Poster #39

Biostatistics Shared Facility

Jeannette Y. Lee

The Biostatistics Shared Facility (BSF) of the Winthrop P. Rockefeller Cancer Institute provides statistical support for study design, analytic plans, and dissemination to investigators. In this presentation, we summarize the BSF's collaborative activities, availability of software and scientific expertise to investigators and recent publications.

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UAMS

Showcase of Medical Discoveries

A Focus on Cancer Research

Wednesday
November 20, 2019
4:30—6:00 p.m.

A Wine & Cheese Reception Featuring UAMS Investigators Discussing their Research and Discoveries.

Location: Winthrop P. Rockefeller Cancer Institute
10th Floor Rotunda

UAMS
Office of Research

Poster #38

Clinical Trials / Regulatory Affairs Office

Alexandra Annis, BA, CCRP; Kristin K. Zorn, MD

The Cancer Clinical Trials and Regulatory Affairs Office (CCTRA) provides comprehensive support for clinical and translational trials done in cancer, cancer prevention, and cancer survivorship. CCTRA coordinates research by facilitating interactions with institutional entities such as Disease-Oriented Committees, the Protocol Review and Monitoring Committee, the Institutional Review Board, and the Office of Research Regulatory Affairs. We ensure that high-quality research is conducted in compliance with all regulations. Services include confidentiality agreements, feasibility assessments, pre-study site visits, informed consent document development, budget building, staff training, adverse event reporting, case report form completion, audit and monitoring visit management, and billing and invoicing coordination. These operations are facilitated by the AR Comprehensive Research Informatics Suite (AR-CRIS), a research platform developed at UAMS that integrates multiple platforms into a portal that can efficiently manage single- and multi-site trials. Our mission is to continue improving access to high-quality clinical trials for cancer patients in Arkansas.

Poster #37

Tissue Biorepository and Procurement Service

Remelle Eggerson and Steven Post

Advances in biomedical research, particularly in gene analysis and proteomics, have the potential to rapidly advance our understanding and treatment of diseases such cancer, Alzheimer's disease, heart disease, AIDS, multiple sclerosis, and a variety of others. Realizing this potential requires a large numbers of human tissue samples with the associated clinical information linked to the tissue. The UAMS Tissue Biorepository and Procurement Facility (TBAPS) provides researchers with a high quality human biospecimen repository that uses best practice collection methodologies and appropriate clinical data capture mechanisms that maintain patient protection. Currently, the facility contains over 15,000 specimens of diseased and normal tissue linked with the associated de-identified clinical and pathological information maintained in a web-accessible, searchable database. TBAPS is thus a valuable research resource for advancing our understanding of disease and translating this into improved patient care.

The UAMS Office of Research is pleased to co-sponsor the 26th Showcase of Medical Discoveries on Cancer research with the Winthrop P. Rockefeller Cancer Institute, College of Medicine, and Office of Institutional Advancement.

Check out the latest collaborative research projects by outstanding UAMS health professionals and researchers!

∞

To augment our efforts to bring you exciting up-to-date research discoveries via the Showcase format, please scan the QR code below and provide your feedback, comments, and suggestions.

- Office of Research

Cancer Showcase Survey

Poster #1

Assessing Clinical Trial Self-Perceived Competence Among International Sites Participating in the AIDS Malignancy Consortium

Jeannette Lee, Maria Botello-Harbaum, Rebecca Medina, Shelly Lensing, and Meredith Zozus

The AIDS Malignancy Consortium (AMC) conducts clinical trials of therapeutic and prevention strategies for cancer in persons living with HIV. The AMC has expanded its activities to Sub Saharan Africa and Latin America and recently identified a need to prepare Clinical Investigators (CIs) and Study Coordinators (SCs) who initiate, manage, and coordinate AMC's protocols. An electronic survey of AMC CIs and SCs assessed their self-perceived competency in several domains based on the Joint Task Force for Clinical Trials Competency. A total of 35 CIs and 17 SCs completed the survey. This formal needs assessment will be used to tailor educational opportunities in clinical trial development and management particularly in domains with the lowest self-perceived scores: engaging with communities, data management and informatics, study and site management, and medication development and regulation for CIs, and preparedness and regulation, adverse event reporting, and study activities at site for SCs.

Poster #36

Experimental Pathology Core Laboratory

Jennifer James and Steven Post

The Experimental Pathology (ExPath) Core Laboratory provides investigators with centralized, comprehensive histological services. The laboratory can process and paraffin embed tissue, and section frozen and paraffin-embedded tissues. Slides can be prepared for staining, molecular studies, and laser capture microdissection. The laboratory provides a variety of standard pathological stains for histochemical analysis of tissues, including hematoxylin and eosin, special stains, and immunohistochemistry. Laboratory staff work with investigators to develop immunostaining approaches for detecting specific targets of interest. The core is equipped with slide scanners for capturing whole-slide images, which can be analyzed using Aperio ImageScope™ software with algorithms for color deconvolution, nuclear and membrane localization, and quantifying positive pixel number and intensity. In addition, the core has a Mantra™ Quantitative Pathology Imaging System for multispectral analysis of up to 6 fluorophores on a single slide. The laboratory director, staff, and pathology consultants have extensive experience in routine histology and immunohistochemistry involving both human and animal tissues.

Poster #35

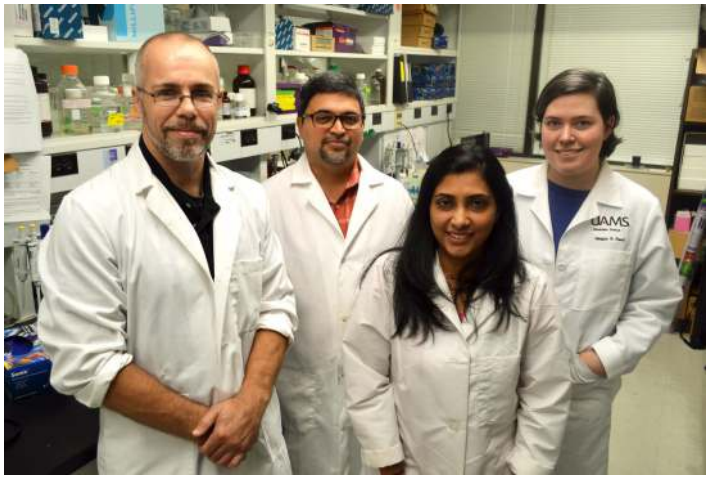
UAMS WPRCI Genomics Core Facility, Science & Services

Donald J. Johann, Jr, Aisulu Usubalieva, Amanda Metz, Meei Liu, Jason Liem, Erich Peterson, and Owen Stephens

The mission of the UAMS Genomics Core is to provide UAMS investigators with convenient access to the latest technologies for Next Generation Sequencing (NGS), microarray, and analytical approaches for the evaluation of bio-molecules, eg, nucleic acids. This is a new core and was officially opened by UAMS administration January 2019. It is fully supported by the Cancer Institute. The specific aims are: i) provide state-of-the-art genomics technologies in order to generate high-quality data with an efficient turn-around time and affordable cost; ii) provide Cancer Institute members with dedicated personnel for time with consultation and technical assistance, in support of experimental design, sample preparation, data acquisition and initial analysis; and iii) maintain state-of-the-art genomics capabilities as well as identify and develop new applications of molecular profiling to advance research within the Cancer Institute.

