2019 ANNUAL CANCER RESEARCH SYMPOSIUM

FRIDAY | FEB. 1 | 2019

Stephenson CANCER CENTER

The UNIVERSITY of OKLAHOMA

A NATIONAL CANCER INSTITUTE DESIGNATED CANCER CENTER

HOSTED BY STEPHENSON CANCER CENTER
In 2012 TSET awarded a five-year, $30.25 million grant to the Stephenson Cancer Center to establish the Oklahoma TSET Cancer Research Program. In 2017 TSET renewed this award for an additional five year period.

The mission of the Oklahoma TSET Cancer Research Program is to decrease the burden of cancer in Oklahoma and nationally through promoting, coordinating and supporting innovative cancer research. It seeks to accomplish this mission through:

- Attracting cancer researchers with grant funding from the National Cancer Institute and other national sponsors to Oklahoma
- Developing trans-disciplinary, collaborative cancer research programs
- Promoting inter-institutional partnerships to leverage unique strengths at research institutions in Oklahoma
- Enhancing research infrastructure and shared resources to enable and support innovative and nationally-competitive cancer research
- Serving as a statewide resource for researchers and institutions that conduct cancer research

The Oklahoma TSET Cancer Research Program supports a wide range of programs, shared resources and initiatives designed to accomplish these goals.

**FIVE YEAR HIGHLIGHTS**

With support from the Oklahoma TSET Cancer Research Program the Stephenson Cancer Center accomplished the following:

- Increased cancer center membership from 75 to 266 members at nine academic institutions across Oklahoma
- Recruited thirty five new cancer researchers to Oklahoma
- Funded fifty seed and directed-research grants to cancer investigators in Oklahoma
- Enhanced five Shared Resource facilities
- Hosted over 270 research seminar speakers
- Hosted annual statewide Cancer Research Symposium that bring together over 250 researchers from around the state
- Hosted over 75 undergraduate students from 25 different universities for a summer cancer research experience
- Opened 627 new cancer clinical trials
- Enrolled 4114 patients to interventional clinical trials
- Enrolled 5089 patients to non-interventional clinical trials
- Opened 114 new Phase I and Phase I/II clinical trials
- Enrolled 786 patients to Phase I clinical trials
Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Research Center (OTRC) for co-sponsoring the 2019 Stephenson Cancer Research Symposium.

The mission of the Oklahoma Tobacco Research Center (OTRC) is to reduce, and ultimately eliminate, tobacco-related morbidity and mortality in Oklahoma through research that informs interventions and policies with a particular emphasis on addressing tobacco-related health disparities.

The following goals help drive our mission:

1. To be a leading tobacco research program with a focus on the entire translational continuum – from the discovery of basic mechanisms of tobacco use, cessation, and relapse, to the development and evaluation of novel tobacco treatments, to the dissemination and implementation of treatments, policies, and education throughout Oklahoma.
2. To effectively and efficiently deliver state-of-the-science, evidence-based tobacco treatment to Oklahomans throughout the State.
3. To train the next generation of tobacco researchers.

In addition, the OTRC provides tobacco cessation services across the state through its Tobacco Treatment Research Program.

The OTRC was established in 2007 with funding from the Oklahoma Tobacco Settlement Endowment Trust (TSET). Recognizing the investments that TSET has made in statewide and community-based cessation and intervention projects, a key feature of the OTRC is establishing partnerships with existing and future TSET-funded projects and the Oklahoma State Department of Health (OSDH) tobacco-related programs. Those partnerships directly link OTRC researchers with tobacco-related issues and initiatives in Oklahoma.

**OTRC DIRECTOR**
Jennifer I. Vidrine, PhD

**OTRC DIRECTOR OF INTERVENTION RESEARCH**
Damon J. Vidrine, DrPH

**OTRC DIRECTOR OF TOBACCO REGULATORY SCIENCE RESEARCH**
Theodore Wagener, PhD.

**OTRC DIRECTOR OF STATE & LOCAL POLICY**
Donald Robert McCaffree, MD, MSHA
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9:30 – 10:30  REGISTRATION & POSTER CHECK-IN

10:30 – 12:00  LUNCH & POSTER SESSION

12:00 – 12:15  WELCOME & STATE OF THE CANCER CENTER
Robert Mannel, MD

12:15 – 1:15  KEYNOTE ADDRESS:
SYMPTOM SCIENCE IN CANCER SURVIVORS: ADVANCES IN BIOLOGY AND MANAGEMENT
Patricia Ganz, MD

1:30 – 2:30  SESSION I

**Cancer Biology Track**
Moderators: Rajagopal Ramesh & Min Li

Develop a Novel Therapy for Pancreatic Cancer
Min Li

Exosomes in Predicting Response to Chemotherapy in Metastatic Endometrial Carcinoma
Katherine Moxley

