B. Baird[1], S. Phatak[1], J.L. Moreno[1], E. Barr[1], J. Begay[1], M. Garcia[1], E. Y. Suh[1], G. Herbert[1], S. Lucas[1], S. Noor[1], M. Campen[1]

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Wildfires across the United States have increased significantly over the past four decades.

The resulting smoke poses serious health risks, including cardiovascular, respiratory, and neurological effects. A key neurological consequence is neuroinflammation, which may lead to both acute and long-term outcomes. This study investigates the immune timeline of woodsmoke-induced neuroinflammation and explores dietary factors and therapeutic interventions. These include a total western diet (TWD) and treatment with resolving D1 (RVD1). Young female C57BL/6 mice were exposed to either filtered air or woodsmoke (500 μg/m³ particulate matter) for 4 hours/day on alternate days over 14 days. We examined the brain at 1, and 28 days post-exposure using high-dimensional flow cytometry to assess markers of peripheral immune infiltration (e.g., CD3, CD4, CD8, LFA-1), resident immune cells (CD11b, ACSA-2), and inflammation-related proteins on endothelial cells (CD31, VCAM, ICAM).

The study evaluated the impacts of a "Western diet" which were found to worsen immune cell infiltration and delay inflammation resolution. The Omega-3 fatty acid Resolvin D1 (RVD1) was administered to assess its anti-inflammatory vascular benefits. Results showed a diet- and time-dependent increase in CD4 T cells (CD3+, RORγ−, FOXP3−, CD44+) and macrophages (Cd11b+, CD45hi) that may play a role in resolving neuroinflammation. Immune markers like LFA-1, ICAM, and VCAM peaked one day after the final exposure, indicating a strong role in the adaptive immune response within the brain. The high-fat western diet prolonged this response beyond 28 days, demonstrating unsuccessfully resolved neuroinflammation. RVD1 effectively countered the pro-inflammatory effects of the Western diet and accelerated recovery, shortening the inflammation timeline by two weeks. This result was especially pronounced in reducing TH1/TH2 activation and lowering macrophage populations. Overall, this study highlights the role of peripheral immune cells in central nervous system inflammation following woodsmoke exposure and demonstrates the potential of dietary and fatty acid interventions to mitigate these effects.

12. Wildfire-Induced Immunological Dysfunction and the Role of Ovarian Hormone Signaling

Thursday, August 21 | 3:15 – 3:35 PM

Katie Zychowski[1]
[1]University of New Mexico

Wildfires are an escalating public health concern, driven by climate change-associated increases in heat and aridity. Aging heightens immunological vulnerability to wildfire smoke (WS) in both males and females. However, the concurrent decline in ovarian hormones during aging and menopause has rarely been explored as a mechanistic contributor. Previous work from our group and others has identified bone marrow-derived immune cells as a particularly sensitive microenvironment to acute WS exposure.

In this study, we used two mouse models of human menopause: 1) ovariectomy (OVX) and 2) the ovary-intact vinylcyclohexene diepoxide (VCD) model to investigate the role of ovarian hormone signaling in the immune response to acute WS (4 h/day for 2 days).

Briefly, we found 1) reduced bone marrow–derived immune cell populations following WS exposure in both models compared with filtered air controls, 2) altered cell-specific transcriptomic markers in OVX-WS mice, and 3) metabolic dysfunction with a possible compensatory response to WS in bone marrow-derived macrophages in OVX mice. Furthermore, our preliminary findings have also ruled out GPER (G-coupled estrogen protein receptor) as a mediator of this WS-effect in macrophages. The sum of our findings suggest that ovarian hormones mediate immune dysfunction post-WS that is likely driven by estrogen or progesterone receptors, other than GPER.

13. Astrocytic STING Signaling is Context-Dependent Across Environmental Insults

Thursday, August 21 | 3:45 – 4:05 PM

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Background: Globally, Parkinson's disease (PD) is the fastest growing neurodegenerative disorder, yet this condition remains etiologically idiopathic and incurable. While a majority of work seeking to characterize the molecular underpinnings of PD remains focused on dopaminergic neurons, mounting evidence supports the critical role of glial reactivity in pathogenesis, including at time points preceding the neurodegenerative sequelae. Recently, the cGAS-STING pathway, which modulates innate interferon signal transduction in response to cytosolic dsDNA, has emerged as a potential therapeutic target in the context of age-related degeneration. Still, our understanding of how this molecular sensor contributes to astrogliosis and whether or not this effect is neurotrophic or neurotoxic remains ill-resolved. Here, we sought to interrogate the effects of acute, low-dose toxin exposure on cGAS-STING signaling in primary glial cells and its effect on primary neuronal cells to address this knowledge gap.

Methods: Primary astrocyte-enriched mixed glial cultures were established via isolation of telencephalon, mesencephalon, and diencephalon of murine neonates from both wildtype (C57Bl/6, WT) and STING ablated (Tmem173^{gt}, GT) strains. We first established IC_{50} concentrations of the examined toxicants in this model by conducting dose-response viability screening following 6- and 12-hour exposure to half-log increasing concentrations spanning relevant literature-informed ranges in wildtype glia. We then determined the effects of toxin treatment on the cGAS-STING signaling transduction cascade across timepoints by performing multiplex immunofluorescence labeling, high content slide scanning microscopy, and automated deep learning-based image analysis which allowed us to establish phenomic populations in each toxicologic context. We further confirmed this engagement of the STING pathway by assessing the supernatant of glial cultures for type I interferon, cytokine, or chemokine secretion using Luminex ELISA multiplexing. Given the evidence of STING activation in these contexts, we then explored the effects of genetic STING ablation on glial survival and inflammatory protein secretion mirroring the techniques above. To confirm the relevance of this STING activation or blunting in the context of neurodegeneration, we assessed the ability of glial conditioned media (GCM) from WT and GT mixed glial populations to influence primary neuronal viability.

Results: We report extensive characterization of the lethal concentrations of wildfire smoke (WFS) extract, manganese (Mn), rotenone (ROT), and western equine encephalitis virus (WEEV) at brain-relevant concentrations. This was accompanied by a substantial activation of STING in GFAP$^+$ALDH1L1$^+$ cells as evidenced by relocalization to the golgi and increased phosphorylation. Following Mn, ROT, and WFS exposure, we observed a protective effect of STING abrogation on glial viability; however, in the context of viral infection, we report heightened sensitivity to cytotoxicity in GT cells. STING ablation further curbed toxin-induced p-IRF3$^+$ area/astrocytic nuclear area. These changes in cGAS-STING signal transduction were accompanied by toxin-specific changes in GCM cytokine/chemokine profiles, and differences between WT and GT cells. For WFS and ROT, GCM induced substantial neurotoxicity following 24 hours of treatment which was blunted in GT GCM for ROT and rescued in WFS GT GCM.

Conclusions: Taken together, these data suggest important and distinct roles of cGAS-STING signaling in the activation of astrocytes and secretion of immune modulatory cytokines dependent upon PD-relevant *in vitro* model. This work motivates the subsequent exploration of this cascade *in vivo* given its likely involvement in astrocyte-mediated neuroinflammation and PD-like motor deficits.

14. Chronic Low-Dose Exposures of Cadmium and Hyperglycemia Drive Dysfunctional Hepatic Mitochondrial Biogenesis and Dynamics

Thursday, August 21 | 4:05 – 4:25 PM

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Metabolic (Dysfunction) Associated Fatty Liver Disease (MAFLD) is a major risk factor of long-term hepatic morbidity and mortality across the globe. Chronic liver disease (CLD) rates are rising in southwestern United States, including here in New Mexico (NM). NM has the highest rates of CLD in the US (36.4/100,000 in 2022), mainly among Hispanic and Native American populations, for unknown reasons. Our main hypothesis is that environmental exposures (e.g., heavy metals) accelerate liver dysfunction in conjunction with innate risk factors such as type II diabetes and obesity, which are high in these populations. Cadmium (Cd), an environmentally pernicious heavy metal pollutant, is linked to chronic metabolic disturbances including obesity, type II diabetes, and MAFLD. The specific role of chronic Cd exposures on sustained oxidative hepatic damage and mitochondrial dysfunction is not well understood. In this study, we investigated the effects of chronic low-dose cadmium exposures (CLEC) and hyperglycemia on hepatic oxidative and mitochondrial damage. The CLEC model paradigm uses liver cell lines, HepG2 and HUH7, to study the impacts of chronic Cd exposures (~24 weeks) and hyperglycemia (15 mM) modeling effects seen in the real world. Key metabolic findings in our CLEC exposure modeling study include – i. CLEC models show enhanced sorafenib induced mitotoxicity under galactose condition (glu-gal assay) ii. CLEC exposures induce superoxide radical production with a hyperglycemic amplification effect iii. CLEC exposure altered mitochondrial density with associated mitochondrial dysfunction - characterized by mitochondrial membrane potential ($\Delta\Psi m$) differences, and morphological alterations and iv. dysregulation of intrinsic mitochondrial parameters such as oxygen consumption rates (↓OCR), ↓ ATP production, and unchanged spare respiratory capacity. Chronic cadmium and hyperglycemia exposures lead to transcriptional and translational changes to key antioxidant genes and mitochondrial dynamic related protein expression (Drp1, MFN2, and Tomm20), exacerbating cellular vulnerability. In summary, chronic Cd exposures have the potential to dysregulate the hepatic mitochondrial homeostasis leading to damaged OXPHOS metabolic cycling and disrupted energy metabolism. Dysfunctional energy metabolism is a key hallmark of MAFLD pathogenesis. We also observe significant hyperglycemia dependent, Cd-induced metabolic deregulatory effects. This data supports our primary hypothesis for a heavy pollutant induced *acceleration* of bioenergetic dysfunction among type II diabetics. Our results underscore the urgent need for investigation into the long-term impacts of heavy metal exposures as a key driver of chronic diseases such as MAFLD and diabetes. Finally, our study also underscores the need for focused attention examining effects of heavy metal pollution in “at-risk” subpopulations such type II diabetics and obese individuals who may be at elevated risk for liver damage compared to normal individuals.

15. Pathological and Biomarker Profiles in Aging Dogs with Cognitive Decline

Thursday, August 21 | 4:25 – 4:45 PM

Abdullatif Alsulami[1,2], Sean W. Boland[1,2], Payton Shirley[1,2], Kapahi Kawai Puaa[1,2], Stephanie McGrath[2,3,4], Evan L. MacLean[5], Caitlin Latimer[6], Martin Darvas[6] and Julie A. Moreno[1,2,4]

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Aging is a major risk factor for neurodegenerative diseases such as Alzheimer's disease and related dementias (AD/ADRD). One challenge in this field is the limited availability of accessible models that capture age-related changes observed in humans. Companion dogs, which naturally develop cognitive decline and share environmental risk factors with humans, present a valuable model for studying these conditions. Canine cognitive dysfunction syndrome (CCD) is a progressive neurodegenerative disease in geriatric dogs, with clinical and pathological features that parallel those of AD. We hypothesize that toxic signaling events underlying CCD involve the accumulation of neurotoxic proteins that drive neuroinflammation through activation of both microglial and astroglial responses, and that specific biomarkers—such as neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and amyloid-beta (Aβ) ratios—can serve as early indicators of pathological change before overt cognitive symptoms emerge. We assessed biomarkers relevant to human neurodegeneration to distinguish healthy aging from CCD and compared to neuropathogenesis. Our results show significant associations between age and dementia-related biomarkers, including reduced plasma Aβ1-42/Aβ1-40 ratios and elevated cerebrospinal fluid NfL levels at older ages. Plasma NfL strongly correlated with both age and cognitive decline, as measured by owner-reported CCD surveys, supporting its potential as a non-invasive diagnostic tool when combined with other biomarkers and clinical assessments. These findings reinforce the translational value of CCD in dogs as a model for AD, with implications for developing therapeutic strategies applicable to both canine and human neurodegeneration.

16. Aging-Associated Glial Activation and Blood-Brain-Barrier (BBB) Degradation in Canine Cognitive Decline Syndrome (CCDS)

Thursday, August 21 | 4:50 – 5:10 PM

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As Alzheimer's Disease (AD) prevalence is projected to double by 2050, the urgency for relevant models to study its pathology intensifies. The vast majority of disease etiology is idiopathic and influenced by a myriad of factors including neurotoxic glial activation and BBB degradation, compounded by neuroinflammation and oxidative stress. The common use of transgenic mouse models in AD, though insightful, often fails to capture the idiopathic and progressive nature of human disease, due to the controlled environment and lack of natural aging. Our study uses CCDS as a more translatable model for AD. Canines share environments with humans, naturally age, and develop CCDS, that mirrors human AD, enhancing translatability. We hypothesize that CCDS-afflicted canines will exhibit increased neurotoxic glial activation and BBB degradation. We have assessed glial morphology, neurotoxic activation, and cytokine panels to analyze neuroinflammation in canine brains. Our results show that activated astrocyte and microglial morphologies from CCDS+ groups, align with neurotoxic profiles, with ongoing analyses on BBB integrity.

17. Mast Cells Are Critical Initiators of Acute Pulmonary Inflammation from Chemical and Environmental Toxicants

Thursday, August 21 | 5:10 – 5:30 PM

Matthew Gibb[1], Angela Cruz-Hernandez[1], Alison K. Bauer[2], Jared M. Brown[1]

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The respiratory tract is a primary interface with the external environment and is highly vulnerable to inhaled toxicants. Mast cells (MCs), strategically located throughout the lung, are among the first immune responders to environmental insults. Upon activation, they rapidly degranulate and release a cascade of inflammatory mediators, including cytokines, chemokines, and lipid mediators, contributing to both acute and chronic pulmonary pathology. Multiple studies in our lab have investigated the role of mast cells in mediating lung injury following exposure to three distinct chemical agents: formaldehyde (FA), chloropicrin (CP), and nitrogen mustard (NM).

FA is a ubiquitous industrial and household pollutant known to cause airway hyperresponsiveness and chronic respiratory disease. CP, used as an agricultural fumigant and chemical threat agent, induces acute pulmonary inflammation and edema. NM, a surrogate for sulfur mustard and a vesicating chemical warfare agent, is associated with immune dysregulation and lung injury, relevant to Gulf War Illness.

To assess mast cell involvement, we utilized wild type (C57BL/6) and mast cell-deficient (B6.Cg-Kit$^{W\text{-}sh}$/HNihr-JaeBsm) mice. Mice were exposed to FA (0–300 ppm), CP (0.1–20 mg/kg), or NM (0.125 mg/kg), and lung responses were evaluated via bronchoalveolar lavage (BAL), spectral flow cytometry, histopathology (H&E and immunohistochemistry), and cytokine/lipid mediator profiling. *In vitro* studies using human mast cell lines (HMC-1.2) and murine bone marrow-derived mast cells (BMMCs) were also conducted. To validate findings from the Kit$^{W\text{-}sh}$ model, we additionally employed an alternative mast cell-deficient strain (Cpa3-Cre; Mcl-1$^{fl/fl}$) using chloropicrin exposure, confirming the mast cell-dependent nature of observed lung injury.

Key Findings:

- Formaldehyde exposure in WT mice led to dose-dependent increases in alveolar macrophages, mast cells, and inflammatory cytokines. Histology revealed alveolar septal thickening and increased type II pneumocytes, effects absent in mast cell-deficient mice. In vitro, FA induced mast cell degranulation and cytokine release, which was inhibited by compound 48/80.
- Chloropicrin exposure caused severe alveolar damage, neutrophilic infiltration, and elevated cytokines (IL-6, IL-8, IL-13, IL-17, IL-33) in WT mice. Mast cell-deficient mice showed preserved lung architecture and reduced inflammation.
- Nitrogen mustard exposure did not induce mast cell degranulation but triggered intermediate and late-phase activation, evidenced by a 30-fold increase in COX-2 mRNA and dose-dependent IL-6 production in BMMCs. *In vivo*, WT mice exhibited significant lung injury, elevated BAL protein, and IL-6 levels, all of which were markedly reduced in mast cell-deficient mice.

These findings collectively demonstrate that mast cells are critical mediators of lung inflammation and injury across diverse chemical exposures. Their activation contributes to both early and late-phase immune responses, highlighting their potential as therapeutic targets in chemical-induced pulmonary toxicity.

18. Metals and Climate Health: Lessons Learned about Community Engagement

Friday, August 22 | 10:00 – 10:20 AM

José M. Cerrato[1,2,3]

[1]University of New Mexico, Gerald May Department of Civil, Construction & Environmental Engineering, Albuquerque, NM; [2]University of New Mexico, METALS Superfund Research Center, Albuquerque, NM; [3]University of New Mexico CHANGES Climate Change and Health Center, Albuquerque, NM

Lessons and perspective about community engagement will be shared from the Director of two centers: the UNM METALS Superfund Research Center and the UNM CHANGES Climate Change and Health Center. Dr. Cerrato will emphasize the importance of building trust and the commitment necessary to build long-lasting community partnerships. Challenges and opportunities in understanding how to strengthen community engagement activities to inform risk assessment and reduction strategies will also be discussed.

19. How Can Immunotoxicology Research Support Community-Based Environmental Health Studies?

Friday, August 22 | 10:20 – 10:40 AM

Esther Erdei[1,2]

[1]University of New Mexico Health Sciences Center College of Pharmacy; [2]University of New Mexico Health Sciences Center Office of Research

This presentation will demonstrate the development and application of immunological biomarkers that are helpful to be employed in community-driven, community-engaged research studies examining environmental toxic metals and various other chemical exposures in humans. Both humoral and cellular immune system measures will be described as well as autoimmunity examinations will be presented using representative case studies.

