silver nanoparticles, and discovered instead that mitochondria are likely a secondary target in this case. Finally, I will discuss work from our group and others examining impacts of mercury and cadmium on mitochondrial DNA.

1180 Cadmium-Induced Lung Toxicity

V. Antony. *University of Alabama at Birmingham, Birmingham, AL.*

Cardiopulmonary disease secondary to environmental insults is well recognized and accepted. It is recognized that all-cause mortality of the population of Medicare age is directly proportional to PM 2.5 exposure even below the EPA accepted levels, irrespective of smoking history. The underlying causes are linked to both pulmonary and cardiac disease. While cardiac disease and stroke remain the primary cause of mortality in the US, Chronic Obstructive Pulmonary Disease (COPD) is the third largest case of death world-wide and is a significant co-morbid condition in both myocardial infarctions and strokes, which are caused by tissue hypoxia in the relevant organ system. Exposure to pollutants causes exacerbation of airways diseases, such as COPD and asthma, leading to hypoxemia that in turn, can lead to increased risk of myocardial hypoxia as well as an increased risk for stroke. Pollutants not only cause exacerbation of underlying lung disease but also may be the primary cause of lung disease. Cadmium (Cd), a metal in cigarette smoke (e.g. cigarette contains 2-3 micrograms of Cd), is also a common pollutant from coal fired power plants and coke furnaces and has an *in vivo* half-life of 25 years. Cadmium causes COPD, as well as exacerbation of other metal toxicity, and leads to a procoagulant state with higher levels of fibrinogen/fibrin in the blood and lung. Cadmium exposure initiates autophagy through ferroptosis leading to cell death of lung tissues exposed to it. This leads to both airway and lung parenchymal injury with aberrant responses. A better understanding of these mechanisms will help us develop therapeutic modalities to prevent lung disease following exposure to lung pollutants.

1181 Essential Role of Ferroptosis in the Development of Diabetic Cardiomyopathy

L. Cai. *University of Louisville School of Medicine, Louisville, KY.*

Ferroptosis was described as a form of cell death induced by the small molecule erastin, which inhibits the import of cystine, leading to glutathione (GSH) depletion and inactivation of the phospholipid peroxidase glutathione peroxidase 4 (GPX4). As an iron-dependent form of regulated cell death, ferroptosis occurs through the lethal accumulation of lipid-based reactive oxygen species when GSH-dependent lipid peroxide repair systems are compromised and is also tightly related to amino acid, glutathione, lipid, and iron metabolisms. We have investigated the essential role of ferroptosis in the pathogenesis of diabetic cardiomyopathy (DCM) in mice with type 2 diabetes and a new *ex vivo* DCM model. Advanced glycation end-products (AGEs), an important pathogenic factor of DCM, were able to induce ferroptosis in engineered cardiac tissues (ECTs), evidenced by increased levels of Ptgs2 and lipid peroxides and decreased ferritin and SLC7A11 levels. Typical morphological changes of ferroptosis in cardiomyocytes were observed using transmission electron microscopy. Inhibition of ferroptosis with ferrostatin-1 and deferoxamine prevented AGE-induced ECT remodeling and dysfunction. Ferroptosis was also evidenced in the heart of type 2 diabetic mice. Inhibition of ferroptosis by liproxstatin-1 prevented the development of diastolic dysfunction at 3 months after the onset of diabetes. The protective effect of sulforaphane, NRF2 activator, on ferroptosis was found AMP-activated protein kinase (AMPK)-dependent. Therefore, we concluded that ferroptosis plays an essential role in the pathogenesis of DCM; sulforaphane prevents ferroptosis and associated pathogenesis via AMPK-mediated NRF2 activation. This suggests a feasible therapeutic approach with sulforaphane to clinically prevent ferroptosis and DCM.

1182 Metabolic Effects of Copper Misbalance

S. Lutsenko. *Johns Hopkins Medicine, Baltimore, MD.* Sponsor: L. Cai.

Copper is an essential enzyme cofactor and a signaling molecule required for proper differentiation and functional maturation of most cells. In this presentation, we will discuss how copper misbalance affects the metabolic status of tissues and alters the communications between different cell types within tissues. In particular, we present evidence that in the liver excess copper activates oxidative-stress response factor NRF2, which leads to upregulation of sulfotransferases, misbalance of oxysterols and sulfated sterols, inhibition of nuclear receptors and increased inflammatory response that can be reversed by liver nuclear receptor agonists. The development of liver pathology, especially inflammation and fibrosis depends on copper accumulation in both parenchymal and non-parenchymal liver cells and is affected by copper misbalance in the intestine. The relevance of this altered metabolic signaling to human disorders of copper misbalance such as Wilson disease and obesity will be highlighted.