SHP2 In Cell Signaling, Oncogenesis, and Targeted Cancer Therapy
Jie Wu
**Cancer Prevention & Control Track**
Moderator: Theodore Wagener

**Plenary Talk**
Reducing Cancer by Reducing Addictiveness of Cigarettes
Dorothy Hatsukami

**Experimental Medicine & Developmental Therapeutics Track**
Moderators: Kathleen Moore & C.V. Rao

Exploratory Analysis of Somatic BRCA Mutations in Endometrial Cancer and Its Clinical Implications
Wesley Burkett

APJ Promotes Metastasis and Chemoresistance in Ovarian Cancer
Deepika Neekakantan

Monoclonal ELTD1 Antibody as a Therapy Against Glioblastomas (GBM) in a Mouse Xenograft Model
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Bojie Dai

Diosgenin, a Naturally Occurring Steroidal Saponin, Prevents Colon Cancer in Animal Models of Hereditary and Sporadic CRC
Venkateshwar Madka

**2:30 – 3:30**  
**SESSION II**

**Cancer Biology Track**
Moderators: Xin Zhang & Lauren Zenewicz

Mechanism of Resistance of CLL Patients to Idelalisib Therapy
Asish Ghosh
Different Sensitivities of Protein Tyrosine Kinase Inhibitors Towards Drug-Resistant RET Mutations  
Xuan Liu

ZIP4 Promotes Pancreatic Cancer Chemoresistance through Activating Integrin-ENT1 Signaling Axis by EMT-Transcription Factor ZEB1  
Mingyang Liu

A Whole-genome In Vivo Kinome Screen Identifies IKKβ as a Novel Suppressor of the Human Papillomavirus Oncoprotein HPV 18E6-mediated Cellular Abnormalities  
Mojgan Padash Barmchi

**Cancer Prevention & Control Track**  
Moderator: Theodore Wagener

The Impact of Flavors and Sweeteners on Hookah Tobacco Smoking  
Theodore Wagener

How Psychophysiology Can Inform Tobacco Regulatory Science  
Glenn Leshner

Assessing Youth and Young Adult Appeal for, and Abuse Liability of Menthol Cigarettes using Experimental and Epidemiological Approaches  
Amy Cohn

**Experimental Medicine & Developmental Therapeutics Track**  
Moderators: Kathleen Moore & C.V. Rao

Sweet and Stealthy Drug Delivery; Heparosan-based systems for enhancing therapeutics  
Paul DeAngelis

Model Based Optimization of Combination Chemo-Photodynamic Therapy with Far-Red Light-Activatable Prodrugs: Proof of Concept Study in Preclinical Mice Models  
Mengjie Li
3D Mesoscopic Fluorescence Tomography for Imaging Micro-Distribution of Antibody-Photon Absorber Conjugates During Photoimmunotherapy In Vivo
Qinggong Tang

Celastrol Inhibits High Fat Diet-Induced Obesity and Intestinal Tumorigenesis in APC\textsuperscript{min/+} Mice by Modulating Gut Microbes and Inflammation
CV Rao

Towards Rapid and Reliable Prognosis of Drug-resistant Cancer Cells Using Single Cell Mass Spectrometry and Machine Learning
Renmeng Liu

3:30 – 3:45 Break

3:45 – 4:45 SESSION III

Cancer Biology Track
Moderators: Asish Ghosh & Marie Hanigan

Abated RD3 in Residual Neuroblastoma Cells After Intensive Multi-Modal Therapy Propel Disease Progression
Dinesh Babu Somasundaram

RNA:DNA Hybrids (R Loops) Mediate Cellular Sensitivity to Double Strand Breaks
Julio Morales

Discovery of a MYC-Driven Pre-B Cell Acute Lymphoblastic Leukemia Zebrafish Model
Gilseung Park

Cancer Prevention & Control Track
Moderator: Paul Spicer

Deliberation as Community Engagement: Promoting Dialogue about Genetic Research in the Chickasaw Nation
Jessica Blanchard, Justin Reedy, Justin Lund, Bobby Sukeah, Michael Peercy, Christie Byars
Experimental Medicine & Developmental Therapeutics Track
Moderators: Kathleen Moore & C.V. Rao

Sex Mediates the Innate and Adaptive Immune Environment of Metastatic Colorectal Cancer
Katherine Morris

Quantitative Computed Tomography Image Feature Analysis Predicts Response to Immune Checkpoint Inhibitors in Gynecologic Cancers
Kathleen Essel

Investigation of Post-Immunotherapy Response Rates in Women with Gynecologic Malignancies
Megan Buechel