Heavy metals (e.g., uranium, lead, mercury, nickel) and other metallic compounds (e.g., aluminum, barium, tin) as well as their exposure pathways in humans can be better understood using citizen science approaches and direct research support from community leaders and policy makers. All toxicants that are featured in the CERCLA Priority List of Hazardous Substances are commonly found in Tribal communities and their immunological effects are investigated scarcely via national toxicological efforts. Therefore, these communities strongly depend on academic partnerships in order to generate critical environmental health data for their own use and to even begin envisioning their preventative health measures locally. Cases will be shown about suppressed immunological responses as well as hyperreactive, exaggerated immune activations that were developed in bidirectional, trusted Tribal-academic partnerships in the last 16 years under research supported by NIH and carried out at the UNM HSC COP. This presentation will also feature institutional review board (IRB) requirements and guidelines to manage and support these special type of community-engaged scientific endeavors.

20. The Association Between Chronic Drought Conditions and Metals Exposure in Drinking Water in the San Luis Valley, Colorado

Friday, August 22 | 10:50 – 11:10 AM

Kathy James[1]
[1]University of Colorado Anschutz Medical Campus

The San Luis Valley (SLV) of Colorado is a rural, high-altitude region that has experienced aridification through a 23 year chronic drought intensified by climate change. This community engaged project investigates the relationship between prolonged drought and the concentration of naturally occurring toxic metals in drinking water supplies in the SLV. Using historical hydrological and meteorologic to complement a large community engaged effort to sample representative private wells (n=832) for metals concentrations, we assessed trends in arsenic, uranium, tungsten and manganese—and identified major hydrogeological features associated with changes associated with drought. This talk will present our preliminary results, community engaged methods, and next steps for evaluating the toxicological impact on human health. Communities relying on private wells, often unregulated and unmonitored, appear disproportionately affected. These findings underscore the urgent need for integrated drought mitigation and water quality monitoring strategies in arid rural regions.

21. Impact of Human-Relevant Di-n-Butyl Phthalate Exposure on Ovulation, Fertilization, and Early Embryo Development in a Mouse Model

Friday, August 22 | 11:10 – 11:30 AM

Zelieann R Craig[1]

[1]University of Arizona, School of Animal & Comparative Biomedical Sciences, Tucson, AZ, 85721

Phthalates are used in beauty and personal care products, food packaging, medical devices, and the coating of some medications. Many epidemiological studies have reported associations between phthalate burden and human reproductive health outcomes. Women of reproductive age are considered a high exposure/high risk population based on biomonitoring data showing higher phthalate burden, greater use of cosmetics and personal care products, and higher exposures in the occupational setting. Phthalate exposure in women has been associated with reduced egg yield and early pregnancy loss during medically assisted reproduction. Therefore, it is critical to elucidate the direct impacts of phthalates on ovulation, fertilization, and early embryo development in an animal model. We developed a mouse model of phthalate exposure using dibutyl phthalate (DBP) in which CD-1 female mice are orally exposed to the parent compound DBP at human-relevant doses and its active metabolite, mono-n-butyl phthalate (MBP), is distributed to the ovary. The impact of DBP on ovulation was assessed using naturally cycling adult CD-1 mice that were exposed to tocopherol-stripped corn oil (vehicle), two human-relevant DBP exposures (10 and 100 µg/kg/day), or a classical high dose of DBP (1000 mg/kg/day) for 9-12 days prior to evaluation of endpoints. Hormone-primed ovariectomized and exogenously stimulated ovulation in intact mice were used to determine whether DBP exposure interfered with ovulation via neuroendocrine and/or ovarian sensitivity mechanisms. Our results provide evidence that pituitary hormone release, ovarian sensitivity to gonadotropins, and preimplantation embryo development are impaired following daily oral exposure to DBP. These findings add essential information to help understand the mechanisms responsible for the poor ovulatory and pregnancy outcomes observed in women with high phthalate burden.

POSTER PRESENTATIONS

Poster	Presenter	Title	Institution
1	Finnegan Friday	Polycyclic aromatic hydrocarbons measured following electronic dabbing of *Cannabis* and *Cannabis*-derived products	University of Colorado Anschutz Medical Campus
2	Payton Shirley	Assessment of Cannabigerovarinic acid (CBGVA) Pharmacokinetic parametrs and Toxicity in C57BL6 Mice	Colorado State University
3	Aidan Briggs	Intranasal infection with Western Equine Encephalitis Virus induces dynamic temporal gliosis and progressive neurodegeneration in the hippocampus of C57Bl/6 mice	Colorado State University
4	Samirah Alkhudaydi	Cannabidiol and Trazadone combinational treatment mitigate proteotoxicity in Caenorhabditis elegans	Colorado State University
5	Kristin Weninger	Gene-Environment Interactions and translocator Protein Drug Discovery in a Zebrafish Model of Dravet Syndrome	University of Colorado Anschutz Medical Campus
6	Abdullatif Alsulami	Neuropathological features of Alzheimer's Disease like pathology in aging canines	Colorado State University
7	Abigail Bibb	Astrocytic STING signaling mediates wildfire smoke-induced neurotoxicity in primary murine cells	Colorado State Unviersity
8	Zachary Villaseñor	Systemic inflammation induces tau hyperphosphorylation in Late Onset Alzheimer's Disease (LOAD3ε4) Mice	University of New Mexico
9	Aidan Flanagan	Neuropathology and Neuroinflammatory Hallmarks in Aging Felines with Cognitive Dysfunction	Colorado State University
10	Ember Suh	Sustained, age-dependent neurometabolic changes following wood smoke exposure in mice	University of New Mexico
11	Kapahi Kawai-Puaa	Clinicopathologic Trends in Dogs with and without Cognitive Dysfunction	Colorado State University
12	Sydnee Yazzie	Cell Type–Specific Hippocampal Transcriptomic Responses to Acute Wood Smoke Exposure During Accelerated Ovarian Failure	University of New Mexico
13	Carolyn Dobkins	Investigating Neuroinflammation in Naturally Occurring Canine Dementia	Colorado State University

Poster	Presenter	Title	Institution
14	Mijung Oh	Ovarian Hormone Deficiency Determines Wildfire Smoke-Induced Immune-Metabolic Decoupling: A Bone Marrow Perspective	University of New Mexico
15	Andrea Pasmay	Prenatal alcohol exposure interaction with morphine prolongs allodynia, potentially driven by dysregulation of spinal circRIMS1 and miR-433-3p, modulating the TLR4-NLRP3 signaling pathway	University of New Mexico
16	Adam Schuller	Low-dose rotenone exposure induces astrocytic mitochondrial DNA damage accompanied by STING-dependent neurotoxicity in primary murine cell	Colorado State University
17	Omar Yanouri	Aldehyde dehydrogenase 1 and 2 knockout blunts dieldrin-induced neuronal loss and immune activation	Colorado State University
18	Cassandra Rice	TRPV3 Deletion Enhances Naphthalene-Induced Lung Injury	University of Utah
19	Megan Hager	Juvenile manganese exposure and adult H1N1 infection increase susceptibility to neuronal death and pro-inflammatory microglial activation	Colorado State University
20	Karin Streifel	Enteric glial inflammation and neurodevelopmental perturbations triggered by chronic low-dose exposure to manganese via drinking water in juvenile mice	Regis University
21	Lauren Heine	Arsenite and Its Metabolite Monomethylarsonous Acid Impair Early Human Red Blood Cell Development	University of New Mexico
22	Charlotte McVeigh	Analysis of metabolic and inflammatory biomarkers in human subjects with exposure to tungsten	University of New Mexico
23	Kayla Foster	Sex-Specific Immune and Inflammatory Responses to Tungsten Exposure in Mice	University of New Mexico
24	Jennifer Tjung	Evaluating the Fibrogenic Effects of Tungsten Particulate Exposure in 3T3 Fibroblasts	University of New Mexico
25	Mae Esquibel	Investigating DNA damage in an immune-epithelial interface co-culture model following exposure to uranium bearing dust	University of New Mexico
26	Brianna Maes	Environmental Uranium Perturbs Gut Microbial Composition, Goblet Cells, and Metabolic Signaling	University of New Mexico

Poster	Presenter	Title	Institution
27	Jorge Moreno	Development of an autoimmune prone disease state following inhalation exposure to uranium bearing dust in MRL/MpJ mice	University of New Mexico
28	Rahul Kumar	Chronic Low-Dose Exposures of Cadmium and Hyperglycemia Drive Dysfunctional Hepatic Mitochondrial Biogenesis and Dynamics	University of New Mexico
29	Serena Helewicz	The Effects of Cadmium on Adipogenesis and Breast Cancer Metastasis in the Bone Niche	University of New Mexico
30	Ashwin Chinala	Development and Validation of an HPLC Assay to Measure Anti-Oxidant GSH and Lipid Peroxidation Metabolite MDA to Understand Oxidative Stresses in a Hepatocellular Model	University of New Mexico
31	Alice Rindestig	Emerging chemical exposures and Immune system evaluations in exposed communities living in a Superfund site	University of New Mexico
32	Alvin Yazzie	Literature review of Lumex Fluorat	Navajo Tech
33	Ashley Tafoya	Harnessing Biomolecular Recognition and Protein-Driven Phase Separation for Selective Uranium Preconcentration	University of New Mexico
34	Sebastian Santos	Development and validation of Quantification method of As, Ba, Be, Cd, Co, Cr, Cs, Cu, Mn, Mo, Pb, Sb, Se, Ti, U, V, W and Zn in human urine with ICPMS	University of Colorado
35	Nikita Dougan	Comparison of Uranium Measurement Technologies for Community-Based Environmental Monitoring	University of New Mexico
36	Derek Drechsel	Metal Exposure Associated with Use of Soil and Fertilizer Products in a Commercial Greenhouse Setting with Comparison to Prop 65 Safe Harbor Levels	CTEH
37	Derek Drechsel	Formaldehyde off-gassing from bed sheets and pillowcases: a simulation study and risk assessment	CTEH
38	Angela Reinert	When IgE Isn't the Answer: Profiling the Hidden Drivers of Chronic Spontaneous Urticaria	University of Colorado
39	Laura Santos-Medina	Histone variant-specific epigenetic remodeling in activated CD4+ T cells following exposure to a trichloroethylene metabolite	University of New Mexico
40	Hayley Wondra	Metabolic Reprogramming of $CD4^+$ T Cells in Autoimmune-Prone Mice Exposed to Trichloroethylene	University of New Mexico
41	James Sherrick	The relationship between PFAS exposure and dyslipidemia: an updated review, meta-analysis, and evaluation of bias	J.S. Held

Poster	Presenter	Title	Institution
42	Carly Chesterman	Investigating the Interactive Toxicity of Sugarcane Ash–Derived Silica Nanoparticles and Pesticides in Human Proximal Tubular Kidney Cells	University of Colorado
43	Lei Yin	Rapid Prioritization of Reproductive Toxicants Using a High-Throughput and High-Content Analysis Platform with a 3D Mini-Testis Culture Model	Reprotox Biotech
44	Talia Owen	*In Vitro* Exposure to Dibutyl Phthalate and Mouse Ovarian Follicle Cellular Compartment Size	University of Arizona
45	Risa Smith	Molecular interference of lipids and polymer plastics in mass spectrometry: implications for toxicity and exposure research	University of New Mexico
46	Chelin Hu	Detection and Distribution of Microplastics in Human Semen and Their Potential Impact on Sperm Quality	University of New Mexico
47	Sumira Phatak	Micro/nano-plastics compromise skeletal architecture as modulators of the gut–immune–bone axis	University of New Mexico
48	Sakshi Patil	Micro(nano)plastics in human cerebrospinal fluid and their implications for brain waste clearance	University of New Mexico
49	Sebastian Stoker	Analysis of Micro-Nanoplastic Pollution in the New Mexico Public Water Supply	University of New Mexico
50	Robert Taylor	Trouble in Paradise: Characterization and Modeling of Heavy Metal Adsorption on Microplastics Across Global Beach Locations	University of New Mexico
51	Roger O. McClellan	Chemical Toxicology Review Papers: An Editor's Perspective Based on 50 years of Experience	Toxicology and Risk Analysis
52	Md Helal Uddin	Intergenerational Effects of Environmentally Relevant Concentrations of Dietary Selenium on Zebrafish, *Danio rerio*	University of Saskatchewan

1. Polycyclic aromatic hydrocarbons measured following electronic dabbing of *Cannabis* and *Cannabis*-derived products

Poster #1

Finnegan Friday[1], Gregory Brusoe[1], Michael Armstrong[2], Stephen Goldman[3], Nichole Reisdorph[2], and Alison K. Bauer[1]

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Background and Purpose: Electronic dabbing is the consumption of concentrated *Cannabis* and *Cannabis*-derived products vaporized at temperatures as high as 1000° F. Terpenes found naturally in *Cannabis* and added in excess are responsible for the flavor and aroma profiles characteristic of dabbing. At high temperatures, terpenes such as a-cedrene and b-caryophyllene are known to undergo pyrolysis, forming polycyclic aromatic hydrocarbons (PAHs), but the production of PAHs from dabbing *Cannabis* is largely unstudied. PAHs pose a risk to human health; 16 are U.S.E.P.A priority pollutants and many are known or suspected carcinogens. Our hypothesis is that electronic dabbing of *Cannabis* products, especially those with high terpene concentrations, will lead to production of PAHs and subsequent toxic exposure.

Methods: We developed a method for analyzing PAHs produced during electronic dabbing by collecting vapor produced at 1000° F from an electronic dabbing rig. Vapor was captured using C18 SPE cartridges, followed by measurement of the 16 EPA priority PAHs using gas chromatography/mass spectrometry (GC/MS). Control testing with multiple terpene mixes was performed at CU Anschutz, and various *Cannabis* concentrates were dabbed and prepared at Kaycha Labs in Denver, Colorado, for analysis at CU Anschutz. The *Cannabis* products, control oils, and terpene mixes that we tested are common in the Colorado market. Our protocol was validated by measuring samples spiked with PAHs before and after dabbing.

Results: Our findings suggest the presence of multiple priority PAHs, particularly those of lower molecular weight, such as naphthalene and its methylated derivatives, in vapors produced from the dabbing of both control and *Cannabis*-derived samples, and PAH concentrations increase upon addition of terpenes. However, some PAHs were present at low concentrations in undabbed samples. Notably, the addition of terpenes to multiple *Cannabis* products resulted in significantly increased concentrations of four PAHs, including anthracene.

Conclusions: Our findings support the successful development of a method for the collection and analysis of PAHs from dab vapors. Additionally, our findings suggest that the addition of terpenes to electronic dabbing results in significantly increased production of PAHs. Further testing is underway to compare the effects of various added terpene mixes on PAH production, and current results will be analyzed for unknowns using the NIST17 GC/MS database. Because current U.S. *Cannabis* testing facilities do not test for PAHs, our overall goal is to understand potential user exposures to prevent and protect the public health of Coloradoans by providing evidence to improve regulation of device temperatures and product formulations. This research was supported by the Institute for *Cannabis* Research.

2. Assessment of Cannabigerovarinic acid (CBGVA) Pharmacokinetic parameters and Toxicity in C57BL6 Mice

Poster #2

Payton Shirley[1,2], Sydney Risen[1,2], Kui Kawai-Puaa Kawai-Puaa[1,2], Archer Casper[1,2], Gregory Dooley[1], Stephanie McGrath[2,3], and Julie A Moreno[1,2]

[1]Department of Environmental and Radiological Health Services; [2]Brain Research Center and [3]Department of Clinical Sciences, Colorado State University, Fort Collins, CO, USA

Approximately 50 million people worldwide are affected by epilepsy, making it one of the most prevalent neurological disorders. Currently, 30% of epilepsy cases are classified as drug-resistant, meaning individuals continue to experience seizures despite treatment, along with significant side effects such as increased anxiety, cognitive impairments, and impaired motor function severely impacting quality of life. This underscores the need for novel therapeutics and a deeper understanding of epilepsy's underlying mechanisms. My research investigates Cannabigerovarinic acid (CBGVA), a phytocannabinoid found in cannabis, as a potential treatment. Preliminary data suggest that CBGVA inhibits T-type calcium channels and GPR55, both implicated in seizure activity. T-type calcium channels are low-voltage-activated channels that contribute to neuronal excitability, and their overactivation is linked to epilepsy. GPR55, a cannabinoid receptor, modulates neurotransmission and has been associated with seizure regulation. We hypothesize that a novel preparatory molecular structure of CBGVA will exhibit favorable pharmacokinetics and minimal toxicity. To assess CBGVA's pharmacokinetics, we will use Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) to analyze plasma and brain homogenates from C57BL/6 mice treated with 10 mg/kg and 100 mg/kg doses at various timepoints. Toxicity will be evaluated through histological analysis of vital organs, including the brain, liver, and kidney. CBGVA reached peak plasma concentrations within 15 minutes post-injection at both 10 mg/kg and 100 mg/kg, with corresponding peak brain concentrations at 15 minutes and 30 minutes, respectively, indicating systemic absorption and CNS penetration. H&E staining of the brain, liver, and kidney showed no evidence of toxicity, including necrosis, inflammation, or structural disruption. Future studies will explore CBGVA's mechanism of action using immunofluorescence to examine its interactions with T-type calcium channels and GPR55, assessing its role in modulating neuronal excitability and neuroinflammation. Additionally, CBGVA's anticonvulsant potential will be investigated in a translational canine model of epilepsy, offering valuable insights into its therapeutic potential for drug-resistant epilepsy.