1183 Copper Induces Cell Death by Targeting Lipoylated and Fe-S Cluster Proteins

P. Tsvetkov. *Broad Institute, Cambridge, MA.* Sponsor: L. Cai.

Copper is an essential co-factor for all organisms, and yet it becomes toxic if concentrations exceed a threshold maintained by evolutionarily conserved homeostatic mechanisms. The precise mechanisms through which excess copper induces cell death, are still largely unknown. Our work now establishes that structurally diverse copper ionophores induce a new form of regulated cell death that is distinct from known cell death mechanisms such as apoptosis and ferroptosis. This copper-dependent cell death mechanism is largely dependent on mitochondrial respiration; increased mitochondria respiration promotes copper-dependent cell death whereas blocking cellular respirations attenuates this process. Moreover, this copper-dependent death occurs via direct binding of copper to lipoylated components of the tricarboxylic acid (TCA) cycle in a process that is highly dependent on the function of the ferredoxin 1 (FDX1) enzyme. This results in lipoylated protein aggregation and global iron-sulfur cluster protein loss leading to proteotoxic stress and ultimately cell death. Taken together, our findings suggest that two evolutionarily ancient cellular mechanisms (lipoylation and Fe-S clusters) are crucial targets of copper induced cytotoxicity.

1184 The Future of Fire Safety: Exploring the Intersection of Wildfires and Human Health

C. Wright. *Chemical Insights Research Institute, Marietta, GA.*

Wildfires are an emerging public health threat capable of hindering the economic and social infrastructure on which we daily rely. Climate change will sharpen this threat; therefore, larger conversations among the scientific community are sorely needed to address this unprecedented global issue. Understanding the complexity of wildfires and their impact on human health is key to mitigating loss of life and quality of life as well as reducing environmental consequences, including the reduction of indoor and outdoor air quality. In this session, our panelists will identify challenges in data collection and potential knowledge gaps that impede our ability to fully quantify the human and economic costs of wildfires. Our panel of experts will examine the chemical processes that occur during urban wildfires, discuss the complexity of wildfire emissions, and examine what is known about human exposure and adverse health outcomes. Specifically, our presenters will provide new evidence on biomarkers of exposure, such as brominated flame retardants and per- and polyfluoroalkyl substances and their link to epigenetic alterations found in exposed vulnerable populations, including firefighters. While it is widely known that firefighters have higher cancer incidence rates than the general public, our presenters will reveal recent metabolomic data that may shed light on cancer initiation pathways in first responders. The efficacy of indoor air pollution mitigation strategies on cardiometabolic health in wildfire-affected individuals also will be explored and evaluated. These findings may aid in the development of therapeutic and intervention mitigation strategies to protect exposed first responders and communities during wildfires.

1185 Wildfires at the Wildland: Urban Interface and Their Health Impact on First Responders and Communities

M. Black. *Chemical Insights Research Institute, Marietta, GA.* Sponsor: C. Wright.

In this presentation, we will provide the current state of the science involved in wildland urban interface (WUI) fires. The chemistry and health impacts of WUI fires are poorly understood, but WUI fires can lead to higher human exposures than remote wildland fires because of their proximity to communities. Current knowledge gaps in our understanding of complex fuel sources, their combustion products and contribution to wildfire smoke, and impacts on first responders and community will be examined and discussed. Exposure pathways, including air, water and soil, will be emphasized to enhance the audiences understanding of potential human health risks of wildfire exposures.

1186 Evaluation of Biomarkers of Exposure in Southern California Firefighters Responding to Wildland-Urban Interface Fire Incidents

M. Calkins. *NIOSH, Cincinnati, OH.* Sponsor: C. Wright.

WUI firefighters may experience structural firefighting exposures without wearing the PPE routinely used by municipal firefighters during a structural response (e.g. self-contained breathing apparatus (SCBA), turnout gear) and without the ability to follow recommended decontamination practices for structural fire response. In this presentation, Dr. Calkins will summarize results of the biomarkers of exposure measured in firefighters from southern California enrolled in the Fire Fighter Cancer Cohort Study (FFCCS)—a national collaborative research study with NIOSH and

the Universities of Arizona and Miami. Discussion will include comparisons to the general U.S. population, pre- and post-fire response, and characteristics of the fire incidents.