Poster #2

DNA Polymerase Kappa Acts as a Barrier to Replication Catastrophe in Gliomas

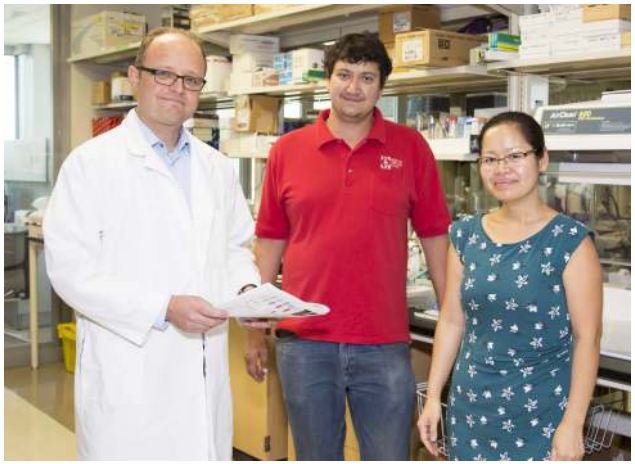


Megan R. Reed, Leena Maddukuri, Amit Ketkar, Narsimha R. Penthala, Peter A. Crooks, and Robert L. Eoff

Constitutive activation of the replication stress response (RSR) allows tumors to tolerate oncogene activation and treatment-induced DNA damage. We have investigated the role of human DNA polymerase kappa in mitigating the high levels of replication stress (RS) in gliomas. Genetic ablation and pharmacological inhibition of pol kappa produced defects in the RSR that resemble replication castastrophe (RC). The protective effect of pol kappa was observed in tumor-initiating glioblastoma stem cells. Our findings shed light on mechanisms that provide adaptive potential and survival advantage to cells experiencing sustained RS.

Poster #3

Gastrointestinal Tract Dysbiosis Enhances Distal Tumor Progression through Suppression of Leukocyte Trafficking



Samir V. Jenkins, Michael S. Robeson II, Robert J. Griffin, Charles M. Quick, Eric R. Siegel, Martin J. Cannon, Kieng B. Vang, and Ruud P.M. Dings

The overall use of antibiotics has increased significantly in recent years. Besides fighting infections, antibiotics also alter the gut microbiota. Commensal bacteria in the gastrointestinal tract are crucial to maintain immune homeostasis, and microbial imbalance or dysbiosis affects disease susceptibility and progression. We hypothesized that antibiotic-induced dysbiosis of the gut microbiota would suppress cytokine profiles in the host, thereby leading to changes in the tumor microenvironment. The induced dysbiosis was characterized by alterations in bacterial abundance, composition, and diversity in our animal models. On the host side, antibiotic-induced dysbiosis caused elongated small intestines and ceca, and distal melanoma and lung carcinoma progressed more quickly than in control mice. Mechanistic studies revealed that this progression was mediated by suppressed TNF-α levels, both locally and systemically, resulting in reduced expression intercellular adhesion molecule-1 (ICAM-1) on tumor endothelial cells and a subsequent decrease in the number of activated and effector CD8+ T-cells in the tumor.

Poster #34

IDeA National Resource for Quantitative Proteomics

Samuel G. Mackintosh, Ricky D. Edmondson, Stephanie D. Byrum, Michael T. Kinter, and Alan J. Tackett

The IDeA National Resource for Quantitative Proteomics is a partnership between the Arkansas INBRE and the Oklahoma INBRE uniting cutting-edge, discovery phase proteomic capabilities at UAMS with state-of-the-art, targeted validation proteomics at OMRF to create a national proteomics resource for the IDeA Program. Services available from the UAMS facility include protein identification, posttranslational modification mapping, label-free protein quantification, gel-based or offline LC-based peptide fractionation for proteomics applications, metaproteomics, tandem mass tag quantitative proteomics, stable isotope labeling, and other custom services for discovery-phase applications. Services available from the OMRF facility include quantification of proteins in various cellular pathways and protein panel development. Discovery proteomics involves the large-scale identification of proteins from a complex biological sample using high-resolution, rapid -sampling mass spectrometers. Discovery proteomics generally utilizes 10s of samples and generates 1000s of candidate proteins for follow-up studies. In targeted proteomics, specialized mass spectrometers are used to quantify a small set of proteins in a large number of samples. Targeted-validation proteomics generally utilizes 100s of samples to measure 10s of target proteins. The IDeA National Resource for Proteomics hosts a series of workshops each year at both facilities emphasizing topics within the field of proteomics research, such as experimental design, interpretation of results, and manuscript and grant preparation.

Poster #33

Spinal Cord Stimulation Prevents Paclitaxel-induced Mechanical and Cold Hypersensitivity and Modulates Spinal Gene Expression in Rats

Eellan Sivanesan, Kimberly E. Stephens, Qian Huang, Zhiyong Chen, Neil C. Ford, Wanru Duan, Shao-Qui He, Xinyan Gao, Bengt Linderoth, Srinivasa N. Raja, and Yun Guan

Paclitaxel-induced peripheral neuropathy (PIPN) is a common dose-limiting side effect of this cancer treatment drug. We examined the inhibitory effect of spinal cord stimulation (SCS) on the development of PIPN pain and changes of gene expression in the spinal cord in rats after SCS. Compared to rats treated with paclitaxel alone or sham SCS, SCS treatment significantly inhibited the development of paclitaxel-induced mechanical and cold hypersensitivity, without altering open-field exploratory behavior. RNA-seq showed that SCS upregulated genes involved in immune responses in paclitaxel-treated rats, including transcription of astrocyte- and microglial-related genes and repressed transcription of multiple gene networks associated with synapse transmission, neuron projection development, gamma-aminobutyric acid reuptake, and neuronal plasticity. Our findings suggest that traditional SCS may attenuate the development of pain-related behaviors in PIPN rats, possibly by causing aggregate inhibition of synaptic plasticity through upregulation and downregulation of gene networks in the spinal cord.