3. **Intranasal infection with Western Equine Encephalitis Virus induces dynamic temporal gliosis and progressive neurodegeneration in the hippocampus of C57Bl/6 mice**
Poster #3

Aidan Briggs[1], Adam Schuller[1], Omar Yanouri[1], Savannah Rocha[1], Abigail Bibb[1], Megan Hager[1], and Ronald Tjalkens[1]
[1]Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO

Arboviruses, including encephalitic alphaviruses such as Western equine encephalitis virus (WEEV), are increasingly emerging in human and animal populations as a result of climate change-induced warmer temperatures and increased rainfall. This expansion of mosquito-occupied territories has increased infectious risk for previously invulnerable groups and presents the possibility for large-scale outbreaks capable of drastically altering the health of these populations. Encephalitic alphaviruses have been characterized to possess neurotropic capacity, associated with longitudinal central nervous system dysfunction. Following viral-induced encephalitis, lingering effects such as chronic neuroinflammation and glial-mediated immune modulation are strongly correlated with the onset and progression of neurodegenerative disorders, including Parkinson's disease and related dementias. These age-related conditions are well characterized in their hallmark features of neuronal loss and protein aggregation; however, the temporal involvement of glial subpopulations in viral-induced inflammatory signaling and subsequent neurodegeneration remain elusive, especially in the context of brain regions involved in learning and memory. Our lab has previously demonstrated that sub-lethal WEEV infection is sufficient to elicit a robust astrocyte-mediated complement response associated with gait aberrancies, dopaminergic neurodegeneration, and pathologic protein aggregation in the substantia nigra of outbred CD-1 mice and wild-type, inbred C57Bl/6 mice. This is associated with the capacity for persistence of viral replication in the brain parenchyma, including within the hippocampus, long after peripheral clearance. Together, these data motivated the longitudinal assessment of hippocampal glial dynamics and neurodegeneration following WEEV infection. Eight-week-old C57Bl/6 mice were intranasally administered 20 µL of 1×10^4 PFU/mL McMillan WEEV under anesthesia. Mice were subsequently sacrificed at one-, two-, four-, and eight-week timepoints (n = 6-10 mice/timepoint/group). Hippocampal sections were labeled using automated multiplex immunofluorescence, high-content batch scanned, and objectively quantified via deep learning-based analysis pipelines trained to at least 100,000 iterations across the extent of the dataset. A substantial increase in % $GFAP^+$ area was observed 1 week post infection (WPI) in the dentate gyrus (DG) and CA1 hippocampal subregion, which resolved in the DG by 4 WPI, but progressively increased in the CA1, CA2, and CA3 regions over the remaining timepoints. Slight elevation in the density of $IBA1^+$ cells/mm^2 in the CA1, CA2, CA3, and DG were initially observed 1WPI, but peaked at 2WPI. Interestingly, this suggests a similar trend of viral-induced microgliosis subsequent to initial astrocyte activation, reflecting the pattern of cellular reactivity observed in the basal midbrain. Additionally, a significant interaction effect accounting for time and infection status was evidenced by progressive decrease in the number of $NeuN^+$ cells/mm^2 in the CA1 region. We further applied spatial phenomics to integrate the complex temporal relationship between glial and neuronal cell number, morphology, infection status, and location, to assess for disease-associated states in infected animals compared to controls. Together, these data highlight the dynamic nature of gliosis and progressive neurodegeneration following WEEV infection in the hippocampus. Future work will aim to investigate the significance of these histologic changes on cognition and executive function and examine the effects of modulating glial inflammatory signaling on the progression of this pathologic sequelae.

4. **Cannabidiol and Trazadone combinational treatment mitigate proteotoxicity in Caenorhabditis elegans**

Poster #4

Samirah Alkhudaydi[1], Abdullatif Alsulami[1], Stephanie McGrath[2], Julie A. Moreno[1]

[1]Department of Environmental and Radiological Health Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO; [2]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University Fort Collins, CO

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that involves a gradual decline in cognitive abilities, marked by significant memory loss and difficulties with reasoning and social interaction, ultimately making everyday tasks challenging. AD characterized by the accumulation of misfolded proteins, including amyloid-β ($A\beta_{1-42}$) and hyperphosphorylated tau (P-Tau), as well as increased oxidative stress and proteostasis dysfunction. These pathological features disrupt neuronal function and are linked to cognitive decline and reduced lifespan. In this study, we investigated the therapeutic potential of cannabidiol (CBD) and trazodone (TRA), two existing pharmaceutical compounds, both of which have previously been shown to attenuate proteotoxicity and oxidative damage in various models. **We hypothesize that these treatments will alleviate proteotoxic stress and oxidative damage in *C. elegans* models expressing human $A\beta_{1-42}$ with an expected outcome of motility improvement and behavioral function, indicating a neuroprotective effect that may support the potential of these compounds for therapeutic repurposing in neurodegenerative disease.** Using *Caenorhabditis elegans* strains expressing human $A\beta_{1-42}$ in the muscles, we assessed the effects of CBD and TRA both individually and in combination on the nematode motility. Our results demonstrate that treatment with CBD and TRA significantly reduced paralysis compared to the control groups as a behavioral outcome in worms expressing $A\beta_{1-42}$, suggesting that these treatments possess a neuroprotective effect. This work highlights the potential of use of CBD, TRA individually and as a synergistic effect as a therapeutic strategy for mitigating neurodegeneration and warrants further investigation in higher model organisms. For the future directions of the study we aim to western blot the Ab proteins and quantitively analyze the *C.elegans* behaviors using WormLab software.

5. Gene-Environment Interactions and translocator Protein Drug Discovery in a Zebrafish Model of Dravet Syndrome

Poster #5

Kristin Weninger[1], Lauryn Adair[1], and Manisha Patel[1]
[1]Department of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus

Dravet Syndrome (DS) is a form of early onset epilepsy with seizures typically occurring in the first year of life, affecting approximately 1 in 15,700 people worldwide. Characterized by prolonged febrile seizures with many seizure types occurring over time, DS is associated with a high risk of Sudden Unexpected Death in Epilepsy (SUDEP). Approximately 80% of cases are linked to *de novo* mutations in the *SCN1A* gene, resulting in non-functional Nav1.1 sodium channels. This dysfunction is thought to impair inhibitory GABAergic interneurons, resulting in neuronal hyperexcitation. While the genetic association is well established, the environmental factors contributing to disease onset and seizure susceptibility remain poorly understood. This led us to develop a paradigm to further explore the *SCN1A* gene environment interaction using the Comparative Toxicogenomic Database (CTD). Bisphenol A (BPA), a widespread environmental contaminant, was identified as strongly associated with *SCN1A* gene expression. Using wild-type and *scn1Lab* zebrafish larvae as a translatable model of DS, behavioral outcomes following BPA exposure were assessed. While no direct correlation between exposure and seizure activity was identified, this approach highlights the value of combining the CTD with the *scn1Lab* zebrafish model to screen for environmental modifiers of genetic disease. In parallel, this study examined potential therapeutics inspired by the ketogenic diet, which is effective in about 65% of DS patients, who often are prone to anti-seizure medication resistance. Previous research in our lab showed mitochondrial and glycolytic dysfunction in *scn1Lab* zebrafish larvae. PK11195, a translocator protein (TSPO) ligand was identified from a phenotypic screen for compounds that improved metabolism and reduced hyperexcitability. Two additional TSPO ligands, etifoxine and XBD173, were also found to decrease ‘seizure-like’ swim behavior and attenuate neuronal hyperexcitability. Building on these results, four additional TSPO ligands were examined. Ultimately, this study found that the TSPO ligand DAA1106 decreased swim behavior and neuronal hyperexcitability in DS larvae. Taken together, the findings show the importance of integrating environmental toxicology with genetic disease models. This dual approach, examining environmental triggers and TSPO targeted therapeutics, offers a promising framework for addressing the complexities of neurological diseases like epilepsy in a changing environment.

Acknowledgements: This research was funded by the National Institutes of Health grant 5R01HD10207-03 (M.P.).

6. Neuropathological features of Alzheimer's Disease like pathology in aging canines

Poster #6

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that currently affects more than 55 million people worldwide and is expected to triple in prevalence by 2050, placing a formidable social and economic burden on global health. Hallmarks of the disease include cognitive decline, amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs), and widespread neuronal loss. Despite decades of research, disease-modifying therapies remain elusive. One factor limiting progress is the full reliance on transgenic rodent models, which do not capture the spontaneous, age-related, and multifactorial nature of human AD. A promising alternative is the naturally aging companion dog, which develops canine cognitive dysfunction (CCD) characterized by age-dependent cognitive decline and neuropathological features that closely parallel human AD. Clinically, dogs are diagnosed with CCD through owner assessment-based surveys, Canine Dementia Scale (CADES) and Canine Cognitive Dysfunction Rating Scale (CCDR). Further, dogs share our households, lifestyles, and environmental exposures, providing a naturalistic context that better reflects the complex interplay of genetic, environmental, and aging factors driving disease. Due to the absence of a standardized neuropathological staging system for CCD, we utilized a whole brain, region specific assessment on aging canine brains. We hypothesized that neuropathological lesions in aging canines follow a similar distribution pattern to human AD. Here we apply human AD criteria, Thal phases for Aβ, Braak staging for NFTs, and CERAD scoring for neuritic plaques, to brains from client-owned dogs. Coupling these assessments with cerebrospinal fluid and plasma biomarker analyses and detailed cognitive testing, we show striking parallels between canine and human AD pathology and establish correlations among neuropathology, biofluid markers, and behavioral decline. These findings position the companion dog as a robust translational model that bridges the gap between rodent studies and human clinical trials, offering a powerful platform to unravel early disease mechanisms and accelerate therapeutic development.

7. Astrocytic STING signaling mediates wildfire smoke-induced neurotoxicity in primary murine cells

Poster #7

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Background: Concurrent with climate change, drastic changes in the frequency and duration of wildfire events across the global landscape necessitate an assessment of extrapulmonary health effects associated with wildfire smoke (WFS) exposure. Recent work highlights the potential of this toxicant to induce neurologic consequences; however, the mechanisms which underlie this dysfunction remain elusive. Our group has previously characterized aberrant parenchymal gene expression profiles in mice chronically exposed to WFS which mirror transcriptomic patterns found in neurodegenerative disease. Further, we have shown that involvement of glia in the pathogenesis of toxin-based models of Parkinson's disease and related dementias often precedes the overt loss of neurons in these disorders. The cGAS-STING signaling pathway, which senses cytosolic nucleic acids and modulates interferon responses to these stimuli, has recently been implicated in the pathogenesis of neurodegeneration as well as age-related neurologic dysfunction. Interestingly, astrocytes have been characterized to play a major role in secreting type I interferons in the brain. Together, these data motivate the assessment of STING-dependent activation in glial cells as a mechanistic contributor to WFS-induced neurotoxicity.

Methods: Simulated wildfire smoke was generated using a laboratory ring furnace apparatus to combust Douglas fir needles at a smoldering temperature. Particulate matter was collected in-line during burns on PTFE filters and then extracted via methanol solvent exchange. To ensure the relevance of our laboratory-generated WFS particulate matter in a neurotoxic context, we applied two techniques of biophysical characterization, transmission electron microscopy (TEM) and dynamic light scattering (DLS), to establish the size and shape of these particles. Wildtype (C57Bl/6, WT) primary murine mixed glial cultures were subsequently liquid suspension dosed with smoke extract at half-log concentrations spanning 1-1000 ng/mL. These cells were initially assessed for cytotoxicity using a permeability-based cell viability assay to establish a range of lethal or non-lethal doses. To further probe the role of cGAS-STING activation in astrocytes, we applied high content imaging and deep learning-based phenomic analysis of glia following 1-, 3-, 6-, and 12-hr exposure to sub-lethal WFS concentrations for phosphorylation of STING and its downstream transcription factor (IRF3). We next employed a genetic STING ablation strain ($TMEM173^{gt}$, GT) to assess the role of STING signaling in WFS-induced cytotoxicity. In both WT and GT cells we measured STING-dependent cytokine secretion patterns in culture supernatant via Luminex multiplex ELISA. Lastly, to assess the relevance of these changes to neurodegeneration, we exposed primary cortical and hippocampal neurons to glial conditioned media (GCM) from WFS-exposed WT and GT cultures to assess the neurotoxic potential.

Results: We first established that the particle sizes of our WFS extracts were relevant to brain uptake by utilizing DLS and TEM to assess particle size. The DLS analysis resulted in two peaks from filter-extracted particles, one accounting for ~90% of the particle size at 81.70 nm (± 13.02) and a second accounting for ~10% of the particle size at 466.8 nm (± 123.1). This was further corroborated by TEM analysis (n = 32 images analyzed) which resulted in a mean ultrafine particle size of 60.89 nm (± 21.02) and a mean fine particle size of 541.4 nm (± 280.4). To subsequently characterize the cytotoxic potential of this toxicant, we established the LD_{50} [WFS] to be 747.5 ng/mL at 12 hours of exposure, a time-point preceding the doubling time of these cells in culture. Next, we applied sub-lethal doses of 100 ng/mL WFS to characterize STING activation in these mixed glial cultures. We report significant increases in perinuclear pSTING between smoke-exposed and vehicle control cells. Concurrently, we observed a greater nuclear localization of

pIRF3 and increased secretion of IFN-β and CXCL10 in the supernatant of these cells, suggesting heightened STING signal transduction. To assess if these effects were STING-dependent, we assessed the same outcomes in GT cultures, and report an inability to calculate an LD_{50} [WFS] for the same dose range. Further, we observed significantly less re-localization of pIRF3 to the nucleus and reduced secretion of IFN-β and CXCL10 in the culture supernatant. Lastly, we explored the effects of GCM from WT and GT cells on neuronal viability. WT GCM induced substantially greater neurotoxicity when compared to GT GCM treatment.

Conclusions: These data suggest that WFS exposure elicits an acute, dose-dependent cytotoxic effect on primary glial cell populations, as well as glial-mediated neurotoxicity, which are both blunted by genetic STING ablation. This work motivates subsequent assessment of the role that air pollution plays in glial-mediated neuroinflammation and neuroimmune modulation *in vivo* to further parse out effects of these phenomena in the context of neurodegeneration.

8. **System inflammation induces tau hyperphosphorylation in Late Onset Alzheimer's Disease (LOAD3ε4) Mice**

Poster #8

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Alzheimer's disease (AD) is a memory disorder characterized by the aggregation of hyperphosphorylated tau (pTau) as neurofibrillary tau tangles and amyloid (Aβ) plaques. Many studies have shown that pTau and Aβ are responsible for impairment of executive function and memory in patients with AD. Recent studies have implicated neuroinflammation also plays a role in disease onset and development, suggesting that microglia- immune cells of the central nervous system (CNS)- play a causal role in the disease. Environmental toxins such as wildfire smoke have also been documented to play a role in inducing neuroinflammation via lung-brain axis, elevating pro-inflammatory molecules such as TNFα and CD45. Our group has shown previously that systemic inflammation via bacterial endotoxin (lipopolysaccharide or LPS) can increase the risk of AD by inducing hyperphosphorylation of tau. To determine whether exposomes increases the AD risk, we are utilizing a mouse model of late onset AD (LOAD3ε4 mice), which accounts for ~70% of AD cases. The LOAD3ε4 mice were developed by the MODEL-AD consortium and expresses human Aß, tau and Apolipoprotein E4/E4 (which is a risk gene for sporadic AD). Here, we administered 5mg/kg single dose LPS i.p. to two age groups (3.0mo and 5.3mo) of LOAD3ε4 mice, and quantified levels of pTau. We observed increased tau phosphorylation (on T231 – an AT180 antibody site; S202 - AT8 antibody site) in the hippocampus of LPS injected LOAD3 mice. Upon quantification, the AT180/total tau (Tau12) ratio was modestly increased, but the AT8/total tau ratio was significantly increased in LPS-injected LOAD-3 mice compared to vehicle treated controls. This work is ongoing, and findings will be shared at MWSOT for the first time. Our forthcoming work seeks to elucidate the impact of multiple environmental insults- including wildfire smoke, metal contaminants, micro/nanoplastics, and the Western diet on tau pathology and dementia risk in LOAD-3 mice.

9. Neuropathology and Neuroinflammatory Hallmarks in Aging Felines with Cognitive Dysfunction

Poster #9

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Neurodegenerative disorders like Alzheimer's Disease (AD) and other Alzheimer's Disease Related Dementias (ADRDs) affect over 55 million people worldwide. Current animal research models rely on genetically engineered rodents that only mimic AD symptoms. What these models fail to account, are differences in environmental exposures, genetics and natural aging pathology, all main contributors to AD. Natural aging pathology presents with aggregation of amyloid beta (Aβ) plaques primarily accumulating in the neocortex which spread inward eventually reaching cerebellum. Aging also exhibits hyperphosphorylation of the tau protein, accumulating as neurofibrillary tangles (NFT) in the trans-entorhinal cortex spreading to limbic areas and neocortex. It is well known that these plaque buildups are associated with oxidative stress and neuroinflammation seen through the activation of glia support cells throughout the CNS. Specifically, microglia and astrocytes are important for upholding homeostasis, decreasing plaque buildup and supporting the blood brain barrier (BBB). Because of the comparability of natural aging pathology, genetic diversity and environmental exposures, the use of companion felines is thought to be a natural and accurate model for AD research. We hypothesize that at different age stages and with increasing plaques and tangles, felines will show heightened levels of neuroinflammation. Our testing utilized immunohistochemistry (IHC) staining of the cortex and hippocampus for Aβ and P-tau as well as microglia marker Iba1, and astrocyte markers S100β and GFAP. We assessed neuroinflammation by number of positive cells and morphological changes in different age groups while neuropathology was accessed by number of Aβ plaques and NFTs. While association in plaques and tangles were seen with age, proinflammatory glial cells had no measurable association to plaques or tangles. In future studies we will look at glia neuroinflammation trends with a larger cohort of felines.

10. Sustained, age-dependent neurometabolic changes following wood smoke exposure in mice

Poster #10

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Background and Purpose: 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. The severity of the neuroinflammatory response that was previously found to be associated with WFS exposure in young mice was dynamic and resolved approximately 4 weeks after exposures ended. Subsequent studies showed that this sustained effect could be worse in aged mouse models. The purpose of the study was to better understand the relationship between aging and neuroinflammation resolution.

Methods: 15-, 18-, and 21-month-old (mo) mice were exposed to either filtered air (FA) or simulated wildfire smoke (WFS; 500 μg/m^3, 4h/d every other day for 14 days) and sacrificed 30-days, 3-months, or 5-months post-exposure. Untargeted metabolomics and targeted metabolomics (NAD^+ pathway) were performed on left brain hemispheres. Pathway analyses were performed following identifications of significantly altered metabolites.