S 1187 Epigenetic Biomarkers of Toxicity in California Firefighters Working in the Wildland-Urban Interface

J. Goodrich. *University of Michigan, Ann Arbor, MI.*

This presentation will focus on DNA methylation and microRNA (miRNA) expression as early indicators of toxicity and exposure in wildland-urban interface (WUI) firefighters. Data derived from baseline and post-exposure evaluations of blood samples (n=100) obtained from the Fire Fighter Cancer Cohort study will be discussed including DNA methylation across 750,000 loci via the Infinium EPIC array along with the relative abundance of 800 miRNAs using a linear mixed model approach. The relationship between differential methylation and miRNA expression across time and the implications on firefighter health will be presented. This presentation aims to establish epigenetic modifications as relevant biomarkers of exposure and disease susceptibility in vulnerable populations during wildfire events.

S 1188 Assessment of Adverse Pregnancy Outcomes among US Female Firefighters

A. Jung. *University of Arizona, Tucson, AZ.* Sponsor: C. Wright.

Several firefighter occupational exposures have been previously linked with adverse reproductive outcomes among non-firefighters. We used cross-sectional survey data to investigate the burden and occupational factors associated with miscarriage, preterm birth, and infertility among a cohort of US women firefighters. Within a subset of these women, we used dried blood spot samples to compare anti-Müllerian hormone levels to non-firefighter controls. The focus of this presentation will be a summary of our analyses, highlighting differences in risk between volunteers versus career firefighters, wildland/wildland-urban-interface (WUI) firefighters versus structural firefighters, and potentially, cumulative occupational exposures.

S 1189 Modulation of PM2.5-Mediated Cardiometabolic Indicators in Wildfire-Exposed Individuals through Residential Air Filtration

J. Zhang. *Duke University, Durham, NC.* Sponsor: C. Wright.

This presentation will describe the design and protocol of a new study to examine the impact of a 6-month residential HEPA filtration intervention on cardiometabolic outcomes during the presence or absence of wildfire events. Participants will be a cohort of ethnically diverse individuals at risk for type 2 diabetes (overweight or obese older adults) residing in the Los Angeles area where air pollution levels are among the highest in the US and is prone to wildfires. We will present preliminary data on wildfire exposure biomarkers, metabolic dysfunction biomarkers, and participants' demographic, housing, and community characteristics. In this crossover trial, participants will be block-randomized to start either the HEPA filtration or the sham (no HEPA) filtration, each lasting for 6 months. With a 6-month washout period between HEPA and sham filtration, each participant will be followed for 18 months, during which wildfire events will be monitored and recorded.

W 1190 Cancers, Chemicals, and the Microbiome

J. Toyoda. *Mote Marine Laboratory & Aquarium, Sarasota, FL.*

The human body is host to as many microbial cells as human cells, and the gut microbiome is estimated to contain 50- to 100-fold more genes than the host. The vast genetic functions of the gut microbiome provide critical services, such as toxicant metabolism, synthesis of nutrients and bioavailable metabolites, and regulation of adaptive immune response. Gut-associated communities impact human health, and increasing evidence indicates dysbiosis, or microbiome perturbation, contributes to a variety of human diseases, including cancer. Despite strong links between dysbiosis and cancer outcomes, mechanisms by which toxicants and microbes interact to influence carcinogenesis remain unclear. The goal of this session is to educate SOT members on the importance of the gut microbiome to cancer onset, development, and therapy by highlighting (1) microbiome interactions with chemical carcinogens, (2) microbiome-mediated mechanisms of cancer development, and (3) how microbiome targeting can improve cancer outcomes. Speakers will share emerging findings in microbiome-carcinogen interactions, including the roles of the gut microbiome in the biotransformation of arsenic and metabolic activation of triclosan. Speakers also will discuss microbiome-mediated cancer outcomes in colon and liver via enzymatic, immune-related, and barrier-associated mechanisms. The Workshop also will explore the potential of the microbiome as a druggable target to reduce chemical toxicity, alter disease progression, and enhance cancer therapy through advantageous modification of the gut microbiome using prebiotics and enzyme inhibitors. Session attendees will better understand the roles microbes play in toxicant metabolism, cell-signaling pathways, gut barrier function, and tumor immunity. Further, they will gain familiarity with a variety of mechanisms by which the microbiome alters cancer outcomes using an array of molecular approaches.