Poster #4

Fragment-Based Discovery of a Dual pan-RET/VEGFR2 Kinase Inhibitor Optimized for Single-Agent Polypharmacology

Brendan Frett, Lingtian Zhang, Francesca Carlomagno, Maria Luisa Moccia, Annalisa Brescia, Giorgia Federico, Valentina De Falco, Brittany Admire, Zhongzhu Chen, Wenqing Qi, Massimo Santoro, and Hong-yu Li

Oncogenic conversion of the RET (rearranged during transfection) tyrosine kinase is associated with several cancers. A fragment-based chemical screen led to the identification of a novel RET inhibitor, Pz-1. Modeling and kinetic analysis identified Pz-1 as a type II tyrosine kinase inhibitor, which binds the "DFG-out" conformation of the kinase. Pz-1 was also shown active on VEGFR2, which can block the blood supply required for RET-stimulated growth. In cell-based assays, 1.0 nM of Pz-1 strongly inhibited phosphorylation of all tested RET oncoproteins. At 1.0 mg/kg/day PO, Pz-1 abrogate formation of tumors induced by RET mutant fibroblasts and blocked phosphorylation of both RET and VEGFR2 in tumor tissue. Pz-1 featured no detectable toxicity at concentrations of up to 100.0 mg/kg, which indicates a large therapeutic window. This study validates the effectiveness and usefulness of a medicinal chemistry/polypharmacology approach to obtain an inhibitor capable of targeting multiple, oncogenic pathways.

Poster #5

Behavioral Physiological Deficits Resulting from Breast Cancer Chemotherapy Treatment

Taurean Brown, Taylor McElroy, Fred Kiffer, Pilar Simmons, Fabio Ntagwabira, Jing Wang, Stephanie D. Byrum and Antiño R. Allen

Breast cancer is the most commonly diagnosed cancer among women and it is estimated that about 30% of newly diagnosed cancers in women will be breast cancers. While advancements in treating breast cancer have led to an average 5-year survival rate of 90%, many survivors experience cognitive impairments as result of chemotherapy treatment. Commonly reported chemotherapy-induced cognitive impairment include acute and delayed deficits in memory, learning, attention, visuospatial skills, and executive function. Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) are commonly administered as treatments for breast cancer. The purpose of this study is to investigate the effects of a clinically relevant regimen of TAC on cognition and dendritic structure in the hippocampus of females. Using behavioral, histological, and proteomic assays we found that the TAC regimen induces deficits in short term and spatial memory, changes in neuronal architecture of the hippocampus, and dysregulation of protein pathways associated with learning and memory respectively.

Poster #32

Molecular Characterization of Primary Plasma Cell Leukemia

Sandra Susanibar, Pingping Qu, Antje Hoering, Sharmilan Thanendrarajan, Jorge Jo Kamimoto, Meera Mohan, Pankaj Mathur, Shadiqul Hoque, Muthukumar Radhakrishnan, Frits van Rhee, Maurizio Zangari, Faith Davies, Daisy Alapat, Gareth Morgan, and Carolina Schinke

Primary plasma cell leukemia (pPCL) is a rare and aggressive form of multiple myeloma (MM) that is characterized by the presence of ≥ 20% circulating plasma cells. Overall survival remains poor despite advances of anti-MM therapy. The disease biology and molecular mechanisms that distinguish pPCL from non-pPCL MM remain poorly understood and given the rarity of the disease, are challenging to study. Here, we retrospectively analyzed 84 newly diagnosed pPCL patients that were treated at the Myeloma Center in Little Rock from 1999-2018. Twenty three and 41 of those patients had whole exome sequencing and gene expression data available; analysis of this data was performed to identify key biological mechanisms that result in the aggressive pPCL phenotype. The results show that pPCL is a heterogeneous disease, that is uniformly characterized by dismal clinical outcome and whose underlying biology shows profound complex structural alterations and high risk mutational patterns.

Poster #31

Doxorubicin Activates Ryanodine Receptors in Rat Lymphatic Muscle Cells to Attenuate Rhythmic Contractions and Lymph Flow

Amanda J. Stolarz, Mustafa Sarimollaoglu, John C. Marecki, Terry W. Fletcher, Ekaterina I. Galanzha, Sung W. Rhee, Vladimir P. Zharov, V. Suzanne Klimberg, and Nancy J. Rusch

Doxorubicin inhibits spontaneous contractions of rat mesenteric lymph vessels *in vitro* and slows lymph flow *in vivo.*

Doxorubicin is a risk factor for lymphedema in cancer patients exposed to surgery or radiation. The mechanisms by which doxorubicin contributes to lymphedema are unclear, but may be due to direct inhibition of lymph transport. Lymph transport relies on the rhythmic contractions of lymph vessels that are mediated by cyclic changes in intracellular calcium concentrations in lymph muscle cells that make up the lymph vessel wall. Transient rises in intracellular calcium in lymph muscle cells activates contractile proteins to support lymph vessel contractions, which ultimately propels lymph flow. Using edge detection and fluorescent imaging, we show that doxorubicin directly inhibits lymphatic contractions and disrupts calcium signaling in lymph vessels isolated from the rat mesentery. Using high-speed optical imaging, we also show that doxorubicin reduces lymph flow in the rat mesentery. Our findings reveal that doxorubicin appears to directly inhibit lymphatic contractile function as a possible mechanism of lymphedema.

Poster #6

Myeloma Patient-derived Bone Marrow Serum Negatively Regulates Natural Killer Cell Activity

Tarun K. Garg, Amy Greenway, Hongwei Wang, Antje Hoering, Brian A Walker, Maurico Zangari, Sharmalin Thanendrajan, Carolina Schinke and Frits van Rhee

We have previously treated high-risk multiple myeloma (MM) patients with highly activated expanded NK cells (ENKs), generated from the PBMCs of healthy donors/myeloma patients. These ENKs further expanded *in vivo* after adoptive transfer, but rapidly lost their activation state. We hypothesized that the ENKs were adversely affected in immunosuppressive myeloma micro-environment. Fresh ENKs were incubated with patients' serum (PT-P), FBS or AB serum for evaluation of their viability, immune synapse (IS) formation and immunophenotypic expression by flow cytometry, and cytolytic ability by standard 51Cr-release assay. Global gene expression profile of ENKs was performed using U133 Plus 2.0 microarrays. PT-P incubation induced apoptosis (15%-32%) in ENKs and reduced their viability (34%-53.8%). Poor cytolytic activity by these ENKs (14%-42%) correlated well with weak IS (12%-41%) and down-regulated expression of receptors (NKp46, NKG2D, CD16, CD226, LFA-1) and cytotoxicity molecules (perforin, granzyme B, TRAIL). Genes related to cell cycle, motility (ANAPC16, AREG, DDIT4, TSC22D3, CXCR4), intracellular signaling molecules (FKBP5, ISG20, DEFB132, ZFP36L2), cell energy and metabolism (RAP1GDS1, GALM, PARP8) were significantly altered in PT-P treated ENKs. These results suggest that myeloma-derived factors are immunosuppressive and induce apoptosis in ENKs, significantly modulate the surface receptor repertoire, IS formation and the cytolytic ability.