Results: Clear metabolomic differences were found in the brains of mice exposed to FA and WFS at age of 15-mo and sacrificed 1-month post-exposure (e.g., L-threonine, asparagine); age of 18-mo and sacrificed 1-month post-exposure (e.g., L-threonine, asparagine); and age of 18-mo and sacrificed 5-months post-exposure (e.g., palmitoylcarnitine). Aging itself affected metabolomics at 15-, 18-, and 21-mo mice exposed to FA and sacrificed 30-days post-exposure. Phe/Tyr/Trp biosynthesis was significantly downregulated while purine metabolism was significantly upregulated in both the WFS-exposed mice and the advanced aged mice. Pathway analyses further revealed that significantly altered metabolites shared between the WFS and aging had significant overlap in purine metabolism and Phe/Tyr/Trp biosynthesis. NAD^+ pathway metabolites were altered in the WFS groups (age of 15-mo and sacrificed 1-month post-exposure; age of 18-mo and sacrificed 3-months post-exposure). Clear NAD^+ metabolic differences were also found from aging only.

Conclusions: The metabolomics data suggests that sustained metabolomic changes (e.g., NAD^+ metabolism) in the brain are influenced by WFS and aging. In other words, the effect of WFS is similar to the effect of aging in neurological metabolism.

11. Clinicopathologic Trends in Dogs with and without Cognitive Dysfunction

Poster #11

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Canine cognitive dysfunction (CCD) is a complex neurodegenerative disorder that exhibits similar clinical, behavioral and pathological changes to Alzheimer's disease (AD) and related dementias (ADRD) in humans. As canines age, they serve as a naturally occurring model for these diseases, offering valuable insight into disease progression. Although routine laboratory values are commonly used to monitor general health in aging dogs, their association with cognitive dysfunction has not been well characterized.

We conducted a cross-sectional analysis of clinical laboratory data from 214 client-owned dogs aged 8 years or older, enrolled in the Dog Aging Project. Cognitive status was assessed using the Canine Social and Learned Behavior (CSLB) survey, with CCD defined as a CSLB score ≥50 (n=22) and cognitively normal defined as CSLB ≤40 (n=192). Dogs scoring 40-49 were excluded to minimize misclassification. We evaluated 91 hematology and serum chemistry biomarkers collected in the same year as each dog's most recent CSLB score. Group comparisons were stratified by sex (females n=108; males n=106) and CCD status. Statistical significance was assessed using Welch's t-tests with false discovery rate correction.

Significant differences were observed in several clinicopathologic markers. CCD-positive dogs showed consistently lower hematocrit and hemoglobin in both the combined group and among females ($q<0.01$), suggestive of anemia or impaired erythropoiesis. CCD positive females also had reduced mean platelet volume ($q< 0.0001$), a change consistent with altered platelet function, which is implicated in neurodegeneration. Elevated potassium and reduced red blood cell counts were also noted in CCD positive females. No statistically significant differences were observed among neutered males (n=9), likely due to limited sample size.

These findings suggest that routine bloodwork may reflect early systemic changes associated with cognitive decline, particularly in female dogs. Longitudinal studies are warranted to explore these trends further and assess their relevance to neurodegeneration in dogs and humans.

12. Cell Type–Specific Hippocampal Transcriptomic Responses to Acute Wood Smoke Exposure During Accelerated Ovarian Failure

Poster #12

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Acute wood smoke (WS) inhalation has been recognized as a driver of central nervous system (CNS) injury through mechanisms involving neuroinflammation, oxidative stress, and synaptic dysfunction. Declining ovarian hormones seen in menopausal transition has been shown to reduce neuroprotective capacity and may exacerbate susceptibility to WS-induced brain injury. However, the spatial transcriptomic profile of molecular responses of hippocampal cell types to WS exposure in the context of ovarian hormone decline remain undefined. In this study, we utilized spatial transcriptomics on hippocampal tissue from ovary-intact, moderate accelerated ovarian failure (AOF) mice exposed to either filtered air (FA) or WS. Clustering patterns identified cell populations including glutamatergic, GABAergic neurons, astrocytes, and oligodendrocytes. In glutamatergic neurons, WS exposure upregulated genes involved in excitatory neurotransmission extracellular matrix remodeling and stress adaptation. GABAergic neurons showed enrichment of transcripts regulating neuronal differentiation, oxidative stress signaling and neuropeptide modulation, suggesting inhibitory network plasticity. Non-neuronal populations displayed downregulation of chromatin remodeling and stress-response genes, coupled with increased expression of glutamate transport and gliotransmission markers, indicating altered astrocytic support and myelination pathways. Gene ontology and KEGG analyses revealed enrichment of synaptic signaling, axon guidance, and membrane organization pathways, alongside suppression of neuronal projection and intracellular transport functions. Overall, these results demonstrate that acute WS exposure contributes to complex mechanisms of adaptive neuroplastic responses and compromised homeostatic processes in the hippocampus in the context of moderate AOF, potentially heightening vulnerability to air pollution exposures.

13. Investigating Neuroinflammation in Naturally Occurring Canine Dementia

Poster #13

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With an aging world population, age-related neurodegenerative disorders such as Alzheimer's disease (AD) are increasingly widespread. AD is characterized by the accumulation and aggregation of misfolded proteins (i.e. hyperphosphorylated tau and β-amyloid) and an increase in neuroinflammation. Long term activation of glial cells like microglia and astrocytes can lead to a chronic pro-inflammatory response, expatriating the damage to synapses and the subsequent neurons.

Animal models have been crucial in understanding the mechanisms behind AD. Traditional models such as *C. elegans* and mice are commonly used, but require genetic modification to simulate AD, leading to questions about translatability. These models also lack the genetic diversity present in a human population. As a result, canines have emerged as an alternative solution. Canines have genetic diversity among breeds, simulating differences present in humans. Most importantly, they naturally acquire canine cognitive disfunction (CCD), a neurodegenerative disorder with comparable characteristics to AD. Owner surveys are used to establish a behavior-based diagnosis of CCD, and we want to see if the histology backs up a positive CCD score. We hypothesize that with a positive identification of CCD through owner surveys, there will be an increase in neuroinflammation represented by activated glial cells. To determine this, we used immunohistochemistry (IHC) staining of glial marker Iba-1, and astrocyte marker GFAP to determine the number of glial cells within two brain region, cortex and hippocampus. Here, we utilized 58 client-owned dogs, staining these regions and performing analysis on the cells identified as positive. We found there are increases in glial cells with a positive CCD score. Going forward, we want to investigate protein aggregates and neuroinflammation together to create a comprehensive model of CCD, creating a highly translatable model for AD.

14. Ovarian Hormone Deficiency Determines Wildfire Smoke-Induced Immune-Metabolic Decoupling: A Bone Marrow Perspective

Poster #14

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The increasing frequency of wildfires elevates public exposure to wildfire smoke (WS), a major health threat. Ovarian hormone deficiency, as seen during menopause, is a key susceptibility factor, but the underlying immunotoxic mechanisms, particularly within the bone marrow, remain unclear. We investigated the impact of WS from a bone marrow perspective using a murine model of ovariectomy (OVX). OVX and sham mice were exposed to WS or filtered air (FA), followed by single-cell RNA-sequencing (scRNA-seq) on whole bone marrow and functional profiling of *ex vivo* differentiated bone marrow-derived macrophages (BMDMs). scRNA-seq revealed that WS exposure in OVX mice induced a systemic shock to the bone marrow, characterized by broad suppression of immune gene programs, including antiviral defense and leukocyte activation. Paradoxically, BMDMs derived from these mice exhibited robustly increased metabolic activity (both mitochondrial respiration and glycolysis). This compensatory metabolic activation was uncoupled from canonical pro-/anti-inflammatory polarization programs, characterized by potent downregulation of M2-associated genes (e.g., *Arg1*, *PPAR-γ*) without concurrent M1 induction. We define this novel state as immune-metabolic decoupling. Our findings demonstrate that hormonal status is a critical determinant of the bone marrow's response to WS, suggesting that WS imprints a lasting, dysregulated program on myeloid progenitors at least up to 7 days post-exposure. This highlights a new paradigm for environmental immunotoxicity with significant translational implications for susceptible populations like postmenopausal women.

15. Prenatal alcohol exposure interaction with morphine prolongs allodynia, potentially driven by dysregulation of spinal circRIMS1 and miR-433-3p, modulating the TLR4-NLRP3 signaling pathway

Poster #15

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Prenatal alcohol exposure (PAE) leads to Fetal Alcohol Spectrum Disorders (FASD), encompassing a range of long-term neurobehavioral deficits and sensory processing issues, the underlying mechanism(s) are still under investigation. Previously, utilizing a minor nerve injury model in adult mice, we demonstrated PAE increases susceptibility to neuroimmune dysfunction. Our previous findings suggest PAE leads to a protracted course of nerve injury-induced pathological pain (allodynia) following morphine treatment, a commonly used opioid for pain management. Under PAE conditions, exposure to morphine (10 mg/kg for five subsequent days) prolongs allodynia via enhanced production of endogenous pain-promoting factor, HMGB1 (human High Mobility Group Box1), activating the TLR4-NLRP3 pathway. Morphine-prolonged allodynia in PAE mice was associated with increased spinal caspase-1 activity, a direct downstream molecule of NLRP3 inflammasome activation that induces the production of proinflammatory cytokine, IL-1β. Emerging evidence shows PAE alters circular RNAs (circRNAs)- non-coding RNAs that regulate gene expression acting as microRNA (miRNA) sponges. Here, we explored non-coding RNAs as potential regulators of PAE-induced proinflammatory bias following morphine treatment. Our next-generation RNA sequencing data identified an upregulation of a circRNA, circRIMS1, in the spinal cord of PAE with morphine-prolonged allodynia. Interestingly, circRIMS1 binds to and sequesters miR-433-3p, a negative regulator of TLR4-NLRP3 activation by targeting HMGB1 for degradation, hence reducing activation of the TLR4-NLRP3 pathway. Interestingly, our real-time PCR data confirmed reduced spinal miR-433-3p expression in PAE mice with morphine-prolonged allodynia. Therefore, we hypothesize that miR-433-3p downregulation in PAE mice may promote TLR4-NLRP3 activation, contributing to morphine-prolonged allodynia. To test this, we administered miR-433-3p mimic or a non-specific control via an intrathecal injection (500 pmol, in 10 µl). Notably, allodynia was fully reversed within 48 hours in mimic-treated PAE male mice. Preliminary data confirmed that miR-433-3p mimic treatment increased spinal miR-433-3p levels and reduced spinal caspase-1 activity, indicating decreased NLRP3 inflammasome activation. Together, these findings suggest a critical role of non-coding RNA in the interaction between PAE and morphine, driving NLRP3- mediated neuroinflammation. Future studies will be geared towards blocking circRIMS1 to confirm the involvement of circRIMS-miR-433-3p axis modulating NLRP3 actions. This study highlights novel neuroimmune mechanisms and indicates the potential of targeting non-coding RNAs to mitigate opioid-related adverse effects in individuals with FASD.

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16. Low-dose rotenone exposure induces astrocytic mitochondrial DNA damage accompanied by STING-dependent neurotoxicity in primary murine cell

Poster #16

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Background: Globally, Parkinson's disease (PD) is the fastest growing neurodegenerative disorder, yet this condition remains etiologically idiopathic and incurable. While a majority of work seeking to characterize the molecular underpinnings of PD remains focused on nigral dopamine neurons, mounting evidence supports the critical role of glial involvement in pathogenesis, including at time points preceding the neurodegenerative sequelae. Recently, the cGAS-STING pathway, which modulates innate interferon signal transduction in response to cytosolic dsDNA, has emerged as a potential therapeutic target in the context of age-related degeneration. Still, our understanding of how this molecular sensor pathway contributes to astrogliosis and whether or not this effect is neurotrophic or neurotoxic remains ill-resolved. Here, we sought to interrogate the effect of acute, low-dose rotenone exposure on cGAS-STING signaling in primary glial cells to address this knowledge gap.

Methods: Primary astrocyte-enriched mixed glial cultures were established via isolation of telencephalon, mesencephalon, and diencephalon of murine neonates from both wildtype (C57Bl/6) and STING truncation (Tmem173^{gt}) strains. We first established that the IC_{50} [Rotenone] = 78.90nM in this model by conducting a dose-response viability screening following 12-hour exposure to half-log increasing rotenone concentrations spanning 1nM to 1000nM in wildtype cells. We next explored the effects of pharmacologic STING modulation or genetic STING ablation on cell survival using a permeability-based viability assay at doses below or above the IC_{50}. To determine if rotenone induced genomic or mitochondrial DNA damage, we extracted DNA from respective cellular fractions and performed commercially available fluorometric detection assays for 8-OHdG and phospho-γ-H2A.X. We further investigated the effect of sub-lethal rotenone exposure on the cGAS-STING signaling pathway across timepoints using high content slide scanning immunofluorescence microscopy coupled with automated deep learning-based image analysis. To verify the effects of STING activation on immune modulatory signal transduction, we explored the effects of rotenone treatment on transcription factor activity, using an NF-kB-GFP reporter system, and coupled this assessment with characterization of cytokine and chemokine release into the culture supernatant. Lastly, to interrogate the effects of STING abrogation on glial-mediated neurotoxicity we performed viability screenings on conditioned media-treated primary neuronal cultures.

Results: We report that 100nM rotenone treatment significantly disrupts mixed glial cell viability, although both STING inhibition and genetic truncation did blunt cytotoxicity. Further, mitochondrial and nuclear DNA both exhibited significantly greater evidence of oxidative damage following rotenone treatment. At 3 hours of exposure, the number of perinuclear p-STING^{+} foci was significantly increased in rotenone-treated cells positive for GFAP and ALDH1L1. This coincided with a greater coverage of nuclear p-IRF3^{+} area in GFAP^{+} ALDH1L1^{+} double-positive cells, which was attenuated by STING ablation. These changes in cGAS-STING activation were accompanied by heightened NF-kB activity over 18 hours of rotenone exposure; interestingly, treatment with DIDS salts to inhibit mitochondrial VDAC oligomerization curbed NF-kB activation suggesting that preventing release of mtDNA into the cytosol may reduce activation of STING. This transcriptional activity was followed by the release of TNF-α, IFN-β, VEGF, and IL-6 into the culture supernatant. Together, this signal transduction resulted in STING-dependent neurotoxicity in primary neuronal cells.

Conclusions: Taken together, these data suggest an important role of cGAS-STING signaling in the activation of astrocytes and secretion of immune modulatory cytokines in a PD-relevant *in vitro* exposure model. This work motivates the subsequent exploration of this cascade *in vivo* given its probable involvement in astrocyte- mediated neuroinflammation and PD-like motor deficits.

17. Aldehyde dehydrogenase 1 and 2 knockout blunts dieldrin-induced neuronal loss and immune activation

Poster #17

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Parkinson's disease (PD) is the fastest growing neurodegenerative disease with epidemiological studies report exposure to occupational and environmental toxins as a risk factor. The environmentally persistent organochlorine pesticide dieldrin is one such toxin, with increases in both serum- and brain-concentration of dieldrin being associated with PD. While the mechanism behind dieldrin neurotoxicity is poorly understood, *in vitro* studies implicate perturbed dopamine (DA) metabolism and the accumulation of the reactive metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). We hypothesize inactivation of aldehyde metabolism in dieldrin-exposed mice will result in the accumulation of reactive DA metabolites, including DOPAL, which will exacerbate dopaminergic (DAn) neurotoxicity. To interrogate this hypothesis, 8-week-old wild-type (WT) C57Bl/6 and aldehyde dehydrogenase 1 and 2 (ALDH1/2) knockout (KO) mice were dosed daily with dieldrin (0, 1, 3 mg/kg) for 6 weeks via oral gavage. Quantitative pathological examination was performed using immunofluorescence labeling of microglia (IBA1) and DAn cells (TH), as well as hematoxylin and eosin staining, on sections spanning the striatum (ST) and ventral midbrain, encompassing the substantia nigra pars compacta (SNpc) and pars reticulata (SNpr). High-throughput slide-scanning fluorescence microscopy was coupled with unbiased, neural-network based cell identification for the stereological quantification of total, pyknotic, and TH+ nigrostriatal neurons. Additionally, cell counts and morphological analysis of IBA1+ cells were performed. We report dose- and genotype-mediated effects on dieldrin neurotoxicity, including a dose-dependent loss of TH+ and total neurons in the SNpc of male mice. Notably, the magnitude of cell loss was reduced in male KO mice as compared to WT counterparts; no significant loss was observed among female mice irrespective of genotype, reflecting sex disparities observed in human PD. Dieldrin treatment resulted in a dose-dependent decrease in ST TH intensity as well as sex and genotype interactions. Quantification of IBA1+ counts reveals a decrease in the ST of male WT mice; conversely, an increase in IBA1+ counts was observed for female KO mice, overall consistent with a statistical main effect and interaction between dose and genotype. We report dose- and genotype-mediated effects on dieldrin neurotoxicity, including a dose-dependent loss of TH+ and total neurons in the SNpc in male, but not female, mice. Moreover, male ALDH1/2 KO mice displayed blunted neuron loss compared to WT counterparts. Dieldrin treatment resulted in a dose-dependent decrease in ST TH intensity, as well as a sex and genotype interaction effect. There was a decrease in IBA1+ cells in the ST of male WT mice, and an increase in female KO mice, treated with 1 mg/kg dieldrin, associated with a statistical main effect and interaction between dieldrin dose and genotype. Morphological characterization of SNpr IBA1+ cells demonstrated dose-, sex-, and genotype-specific variations, with a dose-dependent shift towards an ameboid, reactive phenotype in male WT mice. Together, these findings suggest deletion of ALDH1/2 protects, rather than exacerbates, dieldrin-induced neuropathological changes in male mice. This observation reflects sex-dependent differences in PD distribution, with male humans displaying a greater risk of developing this condition. There is a potential for an alternative mechanism of aldehyde metabolism less susceptible to disruption by dieldrin. Given dieldrin's extreme bioaccumulative ability and persistence, future directions will

explore how chronic sub-acute dieldrin exposure in aged mice influences susceptibility to dieldrin-induced neuropathology.