W 1191 Use of Multi-'omics to Decipher Signaling Molecules of Xenobiotic-Gut Microbiome-Host Interactions

K. Lu. *University of North Carolina at Chapel Hill, Chapel Hill, NC.* Sponsor: J. Toyoda.

The gut microbiome is a key modulator of human health and there is a growing number of studies that evaluate the systemic, regulatory, and metabolic role of the gut microbiome. This work demonstrates that xenobiotics interact with the gut microbiome providing a new angle to evaluate chemical toxicity. Modulation of the gut microbiome is also regarded as a promising approach to treat cancer or improve cancer treatment outcomes. However, how carcinogens, microbiome and host interact at the molecular level remains a significant gap. This not only impedes mechanistic understanding how altered gut microbiome causes or contributes to cancer, but also prevents microbiome modulation to reduce adverse outcomes from toxicant exposure. Toward this goal, with multi-omics and system biology approaches, we demonstrated significant changes in signaling molecules between conventionally raised and germ-free mice and have shown that exposure to carcinogens such as arsenic, benzopyrene, and formaldehyde induced different toxicological responses in mice with different gut microbiomes. We also demonstrated that carcinogen-altered gut microbiome causatively leads to disease in animals. Using arsenic as an example, we have shown how the gut microbiome cross-talks with the host through microbiome-regulated signaling molecules, including bile acids. Ongoing research shows that the gut microbiome plays a key role in affecting the profiles of mutagenic DNA adducts arising from exposure to benzopyrene, a potent human carcinogen. We have also demonstrated that modulating signaling molecules that reflect gut microbiome-host interactions can effectively prevent or treat diseases, including inflammatory bowel disease. Similarly, the administration of microbiome-related metabolites, identified from omics profiling, caused long-term radioprotection, mitigation of hematopoietic and gastrointestinal syndromes, and a reduction in proinflammatory responses during ionizing radiation. Taken together, deciphering microbiome-mediated chemical signaling and involved host signaling pathways provides important research avenues to understand molecular mechanisms underlying carcinogen-microbiome-host interactions, develop suitable biomarkers of gut microbiome toxicity, and discover druggable microbiome targets to improve cancer treatments outcomes or prevent cancer onset.

W 1192 Microbial ß-Glucuronidase Enzymes Induce Colitis and Tumorigenesis by Reactivation of a Common Antimicrobial Additive in Gastrointestinal Tract

J. Zhang. *University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Emerging research supports that triclosan, an antimicrobial agent found in thousands of consumer products, exacerbates colitis and colitis-associated colorectal tumorigenesis in animal models. While the intestinal toxicities of triclosan require the presence of the gut microbiota, the molecular mechanisms involved have not been defined. Here we show that intestinal commensal microbes mediate metabolic activation of triclosan in the colon and drive its gut toxicology. Using a range of *in vitro*, *ex vitro*, and *in vivo* approaches through biochemical analysis, metabolite analysis, crystal structure analysis, and sequencing analysis, we identify specific microbial ß-glucuronidase (GUS) enzymes involved and pinpoint molecular motifs required to metabolically activate triclosan in the gut. Finally, we show that targeted inhibition of bacterial GUS enzymes abolishes the colitis-promoting effects of triclosan, supporting an essential role of specific microbial proteins in triclosan toxicity. In addition to the reactivation of xenobiotics, our recent findings show that microbial GUS enzymes can also act as a promising therapeutic target to address colitis and related problems, and to alter the dysbiotic composition of gut microbiota. Together, our results define a mechanism by which intestinal microbes contribute to the metabolic activation and gut toxicity of triclosan. They further highlight the importance of considering the contributions of the gut microbiome in evaluating the toxic and carcinogenic potential of environmental chemicals.

W 1193 The Microbiome Controls Anti-tumor Immune Responses in the Liver

T. Greten. *National Cancer Institute, Bethesda, MD.* Sponsor: J. Toyoda.

The microbiome includes commensal bacteria and other microorganisms, and their encoded genes and functions, that colonize the epithelial surfaces of our body. Under healthy conditions, the host and its microbiome exist in symbiosis as a metaorganism by providing a nutrient-rich microenvironment in return for aid in digestion and metabolism. In addition, they have been shown to have local and systemic effects on cancer onset, progression and therapy response. Primary sclerosing cholangitis (PSC) and inflammatory bowel disease are risk factors for cholangiocarcinoma. In addition, dysbiosis has recently been shown

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