Poster #7

Use of an EMR-Based Tool for Identification and Referral of Patients Eligible for Cancer Genetic Counseling at an Academic Cancer Center

Melinda E. Simonson, ScM, CGC; Joshua Acuña, MPH; John Jenkins, MBA, RN-BC; Tiffany Hall, RN, MSN; Cyndee Carr, RMA; and Kristin K. Zorn, MD

Up to 10% of all cancers are thought to be associated with an inherited cancer susceptibility. Identification of cancer patients carrying these syndromes has been an increasingly important part of the standard of care, as it can improve outcomes for the patient and their family members. Our objective was to improve referral of patients meeting National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling and evaluation at our center. We designed an adaptive questionnaire as a Best Practice Advisory (BPA) in the Epic electronic medical record (EMR). Overall, BPA use was highest in the first month and declined over the course of the initial three months. This project exhibits that a BPA in the EMR can be used to screen personal and family history in cancer patients.

Poster #30

Characterization of the Immune Impact of Daratumumab by Mass Cytometry in Multiple Myeloma

Sarah K. Johnson, Stephen Burke, Matthew Henry, Amy Greenway, Katie Stone, Brian Walker, Frits Van Rhee and Gareth J. Morgan

We examined the immune sequelae of anti-CD38 antibody therapies in multiple myeloma patients by mass cytometry. Peripheral blood mononuclear cells (PBMCs) from 12 myeloma patients were analyzed pre-DARA and at days 28 and 56 after start of therapy with a pan-immune panel comprised of 38 markers. Data were analyzed by manual gating and clustering, and in an unbiased manner by CITRUS. Comparison of pre-treatment MM PBMCs to post-DARA therapy showed a significant loss of activated NK cells, B regulatory cells, plasmacytoid dendritic cells, and plasma cells. CITRUS identified significant changes in population abundance in CD8+ T cells, NK cells, myeloid/monocytes, and B cells and significant changes in CD55 and CD59 intensity, markers associated with complement inhibition. The CD55 group was upregulated and the CD59 group was reduced at day 28 and 56. Significant changes identified in immune status post-DARA increases our understanding of the varied response to immunotherapy.

Poster #29

A B-cell Developmental Gene Regulatory Network is Activated in Infant AML

Farrar JE, McFadden M, Randolph C, MacLeod S, Bolouri H, Ries, R, Pardo L, Hylkema T, Zhou W, Smith JL, Leonti A, Kaeding AJ, Loken M, Triche TJ, and Meshinchi S

Infants with acute myeloid leukemia (AML) typically bear more structural aberrations and fewer point mutations than older children or adults. Differential expression analysis of ~1500 pediatric AML samples revealed a large number of infant-specific genes, many of which are associated with B cell development and function. 18 of these genes form a well-studied B-cell gene regulatory network, including the epigenetic regulators BRD4 and POU2AF1, and their onco-fetal targets LIN28B and IGF2BP3. All four genes are hypo-methylated in infants compared to older patients. Moreover, micro-RNA Let7a-2 is expressed in a mutually exclusive manner with its target and regulator LIN28B. These findings suggest new avenues for the treatment of infant AML, including bromodomain inhibitors and immune therapies targeting CD19, CD20, CD22, and CD79A.

Poster #8

Carbamate Derivatives of Colchicine Show Potent Activity Towards Primary Acute Lymphoblastic Leukemia and Primary Breast Cancer Cells - In vitro and Ex vivo study

Alicja Urbaniak, Fariba Jousheghany, Youzhong Yuan, Sergio Pina-Oviedo, Magdalena Delgado, Urszula Majcher, Greta Klejborowska, Adam Huczyński, Behjatolah Monzavi-Karbassi, Thomas Kieber-Emmons, and Timothy C. Chambers

Colchicine (COL) shows strong anti-cancer activity related to its ability to bind to tubulin causing microtubule depolymerization, mitotic arrest, and cell death. However, due to the toxicity of COL towards normal cells, identification of new therapeutics based on COL structure is warranted. In order to increase potency and reduce toxicity against normal cells, a library of novel COL analogs, namely N -carbamates of N-deacetyl-4-(bromo/chloro/iodo)thiocolchicine, has been synthesized. COL and several of the derivatives arrested MCF-7 cells in mitosis, and caused microtubule depolymerization. Compounds were then tested against two types of primary cancer cells; adult acute lymphoblastic leukemia (ALL) cells, and human breast cancer (BC) cells derived from newly excised human tumor tissue. These represent more clinically relevant drug screening models compared to established cell lines. Four novel colchicine derivatives showed higher activity towards primary ALL cells (IC50 = 1.1 ± 0.5 to 6.4 ± 1.4 nM) and nine were more potent towards primary BC cells (IC50 = 2.3 ± 0.0 to 10.3 ± 4.6 nM) compared to COL (IC50 = 8.6 ± 0.2 nM and 11.7 ± 3.1 nM, respectively) in cell viability assays. COL and two of the most active derivatives were also shown to be effective in killing BC cells when tested *ex vivo* using fresh human breast tumor explants derived from residual invasive ductal carcinoma and invasive mucinous carcinoma. The present findings indicate that the COL derivatives described here constitute promising lead compounds for targeting acute lymphoblastic leukemia and different subtypes of breast cancer.

Poster #9

Cardiac Toxicity in an Animal model of Local Heart Irradiation and Sunitinib Treatment

Viji Mohanseenivasan, Chanice J. Thomas, Maohua Cao,
Stepan B. Melnyk, Oleksandra Pavliv, and Marjan Boerma

Thoracic radiation therapy is increasingly administered together with the targeted anti-cancer agents, tyrosine kinase inhibitors (TKI). While both thoracic radiation therapy and several TKI, including sunitinib are known to have adverse effects in the heart, side effects of their combined treatment are largely unknown. In this study, male Sprague-Dawley rats received local heart irradiation (9 Gy per day for 5 days) combined with oral sunitinib (8 or 15 mg/kg bodyweight per day) for 2 weeks, starting on day 1 of irradiation. Radiation and sunitinib counter-acted each other in their effects on cardiac function, but did not interact with each other in induction of oxidative stress. On the other hand, the combination of radiation and sunitinib caused more severe changes in mitochondrial morphology and mitochondrial permeability transition pore opening compared to each treatment alone. Long-term effects of combined radiation and TKI treatment on the heart need to be studied.