18. TRPV3 Deletion Enhances Naphthalene-Induced Lung Injury

Poster #18

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TRPV3 is a calcium channel expressed by airway epithelial cells and its expression is induced in response to epithelial damage. In initial studies, over-expression of TRPV3 in airway epithelial cells slowed migration and proliferation, while also enhancing adhesion and promoting transcriptional signatures consistent with an epithelial vs. mesenchymal state. TRPV3 is activated by various botanical and chemical irritants and plays a key role in regulating susceptibility of airway epithelial cells to injury as well as their ability to adapt to and recover from injury. Here we tested the hypothesis that TRPV3 knockout would exacerbate lung injury and interfere with the recovery of airway epithelial cells in mice following treatment with the Club-cell specific pneumotoxin, naphthalene. Wild-type and Trpv3-/- mice were treated with a single i.p. injection of either corn oil or naphthalene (200 mg/kg) and allowed to recover for up to 60h. Changes in pulmonary function were quantified using whole body plethysmography at various timepoints during the injury/recovery cycle and Flexivent analysis was conducted prior to necropsy. Changes in the expression of biomarkers including IL6, an indicator of ongoing injury and inflammation, TRPV3, and Ki-67 (a proliferation marker) were quantified by PCR. Differences in epithelial injury/repair were compared by histology. Trpv3-/- mice exhibited marked differences in breathing patterns at times when injury was most evident in histology samples (~24h after treatment), with more extensive and protracted effects in Trpv3-/- mice. Flexivent analysis demonstrated significant differences in pressure-volume curves (P/V loops) indicative of more fragile lung tissue 36h after treatment. IL6 remained elevated in Trpv3-/- mice after 36h, while Trpv3 and Ki-67 mRNA were suppressed. Further, histology showed more extensive injury to the epithelium, a disordered epithelium after 48h, and extensive parenchymal damage in Trpv3-/- mice. The results show that TRPV3 regulates key aspects of epithelial dynamics essential to the coordination of injury, stress adaptation, and repair. **Support: ES017431**

19. Juvenile manganese exposure and adult H1N1 infection increase susceptibility to neuronal death and pro-inflammatory microglial activation

Poster #19

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Neurodegenerative disorders (NDDs) are the fastest-growing cause of disability among older adults. While the etiology of such disorders is poorly understood, pro-inflammatory immune signaling is implicated in the pathogenesis of such conditions. Additionally, exposure to environmental toxins can increase the risk of NDD development. Manganese is an essential trace mineral that is a cofactor for numerous enzymes and has immune signaling functions. Excess accumulation of Mn in the basal midbrain can lead to Manganism, a neurologic disorder leading to Parkinsonian-like symptoms and cognitive impairment. Recent epidemiological studies implicate lifetime systemic viral infection with the risk of developing NDDs. Specifically, infection with neurotrophic RNA viruses can lead to long-lasting neurological sequelae, including cognitive impairment and motor dysfunction. Following the 1918 Spanish Influenza pandemic, there was a marked increase in encephalitis lethargica. However, it is not known why only select patients surviving H1N1 infection developed post-encephalitic Parkinsonism. The variation of neurological symptomology following H1N1 infection implicates multiple factors working synergistically to create a severe encephalitic phenotype. Previously, our lab demonstrated that manganese exposure in juvenile C57BL/6 mice increases glial inflammatory responses in the substantia nigra following infection with H1N1 influenza virus. In the present study, this dual-hit neurotoxin-pathogen model is employed to investigate how juvenile Mn exposure alters H1N1- induced pathology in the hippocampus. Treated mixed sex mice were given $MnCl_2$ at 50 mg/kg/day in water at P21 for 30 days, then regular water for a month. Intranasal administration of phosphate-buffered saline with 10^3 $TCID_{50}$ A/California/04/2009 H1N1 when the mice were 8 weeks old. Mice were sacrificed at 21 dpi. Coronal brain sections encompassing the hippocampus were stained against IBA1, allowing for assessment of the number and morphology of microglia and invading macrophages across hippocampal subregions. Additionally, hematoxylin and eosin (H&E) staining was performed to identify the number of healthy and pyknotic neurons within the dentate gyrus. Image-level analysis reveals a main effect for Mn on IBA1+ microglia number, and an increase in IBA1+ cells in subregions CA1 and CA3. Mn exposure increased the total area occupied by IBA1+ processes within every hippocampal subregion. Additionally, a Mn interaction with H1N1 was observed, with dual-hit mice displaying a blunted, but not rescued, IBA1+ area. Individual morphometric profiling of microglia was accomplished by measuring the length of IBA1+ processes, the area occupied by IBA1+ cells, and the number of branch points. Region-specific analyses reveal main effects for Mn and H1N1 on all measures; this trend was observed across every hippocampal subregion apart from CA2. Curiously, morphological characterization of IBA1+ cells reveals that Mn treatment did not result in a more ameboid cellular phenotype. Rather, IBA1+ cells from Mn-treated animals display greater cell volume, process length, number of branching points, and number of end points. Preliminary H&E analysis of the dentate revealed a decrease from control in the number of neurons per μm^2 for all treatment groups, as well as a dual-hit specific increase in the ratio of pyknotic neurons and total neurons. Future directions will assess the number and reactive state of astrocytes within hippocampal subregions. These findings highlight the ability of juvenile manganese exposure to create a lasting microglial inflammatory phenotype in the brain that persists independently of viral infection in adulthood.

20. Enteric glial inflammation and neurodevelopmental perturbations triggered by chronic low-dose exposure to manganese via drinking water in juvenile mice

Poster #20

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Manganese, while essential for biological processes, exhibits neurotoxic properties at elevated concentrations, posing significant public health concerns through contaminated drinking water sources worldwide. Exposure during critical developmental windows may contribute to neurodevelopmental disorders, particularly relevant given the prevalence of early childhood environmental manganese exposure. Despite extensive characterization of acute, high-dose manganese effects on central nervous system function, chronic low-dose exposure impacts on the enteric nervous system and gut-brain axis remain insufficiently explored, especially in developing organisms. This investigation examined the consequences of low-dose manganese exposure (15 or 50 mg/kg $MnCl_2$ via drinking water) in juvenile male and female mice over a 13-week period, employing a comprehensive, multisystem approach. High-dose manganese administration elicited sexually dimorphic neurotransmitter alterations, with females demonstrating pronounced central glutamatergic dysregulation while males exhibited significant enteric serotonergic perturbations. These neurochemical disruptions manifested behaviorally as increased stereotypic movements in males and impaired object recognition memory in both sexes by week 13. Immunohistochemical analyses revealed dynamic, sex-dependent alterations in enteric glial distribution, with initial male vulnerability transitioning to persistent female effects during extended exposure. Concurrent microbiome analysis identified progressive dysbiosis marked by substantial Erysipelotrichaceae expansion. Correlation analyses demonstrated significant associations between enteric serotonergic parameters, central kynurenine pathway metabolites, neuroinflammatory indicators, and behavioral outcomes. These findings illuminate manganese's capacity to induce complex, sex-specific disruptions across multiple biological systems in developing organisms, with implications for understanding environmental contributions to neurodevelopmental disorders and informing risk assessment strategies for vulnerable populations.

21. Arsenite and Its Metabolite Monomethylarsonous Acid Impair Early Human Red Blood Cell Development

Poster #21

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Chronic exposure to heavy metals, including arsenic, is linked to adverse health outcomes such as anemia. The trivalent inorganic form of arsenic (arsenite, AsIII) causes hematotoxicity in both in vivo and in vitro models. However, the contribution of AsIII-derived metabolites to early red blood cell (RBC) development remains largely unknown. 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, CD34+ cells were cultured in two parallel systems: HemaTox Erythroid™ medium, selective for erythroid development, and H4330 MethoCult™ medium, which supports both erythroid and myeloid progenitors. HPCs in both systems were exposed to low concentrations of AsIII or MMAIII. After 3 days, viability and early RBC growth were assessed by acridine orange/propidium iodide staining, and erythroid differentiation was assessed by flow cytometry using CD71 and CD235a expression. Hematopoietic impacts were further evaluated by colony formation in H4330 MethoCult™ after 14 days. AsIII and MMAIII reduced the viability and differentiation of early human RBCs in a dose-dependent manner. Flow cytometry revealed impaired erythroid differentiation, with early RBCs failing to mature, resulting in fewer CD235a+ cells. Colony-forming assays likewise showed significant reductions in erythroid colonies (BFU-E and CFU-E) after exposure to both arsenicals. Hematotoxic effects were similar between male and female donors, with MMAIII generally more potent than AsIII. Collectively, these findings indicate that early stages of human RBC development are highly susceptible to hematotoxicity from AsIII and MMAIII. Ongoing mechanistic studies aim to elucidate how arsenic biotransformation contributes to disrupted erythropoiesis and anemia.

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22. Analysis of metabolic and inflammatory biomarkers in human subjects with exposure to tungsten

Poster #22

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Background and Purpose: Tungsten is classified as an emerging environmental toxicant due to increased human exposure and lack of knowledge of the health risks. Epidemiological and in vivo studies have shown that tungsten exposure is associated with increased incidence and/or severity of cardiometabolic diseases including cardiovascular disease (CVD), chronic kidney disease (CKD), and diabetes as well as cancer progression, however there is not a clear understanding of the underlying molecular mechanisms. An epidemiological cohort exposed to increased levels of tungsten is the San Luis Valley Diabetes Study. The San Luis Valley houses the headwaters of the Rio Grande River and has been experiencing regional water insecurity. The water demand in this region are also starting to trend higher than the current supply, putting this population at increased risk of exposure to environmental metals. Previous publications have correlated urinary tungsten concentrations with increased/ more severe diabetes and CKD outcomes. One factor that can drive metabolic diseases is adipocyte dysfunction leading to a pro-inflammatory state. In vivo studies conducted by our lab have also shown that tungsten enhances adipogenesis in the bone marrow niche of mice. By looking at pro-inflammatory cytokines/adipokines in the serum, we aim to draw further conclusions and provide some of the first evidence linking tungsten exposure to adipocyte dysfunction that could play a role in disease pathogenesis including cancer, diabetes, CKD and CVD.

Methods: Utilizing human serum samples from the San Luis Valley Diabetes Study, we conducted a multi-analyte enzyme-linked immunosorbent assays using the multi-plex Luminex platform. Human serum samples were analyzed for adipokine/proinflammatory cytokines as well as several disease biomarkers. The analytes analyzed included: FABP4, Insulin, Leptin, Chemerin, OPN, Adiponectin, Adipsin, Resistin, PAI-1, IL-6, IL-1β, TNFα, MCP-1, IL-8, IL-18, VCAM-1, ICAM-1, VEGF-A, TFF3, MMP-9, MMP1, CRP, Cystatin C, β 2-Microglobulin, Calbindin D, and NGF. Simple liner regression and Pearson Correlation analyses were used to correlate urinary tungsten concentration with analyte concentration in the serum.

Results: N=160 serum samples were analyzed in this study, correlating urinary tungsten values to the values (in pg/mL) of each analyte in the serum. Interestingly, there was a significant positive correlation between increasing urinary tungsten concentrations with increasing levels of analytes MMP-1, $p = 0.0004$; OPN, $p = 0.0448$; and VCAM-1, $p = 0.0644$. And a slight negative correlation between increasing urinary tungsten concentrations with decreasing levels of analytes FABP4, $p = 0.0565$ and Chemerin, $p = 0.0818$.

Conclusions: Overall, this is the first study to correlate tungsten exposure to levels of adipokines/pro-inflammatory cytokines within the serum of humans. This is promising early data to suggest that tungsten exposure could be leading to adipocyte dysfunction. Since epidemiological studies are limited, further studying vulnerable populations such as this one is highly important to be able to determine molecular drivers of tungsten-mediated disease. Further studies need to be completed to include other demographic information into the analysis including sex, age, disease state, etc. In addition, we plan to statistically evaluate the impact of these adipokines/cytokines on the association between tungsten and cardiometabolic and kidney disease outcomes in this cohort.

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23. Sex-Specific Immune and Inflammatory Responses to Tungsten Exposure in Mice

Poster #23

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Tungsten is an emerging environmental toxicant, where exposure to individuals can range from environmental, occupational, and military settings. Studies investigating the toxicity of tungsten have been limited; however, since tungsten exposure is increasing, increased awareness has begun to emerge. Prior studies suggest that inhalation exposure to tungsten increases pulmonary and cardiovascular inflammation in female mice more than in male mice, which could contribute to the development of cardiac injury. However, information on the specific immune cell populations within cardiovascular tissue following exposure is unknown. In addition, a more head-to-head comparison between female and male mice is needed to make direct comparisons. This study will explore how oropharyngeal aspiration of tungsten particulates changes immune cell populations in the lungs and heart between female and male mice. Male and female mice will be evenly split into groups and dosed with 50μg/μL tungsten particles (W) or dispersion media (CTL). After 24 hours, the heart, bronchoalveolar lavage fluid (BALF), and plasma will be collected for analysis. Using flow cytometry, the BALF and heart will be analyzed to characterize immune cell populations. Enzyme-linked immunosorbent assays (ELISAs) will be used to detect the presence of proinflammatory cytokines TNFα and IL-1β in the BALF and plasma. Analysis of BALF showed an increase in the total number of cells in female mice over male mice exposed to tungsten. Flow cytometry immunophenotyping of BALF showed that the predominate immune cell population was macrophages, but there were not statistically significant differences between groups. However, an increasing trend was observed in both female and male mice following exposure. IL-1β was increase in the BALF, but not the plasma of both male and female mice. Flow cytometry immunophenotyping of the heart showed significant decreases in B-cells and macrophages following tungsten exposure in female mice only. These results suggest that in both male and female mice inhalation exposure to tungsten particles induces pulmonary inflammation, but the kinetics might be different between male and female mice. These data also suggests that in female mice there are slight changes in immune cell populations in the heart following acute exposure that should be investigated further to determine how these immune cell populations could be driving cardiac injury.

24. Evaluating the Fibrogenic Effects of Tungsten Particulate Exposure in 3T3 Fibroblasts

Poster #24

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Tungsten is a heavy metal increasingly recognized as an emerging environmental toxicant. Inhalation of tungsten particulates is a key route of human exposure, especially in occupational settings where air concentrations of tungsten in hard metal factories have been reported as high as 6 mg/m^3. Inhalation exposure to particulates has been associated with an increased risk of pulmonary and cardiovascular diseases. However, the systemic implications of tungsten-induced lung injury remain unexplored. Recent epidemiological studies have identified a correlation between tungsten exposure and elevated risk of cardiovascular diseases and stroke, but the mechanistic pathways linking pulmonary exposure to cardiac dysfunction have yet to be elucidated. Prior work from our lab has demonstrated that acute inhalation of tungsten particulates induces IL-1β driven pulmonary inflammation and early signs of cardiac injury, with repeated exposures leading to increased cardiac expression of pro-inflammatory and pro-fibrotic markers. These findings suggest that tungsten exposure could be contributing to cardiovascular disease through IL-1β-mediated inflammation and cardiac remodeling. This study explores how tungsten particulate exposure affects the secretion of pro-inflammatory and pro-fibrotic mediators in immune cells, and how these signals affect fibroblasts activation and gene expression *in vitro*. 3T3-L1 fibroblasts were treated for 72 hours with supernatant collected from THP-1 cells exposed to 200 ng/mL tungsten particulates. RNA was isolated, and gene expression was analyzed using qPCR to assess pro-inflammatory (TNF-α, IL-1β, IL-6) and pro-fibrotic (TGF-β2, α-SMA, Col1α1, Col3α1, MMP-2, & MMP-9) gene markers. These data will provide insight into how tungsten-mediated pulmonary inflammation could contribute to the development of cardiac fibrosis and define gene expression patterns in fibroblasts that could serve as indicators of early fibrotic remodeling following exposure.

25. Investigating DNA damage in an immune-epithelial interface co-culture model following exposure to uranium bearing dust

Poster #25

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Thousands of abandoned uranium mines (AUMs) are present within the western United States. Many of these mines exist on tribal lands in close proximity to indigenous communities. People can be exposed to mine waste through inhalation of waste particulates, drinking contaminated water, or eating plants grown in contaminated soil. Chronic exposure to metal-bearing particulate matter (PM), blown from these AUMs can result in chronic diseases, including autoimmune diseases. Investigating the health effects following exposure to AUM waste is critical to understanding risk. In order to investigate effects following exposure, AUM PM from the St. Anthony mine, located outside of the Pueblo of Laguna in New Mexico was used in an *in vitro* immune-epithelial interface co-culture model of A549 lung epithelial cells and THP-1 derived macrophages. Acute toxicity endpoints were assessed in the presence of increasing concentrations of AUM PM after 24 hrs of exposure using high content imaging. Changes in Claudin-2, Actin cytoskeleton, and γ-H2AX visualization were quantified and analyzed to quantify cellular damage following exposure. Preliminary data suggests an increase in DNA damage within THP-1 macrophage populations following exposure to AUM PM. Results from the present study will provide important information on how exposure to AUM PM can contribute to pulmonary and systemic immune dysregulation, leading to the development of autoimmune diseases. Funding P42ES025589

26. Environmental Uranium Perturbs Gut Microbial Composition, Goblet Cells, and Metabolic Signaling

Poster #26

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Over 260 of the 4,000+ abandoned uranium mines in the U.S. are located in New Mexico, many concentrated within the Laguna Pueblo of the Navajo Nation. Despite long-standing community exposure, the health effects of chronic uranium contamination remain poorly understood. To address this gap, we examined how prolonged exposure to environmentally relevant uranium levels alters the gut and systemic health. Mice were provided drinking water for 42 days from the Rio Paguate River either upstream (<0.5 ppb uranium) or downstream (>580 ppb) of the Jackpile Mine. Although there was no overt intestinal inflammation, as indicated by stable fecal lipocalin-2 (LCN2) levels, uranium-exposed mice exhibited decreased circulating leptin and increased colonic Mucin 2 expression as detected by immunofluorescence in colon sections, suggesting shifts in metabolic signaling and goblet cell dynamics. Metagenomic sequencing revealed uranium exposure reduced alpha diversity and altered beta diversity over time. Notably, we observed enrichment of *Salmonella enterica* and *Clostridium sporogenes*, taxa associated with microbial tryptophan metabolism and immune modulation. Functional annotation of metagenome-assembled genomes (MAGs) showed a significant increase in oxidative stress and metal-resistance pathways, including catalase-peroxidase (katG) and siderophore biosynthesis genes. These pathways were disproportionately represented in uranium-exposed mice, suggesting selective pressure favoring microbial ROS defense and uranium chelation mechanisms. Together, these findings demonstrate that chronic uranium exposure perturbs the gut microbial-mucosal axis by reshaping microbial community function and host epithelial responses in the absence of classical inflammatory markers. This work highlights a previously unrecognized dimension of environmental uranium toxicity, with potential implications for metabolic health and mucosal barrier function in exposed communities.