Poster #28

New Role of Sirt2 in Alleviating Chemotherapy Induced Peripheral Neuropathy Pain

Manchao Zhang, Wuying Du, John R Gillenwater, Hao Yu,
Parmeet Manchada, Ju Hwan Cho, and Fen Xia

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the major health concerns for cancer patients. The natural compound, resveratrol is used to alleviate neuropathy pain in diabetics through activation of the NAD-dependent deacetylase, Sirt2. It would be of great clinical significance to establish Sirt2's role in CIPN regulation. We have established models of cisplatin-induced neuropathy in Sirt2 overexpressing (Sirt2 KI), Sirt2 deficient (Sirt2 KO), and wild-type control (C57BL/6) mice using dosages similar to those used in patients. C57BL/6 and Sirt2 KO mice in the cisplatin treatment group demonstrated significantly higher levels of mechanical allodynia compared to groups treated with vehicle; however, no such difference was observed in Sirt2 KI mice. These findings were recapitulated in Sirt2 KI and C57BL/6 mice bearing Lewis lung tumors and support the role of Sirt2 in protecting peripheral nerves from CIPN. Our future aims are to identify deacetylation targets that modulate this function using proteomics approach.

Poster #27

SIRT2: Tumor Suppressive or Oncogenic?

Wuying Du, Manchao Zhang, John R. Gillenwater, Hao Yu, Shengkai Jin, Parmeet Manchada, Ju Hwan Cho, and Fen Xia

Sirtuins are NAD+- dependent histone deacetylases and ADP-ribosyl transferases involved in multiple cellular pathways associated with cellular stress and survival. Among seven mammalian sirtuins (SIRT1-7), SIRT2 is involved in metabolism, cell cycle regulation, and tumorigenesis. SIRT2's role in tumorigenesis remains unclear and context-dependent as contradictory reports categorize SIRT2 as an oncoprotein and/or tumor suppressor. Our results suggest SIRT2 enhances cancer progression in breast cancer, subcutaneous melanoma, and pulmonary metastasis models in SIRT2-overexpressing (SIRT2-KI) and C57BL/6 (WT) mice. Flow cytometry revealed reduced numbers of tumor infiltrating natural killer (NK) cells in mice overexpressing SIRT2. Furthermore, immunohistochemical staining showed NK cell activation negatively correlated with SIRT2 expression levels within the tumor microenvironment. We further depleted NK cells in SIRT2-KI/WT mice or treated them with SIRT2 inhibitor and saw suppressed tumor growth in the SIRT2 inhibitor-treatment group. These findings reveal an implicit relationship between SIRT2 and NK cell function that implores further study.

Poster #10

Development of Interactive Systems Biology Tools for Omics Data

Aaron Storey, Kevin Chappell, Stefan Graw, Samantha Kendrick, Eric Peterson, and Stephanie Byrum

With the advance of mass spectrometry and increasingly larger data sets, streamlined methodologies for analysis and visualization of phosphoproteomics and histone post-translational modification are needed both at the protein and modified peptide levels. To assist in addressing these needs, we developed ProteoViz and PTMviz, which include R scripts that perform normalization, differential expression analysis of both the proteins and modified peptides, and display the results in an interactive Shiny dashboard. The tools generate interactive visualization plots that allow users to interact with the results and quickly identify therapeutic targets. Here, we present the workflow and demonstrate the functionality of ProteoViz by analyzing a phosphoproteomic data set from two lymphoma cell lines treated with kinase inhibitors. We also demonstrate PTMviz functionality by analyzing epigenetic changes in histone modifications in the brain due to methamphetamine exposure in mice. The tools presented here can be easily applied to other cancers and diseases.

Poster #11

Subject Recruitment for Phase II Randomized Double-blind Study With Two Treatment Arms: Pepcan, a Therapeutic HPV Vaccine, and Adjuvant-only

Hannah Coleman, Benjamin J. Lieblong, Ph.D., James I. Allred, Horace J. Spencer, III, M.S., and Mayumi Nakagawa, M.D., Ph.D.

Objectives: To inquire about reasons why women agreed or declined to participate, and to identify effective recruitment strategies. Methods: To probe motivations for participation, participants answered a questionnaire at enrollment. Those who declined participation completed a different questionnaire. Recruitment efforts included clinic visits, letters to providers and patients, and advertisements. Results: Motivations for participating were personal health needs (70%), contribution to medical science (16%), free treatment (9%), and others (5%). For those who declined to participate, 57% had individualized reasons. Not knowing whether they would receive vaccine or adjuvant-only accounted for 29%, and lack of transportation in 14%. Participants were recruited via telecolposcopy (40%), outside referral (38%), in-house referral (12%), and advertisement (10%). Of 16 outside patients, 94% were referred from clinics visited by study staff. Conclusions: The primary motivation to participate was personal health needs. Double-blind design did not seem to deter participation. Visiting clinics is an effective recruitment strategy.

Poster #26

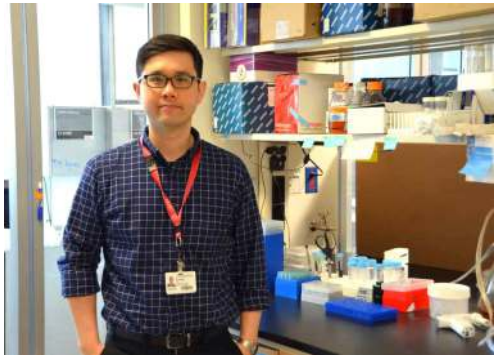
Therapeutic Immunization with P10s-PADRE in Combination with Standard-of-care Chemotherapy in ER-positive Breast Cancer: a Phase Ib Clinical Trial

Issam Makhoul, Saddam Mohammed Ibrahim, Fariba Jousheghany, Eric R. Siegel, Lora Rogers, Angela Pennisi, J. Thaddeus Beck, Laura F. Hutchins, Thomas Kieber-Emmons, and Behjatolah Monzavi-Karbassi

The current study was performed to examine feasibility, safety and immunogenicity of adding P10s-PADRE to the standard-of-care chemotherapy in ER-positive early-stage breast cancer patients. ER-positive breast cancer subjects were treated in a single-arm multi-site phase Ib clinical trial. Five different immunization schedules were considered in the neo-adjuvant setting. The primary immunogenicity endpoint was anti-peptide IgG titer. Activation of NK cells and serum concentrations of Th1/Th2 cytokines were determined. The efficacy endpoint was pathologic Complete Response (pCR). Antibody response was consistent and a significant increase in CD94 and NKp46 expression and cytokines IL-6, IL-10 and IFN-γ release was observed. Treated subjects demonstrated a significant reduction in primary tumor size and 3 subjects achieved pCR. We observed a statistically significant association between pCR and subjects with an increase in NKp46+ CD56dim cells after treatment. Activation of NK cells broadens the vaccine application in terms of target population and combination strategies.