27. Development of an autoimmune prone disease state following inhalation exposure to uranium bearing dust in MRL/MpJ mice

Poster #27

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Background and Purpose: The western United States consists of thousands of abandoned uranium mines (AUMs), many of which are present in the 4 corners region of the Southwestern United States. These AUMs are in close proximity to residential areas, many of which exist on tribal lands. Improper cleanup procedures and lack of remediation have led to significant concerns of windblown, fugitive dust blowing into these communities contributing to chronic health disease, including autommune diseases. Investigation into these long-term chronic health effects following exposure is critical to understand human health risk. We hypothesize that chronic inhalation exposure to AUM particulate matter (PM) will induce an autoimmune prone disease state through immune dysregulation and chronic inflammation.

Methods: 9 - 11 week old female MRL/MpJ mice were exposed through oropharyngeal aspiration to AUM PM from the St. Anthony mine, a former mine near the Pueblo of Laguna in New Mexico and control PM from a coal mine in Colorado containing low metal PM content (Colorado Red). Energy-dispersive X-ray spectroscopy characterization of these dusts revealed that the St. Anthony PM is rich in silica and heavy metals such as uranium and vanadium, while the Colorado Red PM has negligible levels of uranium and vanadium, but similar silica content. Mice were exposed four times in total at a concentration of 50μg/μL of PM in dispersion media across the course of two weeks. Endpoint analysis were evaluated at 2 weeks, 24-hours post the final exposure and 12 weeks, 10 weeks after final exposure. Primary endpoints methodology consisted of analysis of immune cell populations in the bone marrow, spleen, and lungs by flow cytometry, cytokine analysis in the bronchoalveolar lavage fluid (BALF) and plasma using multiplex cytokine arrays, Neutrophil elastase levels in the BALF and plasma by enzyme-linked immunosorbent assay (ELISA), and metal deposition within the lungs and bones by inductively coupled plasma mass spectrometry (ICP-MS).

Results: Our findings illustrate significant alterations in immune cell populations in the lungs following exposure to AUM PM at the 2 week timepoint. In particular, we found recruitment of neutrophils after exposure to the AUM PM relative to both our vehicle control, dispersion media and the environmental dust control Colorado Red. In order to investigate the function of the neutrophils, we ran neutrophil elastase ELISAs and found a significant increase in neutrophil elastase in the lungs and plasma in the AUM PM group relative to the control groups. ICP-MS analysis revealed that in the AUM PM group, there was a retention of heavy metals incluidng uranium, vanadium and aluminum in the lungs, that are not present in the other control groups, even at the 12 week timepoint, providing evidence of long-term metal retention in the lungs that could be contributing to immune dysregulation both in the lungs and systemically.

Conclusions: Overall, we demonstrate that inhalation exposure to AUM PM causes significant alterations to the immune cell populations of the lungs. Particularly, an increased in the levels of activated neutrophils secreting neutrophil elastase, leading towards production of neutrophil extracellular traps (NETs) that can drive immune dysregulation and the development of autoimmunity. Retention of uranium and other heavy-metals from the AUM PM is a unique factor across the conditions that we hypothesize is a leading driver of the effects seen after aspiration exposure to AUM dust.

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28. Chronic Low-Dose Exposures of Cadmium and Hyperglycemia Drive Dysfunctional Hepatic Mitochondrial Biogenesis and Dynamics

Poster #28

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Metabolic (Dysfunction) Associated Fatty Liver Disease (MAFLD) is a major risk factor of long-term hepatic morbidity and mortality across the globe. Chronic liver disease (CLD) rates are rising in southwestern United States, including here in New Mexico (NM). NM has the highest rates of CLD in the US (36.4/100,000 in 2022), mainly among Hispanic and Native American populations, for unknown reasons. Our main hypothesis is that environmental exposures (e.g., heavy metals) accelerate liver dysfunction in conjunction with innate risk factors such as type II diabetes and obesity, which are high in these populations. Cadmium (Cd), an environmentally pernicious heavy metal pollutant, is linked to chronic metabolic disturbances including obesity, type II diabetes, and MAFLD. The specific role of chronic Cd exposures on sustained oxidative hepatic damage and mitochondrial dysfunction is not well understood. In this study, we investigated the effects of chronic low-dose cadmium exposures (CLEC) and hyperglycemia on hepatic oxidative and mitochondrial damage. The CLEC model paradigm uses liver cell lines, HepG2 and HUH7, to study the impacts of chronic Cd exposures (~24 weeks) and hyperglycemia (15 mM) modeling effects seen in the real world. Key metabolic findings in our CLEC exposure modeling study include – i. CLEC models show enhanced sorafenib induced mitotoxicity under galactose condition (glu-gal assay) ii. CLEC exposures induce superoxide radical production with a hyperglycemic amplification effect iii. CLEC exposure altered mitochondrial density with associated mitochondrial dysfunction - characterized by mitochondrial membrane potential ($\Delta\Psi m$) differences, and morphological alterations and iv. dysregulation of intrinsic mitochondrial parameters such as oxygen consumption rates ($\downarrow$OCR), $\downarrow$ ATP production, and unchanged spare respiratory capacity. Chronic cadmium and hyperglycemia exposures lead to transcriptional and translational changes to key antioxidant genes and mitochondrial dynamic related protein expression (Drp1, MFN2, and Tomm20), exacerbating cellular vulnerability. In summary, chronic Cd exposures have the potential to dysregulate the hepatic mitochondrial homeostasis leading to damaged OXPHOS metabolic cycling and disrupted energy metabolism. Dysfunctional energy metabolism is a key hallmark of MAFLD pathogenesis. We also observe significant hyperglycemia dependent, Cd-induced metabolic deregulatory effects. This data supports our primary hypothesis for a heavy pollutant induced *acceleration* of bioenergetic dysfunction among type II diabetics. Our results underscore the urgent need for investigation into the long-term impacts of heavy metal exposures as a key driver of chronic diseases such as MAFLD and diabetes. Finally, our study also underscores the need for focused attention examining effects of heavy metal pollution in “at-risk” subpopulations such type II diabetics and obese individuals who may be at elevated risk for liver damage compared to normal individuals.

29. The Effects of Cadmium on Adipogenesis and Breast Cancer Metastasis in the Bone Niche

Poster #29

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Cadmium, a heavy metal widely used in battery production, electroplating, paints, and metal alloys, has also become a significant environmental toxicant with carcinogenic and obesogenic potential. Human exposure to cadmium occurs through occupational hazards in metal industries, inhalation of cigarette smoke, and water contamination due to industrial and agricultural pollution. Our research group has previously demonstrated that the metal tungsten enhances adipogenesis and promotes breast cancer metastasis to the bone. Given that cadmium similarly accumulates in bone tissue and shares carcinogenic and obesogenic properties, we aim to investigate whether cadmium can also drive adipogenesis and breast cancer metastasis in the bone niche. We hypothesize that increased cadmium concentrations will enhance adipogenesis, subsequently promoting breast cancer metastasis in the bone. These findings could hold critical implications for breast cancer patients exposed to high environmental levels of cadmium.

Both in vitro and in vivo models were used to test our hypothesis. OP9 mouse bone marrow stromal cells were used to investigate cadmium-driven adipogenesis and the molecular mechanisms involved. MTT assays assessed cadmium chloride ($CdCl_2$) toxicity in OP9 cells, determining non-toxic doses for further experimentation. OP9 cells were dosed with $CdCl_2$. Cells were stained with Oil Red O to quantify adipocyte formation. In addition, a mouse model was utilized, where $CdCl_2$ was administered through drinking water to assess its impact on bone adipogenesis. Adipocytes were quantified through histological staining of bone tissue sections for the adipocyte marker Plin1. These combined models will provide crucial insights into cadmium's role in altering the bone microenvironment, potentially driving breast cancer metastasis.

MTT assays revealed that the 0.5μM and 1μM concentrations of $CdCl_2$ caused no toxicity after 48 hours. This range of concentrations were subsequently used for phenotypic staining with Oil Red O, where the 0.75μM concentration had a significant increase in the number of adipocytes staining positive.

Quantification of adipocytes within mouse bone marrow orally exposed to $CdC1_2$ revealed that mice orally exposed to $CdCl_2$ had a greater number of adipocytes staining positive for the adipogenic marker Plin1 within their bone marrow at the 5ppm concentration.

The preliminary data suggest that cadmium exposure promotes adipogenesis in OP9 cells, particularly at the 0.75μM concentration and in mice orally exposed to cadmium at the 5ppm concentration. This enhanced adipogenesis could create a more favorable bone microenvironment to promote breast cancer metastasis, paralleling the effects we observed with tungsten. An ongoing in vivo study will further explore cadmium's role in enhancing breast cancer metastasis to the bone following oral exposure. These findings could deepen our understanding of cadmium's contribution to breast cancer progression, potentially impacting the 13% of the U.S. population affected by this disease.

30. Development and Validation of an HPLC Assay to Measure Anti-Oxidant GSH and Lipid Peroxidation Metabolite MDA to Understand Oxidative Stresses in a Hepatocellular Model

Poster #30

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Cadmium (Cd) is a highly toxic environmental and industrial pollutant associated with metabolic syndrome (MetS), obesity, type II diabetes, and metabolic dysfunction associated fatty liver disease (MAFLD). Chronic liver disease rates are the highest in the nation in New Mexico, mainly in Hispanic and Native American communities (36.4/100,000 in 2022). Cd exposure drives cellular oxidative stress via mitochondrial dysfunction to generate reactive oxygen species (ROS). Glutathione (GSH) is the key cellular antioxidant that neutralizes damaging free radicals (ROS) and maintains homeostatic balance and cellular health. Tissues contain 1-10 mM GSH in the reduced form. Reduced GSH levels are a biomarker of oxidative stress, indicating poor cellular health. Lipid peroxidation (LPO) is a cell-damaging process triggered by ROS reacting with polyunsaturated fatty acid residues of phospholipids in cells. Malondialdehyde (MDA) is a highly reactive and toxic byproduct of LPO. Thus, accurate quantification of cellular GSH and MDA levels is helpful to evaluate oxidative stress in cells. In the current study, we established and validated methods to quantitatively measure GSH and MDA using high-performance liquid chromatography (HPLC). Measuring GSH levels in biological samples is difficult due to the rapid autooxidation of GSH, leading to an underestimation of GSH levels. The sulfhydryl groups on the cysteine residues of GSH can be blocked by a thiol alkylating agent such as N-ethylmaleimide (NEM), preventing artificial oxidation. The resulting GS-NEM conjugate is detectable by high-pressure liquid chromatography (HPLC) with a diode array detector (DAD). Measuring MDA levels in biological samples requires a derivatization step, for which 2-thiobarbituric acid (TBA) is commonly used. The resulting MDA-TBA_2 conjugate can be measured fluorometrically by HPLC with fluorescence detection (FLD). The HPLC method is rapid and reliable, with the advantage of increased sensitivity due to the use of a fluorescence detector rather than an absorbance. We established a linear range of detection from 100 uM to 10 mM for GSH-NEM. The established MDA-TBA_2 linear range was from 0.15 to 1 uM. We measured the GSH and MDA levels in two epithelial liver cancer cell lines, HepG2 and HUH7, cultured under normoglycemic (5.5mM) and hyperglycemic (15 mM) conditions representing non-diabetic and diabetic states. Our HPLC GSH and MDA quantification assays are a valuable tool to understand the impact of chronic, low-dose exposures of Cd (CLEC) on cellular oxidative stress of hepatocellular cells. Our assay is a valuable adjunct to understand the long-term impacts of heavy metal exposures on hepatic function.

31. Emerging chemical exposures and Immune system evaluations in exposed communities living in a Superfund site

Poster #31

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The Ramapough Lenapee Nation Turtle Clan has lived in Bergen County, New Jersey, for several hundred years. Their land, contaminated with compounds like aluminum, arsenic, antimony, and benzo[a]pyrene, was declared a Superfund site for a second time. Supported by the NIEHS R01 grant (5R01ES033545), our research team, with strong Tribal community input, investigates contaminant levels in soil, plants, and community members using biomonitoring (n=100).

The presence of 24 urinary metals was determined using ICP-MS, and the presence of 52 PFAS compounds was analyzed from serum samples. TriCore laboratory used serum samples to identify inflammatory conditions, vitamin deficiencies, and liver function. ELISA kits measured serum concentrations of anti-TPO and anti-Tg autoantibodies for thyroid autoimmunity (EDI High Sensitive Anti-TPO ELISA Kit, San Diego, CA). Indirect immunofluorescence (IIF) determined antinuclear autoantibody (ANA) microscopic patterns, which were evaluated according to the International Consensus on ANA Patterns (ICAP) requirements, the gold standard for such analyses.

The ANA staining shows autoimmune biomarkers in many samples, with a handful scoring high on ICAP requirements. More than 50% of study participants had eight or more detectable PFAS compounds in their serum samples. 22% exhibited increased liver function, while 15.6% showed serum indications of non-alcoholic liver disease, a concern associated with heightened PFAS exposures in other communities. The associations between anti-thyroid autoimmunity and chemical and metal exposures were investigated. Anti-TPO autoantibodies showed a strong positive correlation with metals such as Mg, Al, Cr, Fe, Co, Zn, Se, Mo, Cd, and Hg. Conversely, anti-Tg autoantibodies exhibited negative correlations with Al, Be, Cr, and Hg. Vanadium (V) demonstrated a strong positive correlation with Pb, Ba, Sb, Sn, and Cd. Vitamin D deficiency was identified in 53.1% of participants, with only one participant having elevated levels. High levels of CRP-hs were found in 50% of participants, while 18.8% had low levels. Seven PFAS compounds were detected in over 80% of participants.

32. Literature review of Lumex Fluorat

Poster #32

Alvin Yazzie, Nikita Dougan, Gabriel P. Lopez, Thiagarajan Soundappan

Abstract not available.

33. Harnessing Biomolecular Recognition and Protein-Driven Phase Separation for Selective Uranium Preconcentration

Poster #33

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Uranium contamination in groundwater from legacy mining activities poses significant health risks, impacting communities across the southwestern United States. Addressing this challenge requires accessible, field-deployable tools capable of detecting uranium with high specificity and sensitivity. In this work, we present the foundation for a biosensor platform that leverages fusion proteins of elastin-like polypeptides (ELPs) to preconcentrate uranium from water samples. We investigate two complementary protein-based systems that utilize thermally induced phase separation to concentrate uranium. The first system employs a DNA-binding ELP fusion protein, which interacts with a high-affinity DNA aptamer selective for uranyl ions (UO_2^{2+}). Upon heating above the protein's phase transition temperature (T_t), this complex undergoes coacervation, concentrating uranium. The second system features an ELP fused to a super uranyl-binding protein (ELPSUP), which directly binds to uranyl ions and concentrates them upon the addition of heat and salt. We hypothesize that engineered, stimuli-responsive proteins undergoing liquid– liquid phase separation (LLPS) can effectively capture and concentrate uranium either via direct binding (ELP-SUP) or through DNA-mediated complexation. Together, these two strategies, molecular recognition followed by thermally triggered preconcentration, represent promising approaches toward the development of biosensing methodologies for practical, low cost and user-friendly uranium detection and quantitation. Ultimately, our work lays the foundation for technologies to empower communities impacted by legacy mining by enabling near-real-time monitoring of uranium-contaminated water.

34. Development and validation of Quantification method of As, Ba, Be, Cd, Co, Cr, Cs, Cu, Mn, Mo, Pb, Sb, Se, Ti, U, V, W and Zn in human urine with ICPMS

Poster #34

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Trace elemental analysis in biological matrixes is crucial for evaluating environmental exposure to toxic metal, and for monitoring essential elements. As, Ba, Be, Cd and Pb are well-established toxicants associated with adverse effects including cancer, organ dysfunction and neurotoxicity, even at low concentrations. Zn, Cu, Co and Se are involved in several biochemical processes which make them essential at trace levels, although high concentrations are associated with health risks. Elements such as Sb, U and W, which are commonly from industrial sources, pose health risks through accumulation and toxicity. Herein, the method development and validation of the trace analysis of As, Ba, Be, Cd, Co, Cr, Cs, Cu, Mn, Mo, Pb, Sb, Se, Ti, U, V, W and Zn in human urine using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is presented. Precision, accuracy and limit of quantitation validation parameters were evaluated for each element across several analytical schemes. The evaluated schemes were various combinations of analytical conditions, including different modes of detection (Standard, Kinetic Energy Discrimination using helium and Dynamic Reaction Cell using ammonia), internal standards (Ga, Ge, Rh, In, Te, Y, and Ir), and mass-to-charge ratios (m/z). This method has been proven to be repeatable and accurate at a spiking range 0.5ppb to 50ppb for the quantitation of trace element analytes (As, Ba, Be, Cd, Co, Cr, Cs, Mn, Mo, Pb, Sb, Ti, U, V, W). Some naturally occurring elements in urine (Zn, Se, and Cu) were proved to be precise at the entire analytical range but accurate only at the 10 to 50ppb spiking solutions. Limits of quantitation below 1ppb were established for some elements. Precision and accuracy in the sample were confirmed at ppt concentrations for the following analytes: Be (86ppt), Co (10ppt), Cr (91ppt), Pb (13ppt), Sb (7ppt), U (6ppt) and V (12ppt).