Poster #25

The Chromatin-based DNA Damage Response Pathway



Kirk West, Jessica Kelliher, Justin Leung

DNA damage is a constant threat to our genome. Our body has evolved a surveillance mechanism, namely the DNA damage response (DDR) pathway, to protect our cells from genotoxic insults. Defective DDR pathway leads to unfaithful repair of DNA breaks which results in accumulation of mutations, chromosome rearrangement, and genome instability. Although much is known about how chromatin senses and responds to DNA damage, a significant gap in knowledge exists with the poorly characterized mechanism by which damaged chromatin transduces the signal to recruit effector proteins to DNA breaks. Such knowledge is imperative to understand how cells precisely execute the correct pathway by recruiting the right repair protein complex in a temporal and spatial manner which is essential for maintaining our genome integrity. Our research program aims to address this fundamental question in the chromatin-based DDR pathway. Our expertise lies in genome editing, functional proteomics, molecular biology, cell biology, and biochemistry. We combine our techniques of protein purification, confocal microscopy, laser-induced single cell micro-irradiation, cell-based reporter assays, protein tagging, and quantitative mass spectrometry for an overall multidisciplinary approach. Our long-term goals are to obtain a comprehensive molecular understanding of the chromatin-based DDR pathway by; 1) determining the epigenetic profile in the DDR pathway, 2) characterizing the functions of the novel DNA repair proteins, and 3) elucidating the mechanism of how damaged chromatin orchestrates different DNA repair pathways during the cell cycle in the context of damaged chromatin. Overall, our work will open up a new arena for the DNA repair field, provide insight into the etiology of cancer and genome instability-related genetic diseases that will lay the foundation for translational research and therapeutic strategy development.

Poster #12

Investigation of Novel Transcript Splicing in Multiple Myeloma Reveals an Ultra-high Risk Subgroup and Potential Novel Therapeutic Targets

Michael A. Bauer, Cody Ashby, Christopher P. Wardell, Eileen Boyle, Gareth J Morgan, Brian A Walker

Disruption of normal RNA splicing patterns is a major factor in the pathogenesis of a number of cancers. To that end, the role of alternative splicing in Multiple Myeloma (MM) remains largely unexplored. Working with RNA-Seq data, we split newly diagnosed MM samples into three novel splice groups. There was as significant difference in progression free survival and overall survival between the low and high splice groups. Significantly less splicing was identified in the t(4;14) group, a poor prognosis MM subgroup. This led to the finding that there may be a previously undescribed ultra-high risk group of t(4;14). A number of genes were over expressed in the high splice group. We observed an enrichment in genes involved in the G2/M checkpoint and E2F (family of transcription factors) target pathways and a decrease of the p53 DNA repair pathway. Alternative splicing is an important pathogenic disease mechanism in MM that affects important pathways and genes.

Poster #13

Bone-Targeted Inhibition of Notch Signaling Blocks Tumor Growth and Prevents Bone Loss Without Inducing Gut Toxicity in Immunodeficient and Immunocompetent Murine Models of Established Multiple Myeloma

Adam Ferrari, Kevin McAndrews, Jessica Nelson, James Bell, Venkatesan Srinivasan, Frank H. Ebetino, Robert K. Boeckman Jr, G. David Roodman, Teresita Bellido, and Jesus Delgado-Calle

We generated a bone specific Notch inhibitor (BT-GSI) by using a hydrolyzable linker to conjugate GSI-XII to a targeting agent with high affinity for bone (BT). BT-GSI was first examined in immunodeficient mice injected with JJN3 human MM (hMM) cells. BT-GSI decreased Notch in bone but not in the brain or gut, and decreased by ~45% tumor burden and osteolytic area. Moreover, BT-GSI decreased resorption by 30%, but did not affect bone formation. BT-GSI was also tested in immunocompetent mice injected with 5TGM1 murine MM cells (mMM). BT-GSI decreased tumor burden and the number of osteolytic lesions by ~50%. These results show that bone-targeted Notch inhibition reduces MM growth and preserves bone mass in mice with established MM. Because BT-GSI inhibits Notch signaling selectively in the bone-MM niche and lacks gut toxicity, it is a promising therapeutic approach to inhibit tumor growth and prevent bone loss in MM.

Poster #24

Macrophage Class A Scavenger Receptors Bind Tumor-associated Carbohydrate Antigens and Promote Growth and Metastases of Breast Cancer in Mice

Behjatolah Monzavi-Karbassi, Thomas Kelly, Christy Simecka, Asangi Kumarapeli, Eric R. Siegel, Jessica Webber, Fariba Jousheghany, Beixiang He, Trevor Meece, Taylor Wadley, and Steven R. Post

Tumor-associated macrophages play a key role in determining the immune response in cancer. Macrophages express pattern-recognition receptors, such as Class A Scavenger Receptors (SR-A), that bind a range of ligands and regulate macrophage immune phenotypes. SR-A, which is specifically expressed by macrophages, induces an immune-suppressive macrophage phenotype. Thus, we hypothesized that SR-A would enhance the progression of breast cancer. Using mouse models of spontaneous breast cancer, our results show that development of palpable tumors was significantly delayed and the number of lung metastases significantly decreased in mice that do not express SR-A (SR-A-/-). To identify SR-A ligands in tumors, we developed a flow cytometry based binding assay using a soluble SR-A (sSR-A) protein and showed that SR-A binds directly to breast cancer cells. This binding depended on glycosylation indicating SR-A binds to cell-surface glycans on tumor cells, which is important because tumor-associated carbohydrate antigens (TACAs) are associated with immune suppression, tumor progression, and poor prognosis for breast cancer patients. The ability of SR-A to bind TACAs was tested using carbohydrate mimetic peptides (CMPs) that are structurally similar to TACAs. sSR-A bound to CMPs, and a CMP designed to react with mannose-rich structures blocked sSR-A binding to tumor cells. These findings demonstrate that SR-A binds to glycans (TACAs) on breast cancer cells, and that SR-A enhances breast cancer growth and metastases. Our results indicate a model in which SR-A binds to TACAs to induce an immune-suppressive macrophage phenotype, which contributes to immune suppression, tumor growth, and metastases.

Poster #23

An Online Survey and Focus Groups Addressing Cancer Health Disparities in Arkansas

Sumit K. Shah, MD., MPH., Maggie Jones-Carr, Milan Bimali, Ph.D., L. Joseph Su, Ph.D., MPH., and Mayumi Nakagawa, MD., PhD.