35. Comparison of Uranium Measurement Technologies for Community-Based Environmental Monitoring

Poster #35

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The legacy of uranium mining in western New Mexico has left many communities with elevated uranium concentrations in local surface waters. Currently used uranium detection methods, such as inductively coupled plasma mass spectroscopy (ICP-MS), while highly sensitive, are not suitable for rapid and user accessible field testing. This study evaluates the sensitivity of two emerging uranium detection technologies—the Alpha Measurement Solutions ANDalyze™ and Lumex Instruments Fluorat™—in comparison to ICP-MS. The ANDalyze system employs a DNAzyme-based fluorescence biosensing method with a reported dynamic range of approximately 1–60 µg/L, while the Fluorat spectrophotometer system measures formation of luminescent uranium complexes over a reported range of approximately 1–2,000 µg/L. Both ranges span the value of the U.S. Environmental Protection Agency (EPA) maximum contaminant limit (MCL) for uranium in drinking water of 30 µg/L. Uranium detection, specifically the uranyl ion (UO_2^{2+}) was evaluated under two experimental conditions: laboratory-prepared samples of known uranium concentration and surface water samples collected from the Pueblo of Laguna's Rio Paguate. Results demonstrate strong linear correlations among all three methods, especially in lab-prepared samples. However, both devices showed consistent underestimation of uranium levels under both testing conditions, with the greatest underestimations being UO_2^{2+} concentrations below the EPA's MCL in collected field samples. These findings support the potential of ANDalyze and Fluorat as methods for uranium sensing in community-based environmental monitoring, while highlighting the need for further research into these technologies.

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36. Metal Exposure Associated with Use of Soil and Fertilizer Products in a Commercial Greenhouse Setting with Comparison to Prop 65 Safe Harbor Levels

Poster #36

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Agricultural products such as soils, fertilizers, soil conditioners, and pest control agents may contain varying levels of metals. This assessment was conducted to quantify potential occupational exposures to metals (e.g. arsenic, cadmium, chromium, lead, among others) from use of such products in a commercial greenhouse setting. The exposures were compared to established or derived Safe Harbor Levels to determine product warning requirements for California Proposition 65 regulations. An exposure analysis was conducted for a variety of metals based on the intensity, frequency, and duration of typical exposures associated with commercial use. For a given product, relevant routes of exposure (e.g. oral, inhalation, dermal) were determined based upon product formulation (solid vs. liquid) and intended use. Exposure scenarios considered in the assessment were based upon potential direct contact with solid or liquid product, contact with diluted or dissolved liquid product, and contact with soil to which product was applied. For screening-level purposes, bioavailability and form of each metal in the products were generally not considered. Where appropriate, exposure estimates were based upon parameters described by USEPA human health risk assessment guidelines for heavy metals in contaminated soils and agricultural fertilizers, CalEPA regulations, and USEPA Exposure Factors Handbook.

Liquid fertilizer products were associated with highest potential metal exposure followed by soils and dry fertilizer products, which were greater than pest control products, with soil conditioners showing the least contribution to exposure. The oral route was the highest contributor to exposure followed by inhalation and dermal routes for all metals, with the exception of arsenic. As an example, assuming that a given product contained cadmium at a concentration of 10 mg/kg, estimated daily exposure from a given product ranged from 0.2 to 0.6 µg/day. Meanwhile, product-specific estimated exposures to arsenic were generally higher, ranging from 0.4 to 4.8 ug/day, based on higher contributions from dermal exposure due to greater skin absorption of arsenic compared to other metals. Based on the specific routes of exposure for each product, maximum allowable metal concentrations were determined to permit compliance with Proposition 65 Safe Harbor Levels and warning requirements. For cadmium, product-specific maximum allowable concentrations were 118 mg/kg for soils and dry fertilizers, 79 mg/kg for liquid fertilizers, 77 mg/kg for pest control agents, and 782 mg/kg for soil conditioners.

The approaches of this screening-level assessment are adaptable to a variety of product types and exposure scenarios. The results can be used to estimate occupational and consumer exposures, determine compliance with relevant guidelines or regulatory standards, set product specifications, identify sources of exposure control, or further assessment if required.

37. Formaldehyde off-gassing from bed sheets and pillowcases: a simulation study and risk assessment

Poster #37

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Formaldehyde and formaldehyde-containing resins are used in clothing and other textiles, particularly those made from natural fibers to impart strength, durability, and wrinkle-resistance. Historical concerns of potential health effects associated with elevated formaldehyde levels have prompted improved testing and regulatory standards in the textile industry. Clothing has been a major focus of these efforts due to the occurrence of allergic contact dermatitis among consumers. Meanwhile, the highest airborne concentrations of formaldehyde are generally found indoors as a result of off-gassing from building materials and consumer products. The inhalation of formaldehyde released from bed linens (e.g. sheets and pillowcases) represents a unique circumstance for consumer exposure. Specifically, a large surface area, frequent and extended duration of use, and close proximity of the product to one's breathing zone may result in the potential for higher exposures compared to other textiles found in the home and clothing. Since 2020, nearly 20 notices have been issued to manufacturers and retailers under California Safe Drinking Water and Toxic Enforcement Act (also known as Proposition 65) for potential warning label violations related to formaldehyde exposures from bed linens

This study was conducted to measure airborne formaldehyde levels resulting from off-gassing from bed linens during expected consumer use scenarios. An initial screening-level study was performed on ten sets of bed linens of various fabric types to determine formaldehyde release under accelerated storage conditions according to AATCC TM112 standard methodology. In general, microfiber-based products released lower amounts of formaldehyde (0-3 µg/g), followed by cotton-blends (0-6 µg/g), and 100% cotton (2-17 µg/g), while the highest levels were found with bamboo fiber-based products (20-48 µg/g). Two bamboo fiber-based bed linens were selected for further evaluation of formaldehyde release during an 8-hour simulated sleeping period in the bedroom of a residential home. Personal and area samples were collected under four conditions for each product: 1) immediately after unpackaging 2) one-week after initial test, 3) following one wash/dry cycle, and 4) one-month after initial testing with weekly wash/dry cycles. Background samples collected weekly in the absence of products showed an average airborne formaldehyde concentration in the test bedroom of 30 to 45 µg/m^3. Personal samples collected during testing of the first bamboo-based bed linen product showed airborne concentrations of 49 µg/m^3, 59 µg/m^3, and 50 µg/m^3 for initial, one-week, and first wash testing, respectively. Testing of the second bamboo-based product found airborne concentrations of 72 µg/m^3, 58 µg/m^3, and 48 µg/m^3 during the same scenarios. By one month after initial testing, formaldehyde release from both bamboo fiber-based products was similar to background levels, demonstrating that release is substantially decreased with time and washing.

These results indicate that the potential exposure to formaldehyde from bed linens is low and comparable to background levels of formaldehyde observed in indoor environments. Therefore, formaldehyde release from bed linens is not expected to present a health risk to consumers based upon health-based guidance values established by USEPA or state agencies for non-cancer and cancer effects in humans.

38. When IgE Isn't the Answer: Profiling the Hidden Drivers of Chronic Spontaneous Urticaria

Poster #38

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Chronic spontaneous urticaria (CSU) affects nearly 25% of the population over their lifetime. CSU is a skin disorder triggered by unidentified mast cell activators, leading to pro-inflammatory responses that cause hives, welts, and other painful skin conditions lasting up to six weeks during flare-ups. Current treatments, primarily anti–Immunoglobulin E (IgE) therapies, are effective in only ~50–60% of patients. Consequently, a substantial proportion of individuals experience non-IgE-mediated symptoms that remain poorly understood and understudied. In this study, we applied untargeted metabolomics and elemental analysis to assess potential toxicological exposures and metabolic changes in CSU patients (n = 19) compared to rhinitis-treated patients (n = 24). Rhinitis patients were selected as the control group to better account for comparable antihistamine and other medications used relative to CSU patients. Data analysis is ongoing to identify environmental and metabolic signatures associated with IgE-independent CSU, with the goal of informing future diagnostic and therapeutic strategies.

39. Histone variant-specific epigenetic remodeling in activated CD4+ T cells following exposure to a trichloroethylene metabolite

Poster #39

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Environmental toxicants such as trichloroethylene (TCE) have been linked to immune dysregulation and autoimmune disease, yet the epigenetic mechanisms remain incompletely defined. Prior work from our lab identified DNA methylation changes at histone-related genes and Polycomb binding sites following TCE or its metabolite trichloroacetaldehyde hydrate (TCAH) exposure, but many alterations did not align with expected gene expression patterns, suggesting additional epigenetic layers may be involved. In this study, we investigated how TCAH impacts histone post-translational modifications (PTMs) and DNA methylation in naïve CD4+ T cells from autoimmune-prone MRL/MpJ mice activated for four days +/- 0.5 mM TCAH. Histone mass spectrometry revealed widespread TCAH-induced remodeling, with replication-dependent H3.1 domains maintaining repressive stability, while replication-independent H3.3 regions enriched with active loci showed pronounced loss of restraint, including reduced H3K27me2 and increased H3K36me2/3, consistent with transcriptional elongation. Pyrosequencing of heterochromatin-associated repeats revealed site-specific hypomethylation at D4Z4 and hypermethylation at NBL2, indicating region-specific chromatin instability. These findings show that TCAH disrupts multiple epigenetic layers in a histone-variant and locus-specific manner, potentially priming activated CD4+ T cells for transcriptional dysregulation. This work underscores the importance of variant context in environmental epigenetics and its implications for immune function and autoimmunity risk.

40. Metabolic Reprogramming of CD4$^+$ T Cells in Autoimmune-Prone Mice Exposed to Trichloroethylene

Poster #40

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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 containment, 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 MRL-MpJ mice (MRL). RNA sequencing was conducted to determine the direct effects of TCAH (a metabolite of TCE and used in in vitro experiments) on gene expression in CD4+ T cells. Because RNA-sequencing revealed alterations in metabolic pathways, some 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 and activated 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. Because gene expression profiles indicated TCAH-mediated metabolic changes, extracellular flux assays (Seahorse assays) were performed to confirm these findings and further explore the metabolic alterations in TCAH-treated CD4+ cells. Naive CD4+ T cells will be isolated and purified from MRL/MpJ mice and will be cultured +/- TCAH over time to capture activation (1,2 days) and differentiation (3-4 days). These naive CD4+ T cells will be resting, activated, or polarized towards a Th1 phenotype to analyze the pro-inflammatory profiles seen in vitro. Glycolytic rate assays using Seahorse technology were undertaken to assess the metabolic function of these cells in the presence or absence of TCAH across various concentrations to establish a dose response (0, 0.25, 0.50, 0.75 mM).

Results: RNA-sequencing results revealed key sex-dependent differences in activated CD4+ T cells treated with TCAH in MRL mice. Females exhibited reduced expression of genes involved in glycolysis, TCA cycle, and HIF-1 pathway, alongside upregulation in genes associated with one-carbon metabolism and glutaminolysis genes. To confirm and expand on transcriptomic findings, Agilent Seahorse metabolic assays were conducted, showing a trend in a decrease in basal and compensatory glycolysis in TCAH-treated cells at 24 hours, followed by an increase at later time points compared to controls in female MRL mice. Cell viability at 48 hours was also assessed using the Cell Titer-Blue assay, where TCAH-treated groups exhibited higher metabolic activity compared to CD3- and baseline controls.

Conclusions: Our findings suggest that disruption of metabolic programming by TCE may represent one mechanism by which TCE promotes autoimmunity in human populations. Understanding how TCE affects metabolic pathways mechanistically may help with future therapies for TCE-exposed individuals.

41. The relationship between PFAS exposure and dyslipidemia: an updated review, meta-analysis, and evaluation of bias

Poster #41

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Due to their widespread use and environmental and bodily persistence, there is growing concern that exposure to per- and polyfluoroalkyl substances (PFAS) can result in adverse health effects. Potential PFAS-induced change in serum lipids, is one such outcome of concern, yet evidence to date has been insufficient to establish causality in humans. The objective of this analysis was to reevaluate literature relating blood or serum concentrations of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) to alterations in serum lipids in adults. A total of 89 articles examining serum lipid outcomes and exposure to PFOA or PFOS were identified through systematic review. Excluding studies of infants and children, 69 studies were evaluated in a directional analysis while 38 studies were subsequently used in meta-analysis of lipid outcomes and bias analysis.

As in prior reviews, PFOA and PFOS exposures were positively associated with TC and LDL, with PFOA also being positively associated with HDL (non-significantly) and TG, while PFOS was positively associated with HDL and inversely with TG (non-significantly). TC and LDL estimates in particular demonstrated high levels of heterogeneity, peaking primarily within cross-sectional and non-occupational studies that made up the majority of the meta-analysis. However, pooled estimates from the fewer longitudinal investigations trended closer to null than cross-sectional studies and were not statistically significant. Potential reasons for this heterogeneity were identified in bias analysis, primarily concerns of inconsistent confounding control and potential for selection bias when recruiting PFAS-exposed populations. These factors point to inconsistencies in PFAS-lipid literature requiring additional investigation.

42. Investigating the Interactive Toxicity of Sugarcane Ash–Derived Silica Nanoparticles and Pesticides in Human Proximal Tubular Kidney Cells

Poster #42

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Sugarcane workers, especially cane cutters, endure severe heat and face significant risks from exposure to agrochemicals, heavy metals, and silica. These workers are at risk for developing chronic kidney disease of unknown etiology (CKDu). We hypothesized that the practice of harvesting and burning sugarcane may play a role in the development of CKDu. Sugarcane stalks are composed of approximately 80% amorphous silica, and our research has shown that burning sugarcane generates nano-sized silica particles, around 200 nm in size. In addition to silica, we have reported that sugarcane workers have high levels of several pesticides in urine, and this increases during the harvest season which could further contribute to the risk of CKDu. These substances, when inhaled or absorbed, may have toxic effects on the kidneys and other organs, compounding the dangers associated with the burning and harvest process. To investigate what effect such exposures may have on kidney cells, we utilized a human proximal convoluted tubule (PCT) cell line (HK-2). HK-2 cells were subjected to treatments with concentrations 2.5µg/mL and 25µg/mL of sugarcane ash derived silica nanoparticles (SAD particles), and pesticide treatments which included carbofuran, metolachlor, diquat, and paraquat that were found in urine of workers. SAD particles and pesticides were treated separately and together to evaluate if an interaction was occurring. Following 24 hours of exposure, we utilized MTS, CellRox, and MitoSox assays to evaluate viability, ROS generation, and mitochondria superoxide generation respectively. Treatment with SAD particles and pesticides showed changes to viability, SAD particle treatment alone reduced mitochondrial activity as well as in combination with pesticides. All treatments resulted in detectable ROS generation with SAD particle treatment alone demonstrating the highest levels of ROS generation. Such changes suggest that a mixture exposure to sugarcane ash and pesticides could synergistically effect viability, increase ROS generation and promote mitochondrial dysfunction of human PCT cells.

43. Rapid Prioritization of Reproductive Toxicants Using a High-Throughput and High-Content Analysis Platform with a 3D Mini-Testis Culture Model

Poster #43

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Background and Purpose: A worldwide decline in male fertility has been observed over recent decades, with exposure to environmental toxicants identified as a significant contributing factor. This study presents reproductive toxicant profiling of 87 compounds from the NTP (National Toxicology Program), using high-throughput screening (HTS) and high-content assays (HCA) targeting adverse reproductive outcomes. Our objective was to develop a practical HTS/HCA in vitro 3D Mini-Testis platform to rapidly evaluate and prioritize potential reproductive toxicants. **Methods:** 87 compounds were tested using a 3D Mini-Testis model in a 96-well format, consisting of mouse spermatogonia, Leydig, and Sertoli cells. Key endpoints assessed were nuclear measurements, DNA damage response (γH2AX), and cellular structure (F-actin), with a total of ten parameters evaluated using HCA analysis. Concentration-response data was used to derive points-of-departure (POD), which were integrated using the Toxicological Priority Index (ToxPi) to serve as surrogate NAM-based PODs for risk characterization. Hierarchical clustering and single-cell analysis revealed compound-specific mechanisms, the presence of subpopulation, and a positive correlation between the nucleus area, F-actin total intensity, and γ-H2AX total intensity. The integrated ToxPi scores were calculated for each compound, allowing for a prioritized ranking of the 87 compounds. **Results:** Using the POD values, the integrated ToxPi scores were calculated and ranked through the ToxPi visualization tool. Compared with existing male reproductive data in the literature, the results showed a high degree of alignment, with 91.48% sensitivity, 93.75% specificity, and 93.55% concordance. Notably, 14 compounds with no prior reproductive toxicity data were identified as toxic, and 52 compounds without previous γH2AX activity data displayed increased γH2AX total and mean intensity. Among 87 compounds, several classes of environmental chemicals, including BPAF and heavy metals, ranked high in toxicity, consistent with previous reports. **Conclusions:** These findings underscore the potential of this in vitro screening platform for rapid, risk-based chemical assessment, with capabilities in ranking, clustering, and assessment that align with in vivo toxicity and present a robust tool for testicular toxicity screening. (NIEHS R44 ES027374 and R43 ES031890)

44. *In Vitro* Exposure to Dibutyl Phthalate and Mouse Ovarian Follicle Cellular Compartment Size

Poster #44

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Ovarian follicles are small, fluid-filled sacs in the ovary which contain the egg required for ovulation and fertilization, and the granulosa and theca cells which produce estrogen. The antrum is a fluid-filled space containing secretory material from the growing oocyte and granulosa cells and a hallmark of follicular maturation towards a pro-ovulatory state. Based on the critical importance of ovarian follicles to female fertility, ovarian follicle cultures have been used to screen environmental chemicals for ovarian toxicity. Dibutyl phthalate (DBP) is a plasticizer in many consumer and medical products, known to disrupt ovarian function. The impact of DBP exposure on the size of intrafollicular cellular compartments and antrum formation in mouse ovaries have not been evaluated. Therefore, this study was developed to identify DBP impacts on follicular cell compartment growth and antral cavity formation in vitro. Ovarian secondary follicles (100-249 µm in diameter) were mechanically isolated from the ovaries of adult female CD-1 mice at 21 days old. Isolated follicles (n=52-69) were individually encapsulated in 0.5% alginate beads and cultured for 8-11 days in individual wells of a 96-well plate containing supplemented media with vehicle (DMSO, 0.075%) or DBP (10µg/mL). Follicles were visually examined every 24 hours under a light microscope to determine survival status, measure diameter and capture images. Follicle compartments were outlined and measured using QuPath software and the growth of each compartment compared to their respective baseline measurements. Follicle diameter, compartment and antrum data were compared using Mixed-effects analysis. Statistical significance was assigned at $P<0.5$ for all tests. Encapsulated secondary follicles treated with DMSO increased their diameter on average by 67.6% over the 11-day culture period (baseline: 158.1 µm vs Day 11: 265 µm), while those treated with DBP10 increased by 45% (baseline: 151.7µm vs Day 11: 220 µm). Oocyte area growth was similar between treatments (DMSO: 3.95% vs DBP10: 3.29%) but there were differences in granulosa (DMSO: 201% vs DBP10: 161%) and theca (DMSO: 179% vs DBP10: 65.4%) cell area growth between treatments. By day 8 of culture, 60% of viable DMSO follicles and 50% of DBP-treated follicles formed an antrum. Our findings suggest that direct exposure to DBP results in reduced follicle maturation by preventing the growth of the granulosa and theca compartments and the formation of the antral cavity. Future work will evaluate the impact of DBP exposure of follicular hormone production. This work was supported by NIEHS Grants R01ES034690 and R25-ES025494 (Environmental Health Sciences – Transformative Research Undergraduate Experience).