Higher cancer-associated mortality in Arkansas can be partially attributed to underutilization of prevention measures. Online survey and focus groups were conducted to assess feasibility of creating a volunteer-based program. We also determined knowledge and compliance with recommended cancer prevention measures. Willingness to play some role in promoting cancer prevention measures was 67.7% (n=1,056), however, only 30.3% (n=442) were willing to volunteer for the program and only 35 individuals participated in focus groups. Self-reported adherence to breast, cervical, and colon cancer screening were 82.6% (n=954), 75.8% (n=541), 76.7% (n=453), respectively. Associations revealed that personal cancer history significantly increased colorectal cancer screening uptake (p=0.04), but significantly decreased mammography uptake (p=0.007). People with salary >$40,000 and having a Bachelor's degree or higher showed higher compliance with Papanicolaou test (p=0.007 and p=0.001, respectively). Participation in the volunteer program alone is not likely to be sufficient, and multifaceted approaches are likely needed to increase awareness.

Poster #14

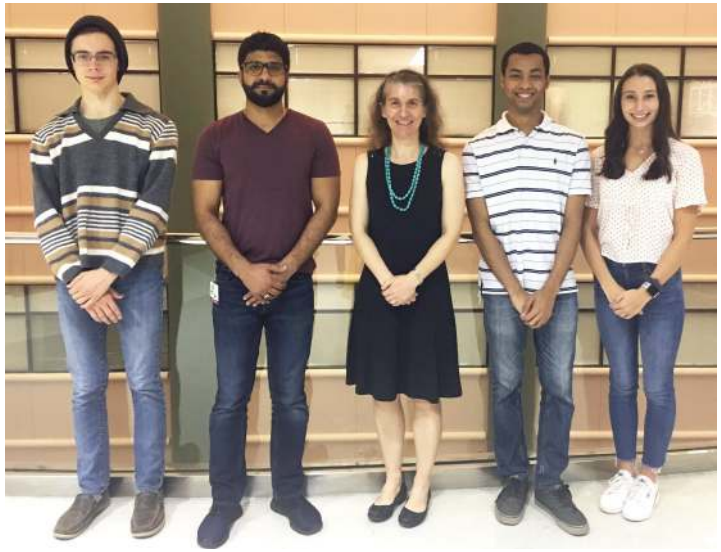
Methionine Dependence: A Metabolic Vulnerability of Cancer

L. Clai Morehead, Isabelle R. Miousse

Most cancer cells display an increased reliance on exogenous methionine compared with normal cells, a phenomenon called "methionine dependence." Methionine depletion potentiates chemotherapy and radiotherapy *in vivo*, but the molecular bases of methionine dependence remain unknown. Aging studies show that restricting dietary methionine by 80% improves glucose and lipid metabolism and increases lifespan in an autophagy-dependent manner. Our results indicate that this level of methionine restriction is sufficient to impair tumor growth, while maintaining body weight. In an effort to identify a mechanism of action, we performed a proteomic screen of two melanoma cell lines divergent for methionine dependence. Both cell lines appropriately sensed methionine stress, and we observed few differences in pathway activation in response to treatment. Future experiments will focus on identifying subcellular translocation events linked to methionine dependence. These results contribute towards the integration of methionine dependence into clinical practice and the discovery of novel drug targets.

Poster #15

Human DNA Helicase B Protects Stalled Forks from Degradation After Replication Stress



Maroof Khan Zafar and Alicia K. Byrd

Genomic DNA is constantly under threat from environmental factors and intrinsic sources of DNA damage resulting in activation of the replication stress response to protect the integrity of genomic DNA. Deficiencies in this process are associated with cancer and aging. In response to replication impediments, replication fork reversal can protect cellular DNA from genomic instability. The regressed arm of the reversed fork must be protected from resection by the enzymatic activity of nucleases to maintain genomic stability. Several proteins such as BRCA1/2 and RAD51 are involved in protecting reversed forks from degradation, thereby enabling replication restart although the mechanism is unknown. Recently, Human DNA Helicase B (HELB) was identified as a negative regulator of homologous recombination by inhibiting end resection. We have found that loss of HELB causes nascent strand degradation in response to replication stress, which suggests HELB protects stalled replication forks from aberrant degradation by nucleases.

Poster #22

Feasibility of Reducing Animal Numbers in Radiation Countermeasure Experiments

Reid D. Landes, Horace J. Spencer, Kimberly J. Jurgensen, Lynnette H. Cary, William K.J. Skinner

Background: Researchers investigating radiation countermeasures often estimate dose reduction factors (DRF). The DRF compares the radiation dose lethal to 50% (LD50) of animals receiving countermeasure to the LD50 for control animals. DRF experiments historically use large numbers of animals. We develop a power analysis method for planning DRF experiments. Purpose: Evaluate agreement between theoretical and "post-hoc" power. Methods: We statistically planned two DRF experiments, calculating N=82 mice would provide about 0.90 power. With the real data from each experiment, we conducted a feasibility analysis, comparing theoretical power to "post-hoc power" for a range of sample sizes. Results: "Post-hoc" power was about 0.90 when N=60 for both studies. Fewer animals than calculated were actually needed. Conclusion: These results convincingly verify that reasonably powered DRF experiments are possible with strikingly fewer animals than are often used. Planning DRF experiments with our method will save animals, time, and money.

Poster #21

Mutant KRAS Enhances Stress Granules and Resistance to Proteasome Inhibition via 15-d-PGJ2 in Multiple Myeloma

Ya-Wei Qiang, MD, PhD, Shiqiao Ye, PhD, Yu Chen, Joshua Epstein, DSc, Faith E Davies MD, DSc, Gareth J Morgan MD, PhD. Brian A Walker, and Frits van Rhee, MD, PhD

Mutant RAS leads to activation of the MEK/ERK pathway in approximately 50% of multiple myeloma (MM). Stress granules (SGs) are non-membranous structures composed of mRNA, ribosomal proteins, and RNA-binding proteins, which form in response to different stress stimuli and chemotherapeutic treatment. However, it is unclear the function of mutant KRAS-mediated SGs in MM pathobiology and chemotherapeutic resistance. In this study, we investigated the role of mutant RAS in GS formation and mechanism of the action using a panel of MM cells with different Ras mutation status (KRASM, NRASM and KRASWT). The level of SGs were significantly higher in six KRASM, but in N-RAS or KRASWT cells. Genetic knockdown KRAS (KRASM/KO) by shKRAS (KRASM/KO) inhibits SG formation, while overexpression of KRAS/G12A promotes SG formation. Furthermore, we showed that KRAS induces SG formation via upregulates 15-d-PGJ2, which is regulated by COX2 activity. Inhibition of COX2 activity led to increase in sensitivity of MM to proteasome inhibitors. Our results suggest that mutant KRAS upregulates SG formation via COX2-mediated 15-d-PGJ2 and targeting SG formation might be represent an effective strategy to treatment of KRAS mutant myeloma.

Poster #16

EZH2 Protects Tumor-infiltrating Lymphocytes from Metabolic-stress induced Cell Death and Exhaustion

Brian Koss, Bradley D. Shields1 Erin M. Taylor, Aaron J. Story, Stephanie D. Byrum, Kimberly J. Krager, Tung-Chin Chiang, Samuel G. Mackintosh, Rick D. Edmondson, Nukhet Aykin-Burns, and Alan J. Tackett

T cell exhaustion in cancer is strongly linked to poor clinical outcome and evidence suggests T cell metabolic changes often precede functional exhaustion. Factors regulating the development and maintenance of metabolic exhaustion are potential targets for therapeutic intervention and must be explored. Tumor infiltrating lymphocytes undergo epigenetic changes and through systematic evaluation of EZH2(H3K27me3) loss we have discovered a mechanism contributing to the development of tumor-induced metabolic exhaustion. Our data demonstrate the potential for manipulation of EZH2 in cellular therapies for solid tumors with harsh metabolic conditions.

Poster #17

Discovery of DNA G-quadruplexes as a New Target for B-cell Receptor Signaling Inhibition in Diffuse Large B-cell Lymphoma

Ying-Zhi Xu, Thomas Raney, and Samantha Kendrick

The activated B-cell-like (ABC) subtype, a refractory subset of diffuse large B-cell lymphoma (DLBCL) patients, relies on constitutive B-cell receptor (BCR) signaling. The emerging field of DNA secondary structures implicate guanine (G)-quadruplexes (G4) act as transcription regulatory units, or switches, that can turn gene expression on/off in the presence of nuclear proteins and small molecules. CD analyses revealed that the G-rich sequences within BCR genes critical for ABC DLBCL cell survival, CD79A, CD79B, CARD11, and MYD88, form stable G4 structures with classic spectra. We then developed a high-throughput screening assay based on FRET to identify G4 interactive compounds from the NCI Diversity Set IV library that uniquely interact with each of the BCR G4 sequences. Overall, the screen resulted in a ~1% "hit" rate for each BCR target. This study identifies DNA G4 as a new class of molecular targets for inhibiting genes an important oncogenic pathway in DLBCL.

Poster #20

Combating Chemobrain with Redox Modifier MnTnBuOE-2-PyP: Cognition and Hippocampal Physiology following AC-T Chemotherapy

Taylor McElroy, Fred Kiffer1, Taurean Brown, Pilar Simmons-Brown, Alexis Howe, Jing Wang, Stephanie Byrum, Rebecca Oberley-Deegan, and Antiño R. Allen

The brain is susceptible to oxidative stress due to its high-energy requirements, limited anaerobic respiration capacities, and limited antioxidant defenses. Breast cancer chemotherapy treatment up regulates oxidative stress resulting in long term cognitive impairments. The goal of the current study is to determine if the manganese porphyrin SOD mimetic MnTnBuOE-2-PyP (MnBuOE) could ameliorate the effects of doxorubicin, cyclophosphamide, and paclitaxel (AC-T) on mature dendrite morphology and cognitive function in female mice. AC-T treatment significantly decreased dendritic length in the DG and CA1 regions. We found that MnBuOE normalized dendritic length in these regions. MnBuOE also protected short-term spatial memory during the Morris water-maze, while AC-T treatment impaired spatial memory retention. MnBuOE treatment alone increased mushroom spines in the DG/CA1 regions. Proteomic analysis revealed protein networks associated with cell morphology in both the AC-T and AC-T/MnBuOE treatment groups.

Poster #19

Biomarkers of Environmental Heavy Metal Exposure as a Predictor for Obesity Among Women Living in Rural Arkansas

Joseph Su, Shelbie Stahr, Lora Rogers, Gail Runnells,
Tung-Chin Chiang, and Susan Kadlubar

Environmental heavy metals, such as arsenic, cadmium, and chromium, are widely distributed in the soil in certain regions in the U.S., including Arkansas. As the result, much of the vegetation grown in this region may have higher heavy metal content. This is particularly concerning in rural Arkansas, where generations of residents consume locally grown produce and experience prolonged exposure to contaminated dust due to low population mobility. At the same time, prevalence in obesity and metabolic syndrome in Arkansas is among the highest in the US. We hypothesized that heavy metal exposure is associated with obesity, which subsequently may impact cancer outcomes. Saliva samples and lifestyle factors were obtained from women who participated in the Arkansas Rural Community Health Study cohort. Heavy metal concentrations were analyzed using ICP-MS. Obesity was based on self-reported height and weight. We found significant positive association between heavy metal exposure and obesity in the study population.

Poster #18

Understanding Adolescent Exposures of Tobacco Products by Urine Metabolomics

Ping-Ching Hsu, Eryn Matich, Min-Ae Song, Kenneth Riedl, Morgan Cichon, Quentin A. Nickerson, Brittney L. Keller-Hamilton, Amy K. Ferketich, and Peter G. Shields

Most smokers/smokeless tobacco (ST) users begin before the age of 18. In adolescents, the prevalence of ST and e-cigarette (e-cig) use has been increasing and the prevalence of dual use is high, and even higher in Ohio than many other states. Methods: A cohort of both rural and urban adolescent males in Ohio was used to determine the differences in exposure to tobacco toxicants for smokers, ST users, e-cigarette users, and dual/poly users among adolescents using untargeted metabolomics controlling for urinary cotinine levels. Results: Among 94 adolescent who reported using any tobacco product, 36.2% used more than one product and 23% had used all three products (cigarette, ST, and e-cig). For single users, e-cig was the highest (16%) compared to cigarette use (12.8%) and ST use (11.7%). Significant differences were observed in global metabolomic profiles between active tobacco users and those with background cotinine levels (< 100ng/ml), as well as e-cig users vs. cigarette and ST users. Among active tobacco users, the nicotine metabolic ratio (NMR) was used to determine their metabolic capacity for nicotine. 15 urinary metabolites were significantly higher among fast than slow metabolizers ($p < 0.05$, absolute fold change > 2), including metabolites of flavorings, cigarette, and known biomarker with hepatotoxic effects. Conclusion: Metabolomic profiling is distinguishing adolescents who choose different types of tobacco products, including their ability to metabolize nicotine. Such profiles may be useful as biomarkers of exposure, and identify disease mechanisms and pathways differentially affected by product choice.