45. Molecular interference of lipids and polymer plastics in mass spectrometry: implications for toxicity and exposure research

Poster #45

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Micro- and nano-plastics (MNP) are widespread in the environment and have been found in human tissues, including the brain, raising concerns about their potential toxicity. MNP exposure can lead to organ dysfunction, reproductive and developmental toxicity, and neurotoxicity. Cholesterol and sphingolipids are essential components of brain structure, playing a vital role in neuronal membrane architecture alongside phospholipids, while serving a foundational function in essential biochemical processes. Any alterations in lipid turnover within the brain or disruptions in cellular lipid balance may significantly contribute to the onset of neurodegenerative diseases. This study aims to investigate potential molecular interference between brain lipids and plastics on mass spectrometry by spiking cholesterol, sphingomyelin, and docosahexaenoic acid with a known amount of polyethylene or a mixed polymer standard. The methodological approach consists of sequential digestion using potassium hydroxide (KOH) followed by secondary solvent washes (cyclohexane or nitric acid) to degrade lipids while preserving polymer integrity. The recuperated digested samples with varying conditions were analyzed using the pyrolysis gas chromatography-mass spectrometry (Py GC-MS). Initial results from the Py GC-MS analysis indicated that pure cholesterol leads to an estimated 6% false positive recovery of polyethylene, which drops to 0.7% after KOH digestion. Additionally, when cholesterol is present in the samples, we observed an underestimation of polyethylene, with recovery percentages falling below 50%. This suggests that the digestion and filtration procedures may contribute to the overall loss of polymer weight recovery in the analyzed pellet when cholesterol is part of the sample. Ultimately, this project aims to shed light on how lipids and plastics may affect molecular detection and quantification in Py GC-MS.

46. Detection and Distribution of Microplastics in Human Semen and Their Potential Impact on Sperm Quality

Poster #46

Chelin Jamie Hu[1], Marcus Garcia[2], Hannah Collins[3], Michael Reed[3], Anna Quintana[1], Jim Thompson[3], Gary D Smith[3], Matthew Campen[2], Xiaozhong John Yu[1]

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The ubiquitous presence of micro- or nano-plastics (MNP) in the environment has raised growing concerns about their entry into the human body and associated health risks. Recent studies, including work from our lab, has demonstrated the presence of various types of plastic polymers in human and dog testis, highlighting potential effect on male reproductive health. This study aimed to investigate the presence of microplastic polymers in human semen and to examine their potential association with semen quality. Additionally, we sought to determine the distribution of MNPs between seminal plasma and sperm cell fractions to explore possible routes of exposure and mechanisms of reproductive toxicity. Semen samples were collected from 16 men (age 28 – 52 years) attending a fertility clinic. All samples were evaluated for semen quality according to the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen (6th Edition). For MNP detection, we applied pyrolysis gas chromatography/mass spectrometry (Py-GC/MS) to detect twelve types of common consumer plastic polymers including PE, PP, PS, ABS, SBR, PMMA, PVC, PU, PET, N6 and N66. In a subset of 6 samples, MNP levels were separately quantified in the seminal plasma and the washed sperm cell fractions. Microplastics were detected in all 16 semen samples, with total MNP concentrations ranging from 10.79 to 334.30 μg/ml (mean: 116.69 ± 94.78 μg/ml; median: 109.01 μg/ml). Polyethylene (PE) and polyurethane (PU) were the most frequently detected polymers, accounting for 47.9 ± 14.2% and 20.3 ± 16.8% of the total MNP load, respectively. Regarding semen quality, only 5 of 16 samples met all normal criteria (above the 5th percentile) across major WHO indices, including semen volume, sperm concentration, motility, morphology, and viscosity. Eight samples had 1–2 parameters below normal thresholds, and three samples showed multiple abnormalities (e.g., oligozoospermia, asthenozoospermia, teratozoospermia). No significant association was found between the level of total MNP vs any individual or combined semen quality indices. Interestingly, the majority of MNP were found in seminal plasma fraction (range from 31.4 – 92.7% of the whole semen; mean 70.7 ± 24.1%, N=6) whereas levels of MNP in the cellular (washed sperm cells) fraction were below the detection threshold in our assays. This study demonstrates that microplastics are present in human semen and primarily reside in the seminal plasma fraction. Although no significant relationship with semen quality parameters was identified, the presence of MNPs in all samples underscores the need for larger-scale studies to evaluate potential reproductive health implications and to understand the mechanisms by which environmental microplastics may influence male fertility.

47. Micro/nano-plastics compromise skeletal architecture as modulators of the gut–immune–bone axis

Poster #47

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Micro/nano-plastics (MNPs) are emerging dietary contaminants that have become ubiquitous in the human food chain. Despite growing concern of widespread human exposure, the physiological consequences of chronic dietary MNP exposure remain incompletely understood. Here, we examined the long-term impact of chronic dietary MNP exposure in mice- integrating skeletal, gastrointestinal, immune, and metabolic outcomes with attention to dietary composition. Female and male C57BL/6J mice were fed AIN93M, DIO, and a high fiber formula containing polystyrene MNPs (0.5–5 µm) for up to 12 weeks, beginning in adolescence. Across diets, MNP exposure impaired trabecular and cortical bone architecture without inducing classical systemic inflammation, but elevated circulating and hepatic serotonin- a known inhibitor of bone formation. This effect was not attributable to direct stimulation of intestinal serotonin release and occurred despite no differences in food intake, body weight, fat mass, fecal lipocalin-2, secretory IgA, or serum TNFα. However, microbiota transfer from MNP exposed donors reproduced serotonin elevations in germ free recipients. Colonic organoid assays revealed no major changes in intestinal stem cell differentiation, including enteroendocrine cell populations. MNP ingestion altered serotonin mediated gut immune signaling, as *ex vivo* serotonin priming of $CD4^+$ T cells suppressed IFNγ production, suggesting serotonin-mediated dampening of mucosal immunity. Both MNPs and serotonin independently impaired human osteoblast mineralization *in vitro*. Collectively, these findings identify environmental MNPs as previously unrecognized modulators of the gut–immune–bone axis, capable of disrupting skeletal homeostasis through serotonin-mediated pathways and gut microbiota interactions, with potential systemic consequences for multiple organ systems.

48. Micro(nano)plastics in human cerebrospinal fluid and their implications for brain waste clearance

Poster #48

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The human brain is a preferential site where plastics tend to bioaccumulate. Our team has developed a novel approach to isolate and quantify micro(nano)plastics (MNPs) from human tissues using analytical chemistry and advanced spectrometry. Initial findings show that MNPs accumulate more in the human brain than in the liver and kidney, raising concerns about brain waste management and potential toxic effects on central nervous system (CNS) function. Here, we assess the quantity and physicochemical properties of MNPs in human cerebrospinal fluid (CSF) using state-of-the-art spectroscopy and microscopy techniques. The methodological approach consists of using different digestion protocols to isolate and purify the MNPs extracted from human CSF samples obtained from a cohort with aneurysmal subarachnoid hemorrhage, traumatic brain injury, and other acute injuries. The KOH (10%) digestion was completed with successive procedures involving benzene washes to increase efficiency in isolating polymer plastics in nano-metric and submicron sizes, with a complete dissolution of lipids and proteins. The initial quantitative measurement using pyrolysis-gas chromatography-mass spectrometry (Py-GC-MS) was conducted on CSF samples (n=14). Polymer concentrations ranging between 13.3 and 82.8 µg/ml were detected, with a mean of 22 µg/ml for the summed polymer concentrations. These elevated concentrations observed in CSF are higher than those reported in other biological fluids, such as blood. Transmission electron microscopy images detected heterogeneous aggregates containing particulates in sub-micron and nano-metric sizes with crystalline structures in the extracted MNPs pellet. Further research will determine whether plastics contribute to neurodegeneration by investigating their association with metal clearance dysfunction in CSF and glymphatic system biomarkers. This study establishes advanced methods to isolate and quantify purified MNPs from human CSF to implement accurate correlation studies with brain waste clearance and CNS pathologies.

49. Analysis of Micro-Nanoplastic Pollution in the New Mexico Public Water Supply

Poster #49

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Micro- and nanoplastics (MNPs) are emerging environmental contaminants that have been increasingly associated with a wide range of adverse health outcomes. Due to their small size, MNPs are capable of crossing biological barriers, including the blood-brain barrier and accumulating in soft tissues, thereby posing systemic health risks. In biological systems, contaminated food and water serve as the most pervasive entry routes for MNPs into organisms, contributing to the biomagnification of the contaminant. This research aims to assess the concentration and polymer composition of MNPs in various water sources throughout New Mexico; including the Rio Grande, treated effluent from a wastewater treatment facility along the Rio Grande, municipal tap water, a private shallow well, and a private deep well. Samples were systematically collected, with sediment removed via density separation using sodium iodide (NaI) solution. Following this, samples were filtered onto glass fiber filters and analyzed using pyrolysis-gas chromatography/mass spectrometry (Py-GC/MS). It is hypothesized that water samples from the Rio Grande and the wastewater effluent will exhibit the highest concentrations of MNPs due to higher exposure to pollution, with the Rio Grande potentially serving as a major MNP sink. Conversely, the deep well is expected to exhibit the lowest concentrations owing to its natural filtration through geologic substrates and limited exposure to pollution. Based on prevalence in the environment and previous literature, polymers such as polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), butadiene, nylon, and polyester are predicted to be the most dominant polymer types. Given their persistence and potential toxicity, MNPs represent a critical threat to both ecological and human health. Characterization, quantification, and tracking of MNPs in local water sources are essential first steps toward effective mitigation strategies, public health interventions, and the development of future policy focused on pollution control and environmental remediation.

50. Trouble in Paradise: Characterization and Modeling of Heavy Metal Adsorption on Microplastics Across Global Beach Locations

Poster #50

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Microplastics (MPs) are emerging as vectors for heavy metals and metalloids (HMs), presenting significant ecological and human health risks. This study characterizes MPs collected from the beaches of Easter Island, Christmas Island, Hawaii, and Mauritius. These locations span the Indian and Pacific Oceans and were selected to examine regional variability in polymer composition, HM contamination, and adsorption behavior. We employed microscopy, Fourier-transform infrared spectroscopy (FTIR), pyrolysis-gas chromatography-mass spectrometry (Py-GCMS), inductively coupled plasma mass spectrometry (ICP-MS), and thermogravimetric analysis (TGA) to analyze the samples. The mean particle size of cryo-milled MPs across the sites was 81.2 ± 91.7 µm, with light microscopy. Christmas Island MPs had a unique profile with high concentrations of polystyrene (PS) at 85.09 mg/g and significantly elevated levels of HMs (As, 25.24 ± 18.19 ppm), (Cd, 31.08 ± 11.30 ppm), and (Cr, 28.31 ± 7.70 ppm), compared to other sites ($p < 0.001$). The study introduces the “Taylor Isotherm,” a novel modified Langmuir model tailored to the heterogeneous nature of MP compositions, accounting for polymer density and adsorption site variability. This model was used to simulate adsorption behavior across a range of equilibrium concentrations ($\boldsymbol{C_e}$), providing insights into metal interactions with PS-rich MPs. Key findings include maximum adsorption capacities ($\boldsymbol{q_{max}}$) of 0.85 mg/g for As and 0.67 mg/g for Cd, demonstrating the significant role of PS in metal uptake. By revealing the hidden capacity of our favorite beach destinations to accumulate hazardous metals, this study highlights a deeper concern: the increasing presence of MPs could transform these coastal paradises into reservoirs for toxic contaminants, harboring pollutants that may pose risks to both marine life and the humans who cherish these environments.

51. Chemical Toxicology Review Papers: An Editor's Perspective Based on 50 years of Experience

Poster #51

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Critical Reviews in Toxicology (CRT), published by Taylor & Francis, was founded by Leon Golberg in 1971. I have been associated with CRT since its inception and have served as Editor-in-Chief since 1987. The journal has a global audience and is highly ranked among peer-reviewed journals. This presentation will review changes in scientific publishing, focusing on CRT since its origin.

The Toxicology of chemical agents has been the focus of most papers published in CRT. Over the past quarter-century the papers have increasingly been concerned with human health hazards/risk, their mode of action and their regulation. During the last decade an increased number of papers have addressed environmental issues. The growing use of computer-based methodologies and artificial intelligence has also become apparent in recent years. In the early decades of CRT, the vast majority of CRT authors were based in the USA, Canada and Western Europe. The last decade has seen a dramatic increase in submissions from regions beyond North America and Europe such as India and China, reflecting CRT's expanding global readership and contributor base. A constant over the decades has been the attention CRT gives to obtaining critical reviews by scientific experts for all submitted manuscripts that are sent for external review. Authors regularly note that the external reviewers' comments significantly improved their published paper.

The following are suggestions for prospective authors submitting papers to CRT and other review journals. 1) Select a topic of broad and current global relevance. 2) Assemble a team of authors with mixed expertise, include researchers who have published primary research on the subject of the review. 3) Conduct a rigorous literature review using well-established frameworks such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). 4) Critically evaluate the literature with a process that is well-described and goes beyond summarizing the findings. 5) Organize the text of the paper strategically so that it is well-structured, flows logically and is easy to read. 6) Use figures and tables that are informative. 7) Draw conclusions and, where appropriate, provide recommendations on policy or practice based on the literature review. Above all prepare a manuscript that is accessible to scientists from multiple disciplines as well as informed readers such as regulatory authorities. Remember, the role of scientists and science is to ultimately serve Society-at-Large and improve human health and well-being around the globe.

52. Intergenerational Effects of Environmentally Relevant Concentrations of Dietary Selenium on Zebrafish, *Danio rerio*

Poster #52

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Selenium (Se) is an essential trace element for fishes; however, it becomes extremely toxic at concentrations slightly above physiological requirements. While the toxicological effects of Se on adult fishes are well documented, its intergenerational and neurobehavioural impacts remain poorly understood. Selenomethionine (SeMet), the predominant organic form of Se in aquatic food webs, is primarily acquired through diet, yet most existing studies have relied on artificial SeMet-spiked diets that do not accurately reflect environmental exposure routes. To address this limitation, we conducted a trophic transfer study by exposing blackworms (*Lumbriculus variegatus*) to waterborne SeMet (50 and 200 µg/L) for 14 days, resulting in Se accumulation of 17 and 43 µg/g dry weight, respectively. These Se-enriched blackworms were subsequently used as a dietary source for adult zebrafish (*Danio rerio*) over 60 days. Following exposure, adults were bred and the F1 larvae were reared in clean water until 5 days post-fertilization (dpf) to assess intergenerational effects. Our results demonstrated a significant increase in larval mortality and deformities in both Se-exposed groups compared to control. Behavioural assays revealed impaired thigmotactic and reflexive responses, indicating neurobehavioural dysfunction. Moreover, Se exposure led to dose-dependent increases in reactive oxygen species (ROS) production and apoptosis. Molecular analyses showed dysregulation of genes and proteins associated with dopaminergic, serotonergic, and cholinergic pathways, as well as disruptions in neurogenesis. These findings provide novel evidence that dietary exposure to environmentally relevant concentrations of SeMet can exert significant intergenerational neurodevelopmental toxicity in zebrafish. This study underscores the ecological relevance of trophic transfer in Se toxicity research and highlights the need for improved regulatory guidelines to mitigate Se contamination in aquatic ecosystems.

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We look forward to seeing you all again at the **Society of Toxicology 65th Annual Meeting and ToxExpo** from **Sunday, March 22 to Wednesday, March 25, 2026**! Make sure to check out the **"Metal Toxicity Meets Stem Cell Innovation: Early Stage Scientists Forging New Frontiers in Environmental Health" Symposium** endorsed by the Stem Cells Specialty Section and the Metals Specialty Section! See you soon at **San Diego**!

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