4:45 – 5:00  Break

5:00 – 5:15  Awards & Closing Remarks

5:15 – 6:15  Reception
Patricia A. Ganz, M.D., a medical oncologist, is Distinguished Professor of Medicine and Health Policy & Management at UCLA. Since 1993 she has been Associate Director for Population Science at the Jonsson Comprehensive Cancer Center. In 1999 she was awarded an ACS Clinical Research Professorship and was elected to the National Academy of Medicine in 2007. She served on the NCI Board of Scientific Advisors from 2002-2007 and on the ASCO Board of Directors from 2003-2006. She received the ACS Medal of Honor in 2010. Dr. Ganz is a pioneer in the assessment of quality of life in cancer patients, focusing much of her research on breast cancer and its prevention. Her major areas of research include cancer survivorship and the late effects of cancer treatment, measurement of patient reported outcomes in clinical treatment trials, and quality of care for cancer patients. In July 2017, Dr. Ganz became Editor-in-Chief of the Journal of the National Cancer Institute (JNCI).
In this presentation, I will review information on the growing number of cancer survivors, and the evidence for the symptom burden associated with cancer treatments. Because there are now more than 15 million cancer survivors in the US, and nearly 30 million worldwide, understanding the biology and management of common symptoms is critical. I will focus on describing emerging evidence regarding the association of common symptoms of fatigue and cognitive difficulties with treatment-associated inflammatory biology. Further, I will show research from our laboratory and others that finds that various beneficial integrative oncology approaches are associated with improvements in inflammatory biology. Understanding the biological mechanisms underpinning common symptoms in cancer survivors is a first step in finding pharmacological and non-pharmacological approaches to their alleviation.
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<td>A Whole-Genome In Vivo Kinome Screen Identifies IKKβ as a Novel Suppressor of the Human Papillomavirus Oncoprotein HPV 18E6-Mediated Cellular Abnormalities</td>
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<td>Department of Biology</td>
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SESSION III
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3:45 – 4:00 PM  ABATED RD3 IN RESIDUAL NEUROBLASTOMA CELLS AFTER INTENSIVE MULTI-MODAL THERAPY PROPEL DISEASE PROGRESSION
Dinesh Babu Somasundaram
Department of Radiation Oncology
The University of Oklahoma Health Sciences Center

4:00 – 4:15 PM  RNA:DNA HYBRIDS (R LOOPS) MEDIATE CELLULAR SENSITIVITY TO DOUBLE STRAND BREAKS
Julio Morales
Department of Neurosurgery
The University of Oklahoma Health Sciences Center

4:15 – 4:30 PM  DISCOVERY OF A MYC-DRIVEN PRE-B CELL ACUTE LYMPHOBlastic LEUKEMIA ZEBRAFISH MODEL
Gilseung Park
Department of Cell Biology
The University of Oklahoma Health Sciences Center
Pancreatic cancer (PC) is the leading cause of cancer-related deaths in North America. The poor outcome of PC is due to the lack of early diagnosis and effective therapies once metastasis has occurred. Standard chemotherapy and radiotherapy do not offer significant improvement of survival, and PC often develop drug resistance. Therefore, it is urgent to identify novel molecular markers and therapeutic targets in PC that could lead to better diagnosis and more effective treatment for this devastating disease. We recently found that zinc transporters played critical roles in cancer pathogenesis and progression. Zinc is an essential trace element functioning as a catalytic cofactor for many metallo-enzymes and transcription factors, which are involved in cancer growth and metastasis. Aberrant expression of zinc transporters leading to altered intracellular zinc levels are involved in the pathogenesis of multiple cancers. We have recently demonstrated a novel biological role for the zinc importer ZIP4, encoded by the SLC39A4 gene, in PC. Our study has indicated that ZIP4 is overexpressed in human PC and promotes cell proliferation, EMT, cachexia, tumor growth and metastasis, suggesting that ZIP4 can serve as a novel prognostic and predictive marker for PC, which may provide new insights on targeted therapy for this devastating disease.

Presenting Author’s EMail: Min-Li@ouhsc.edu
EXOSOMES IN PREDICTING RESPONSE TO CHEMOTHERAPY IN METASTATIC ENDOMETRIAL CARCINOMA

Katherine Moxley, MD
Section of Gynecologic Oncology, College of Medicine, University of Oklahoma Health Sciences Center

Endometrial carcinoma represents the most common gynecologic malignancy in the US affecting 60,000 women annually. Early stage cancers are curable, but the treatment of metastatic disease remains challenging. The most active standard therapy is a platinum-taxane combination which yields response rates of 55-60%. Despite this, drug resistance develops readily with median time to survival of only six to eight months. The rapid progression and lack of therapeutic response to both cytotoxic and targeted therapy represent treatment challenges unique to this highly lethal disease state and underscore the need for identification of molecular targets of drug resistance.

Alterations in the protein expression unique to cancers are implicated in tumorigenesis and drug resistance across malignancies. Changes in non-coding RNA and downstream protein products necessary for cellular proliferation and differentiation develop during carcinogenesis and under the stress of chemotherapy in many solid tumors. While alterations that develop during the course of chemotherapy, particularly those that predict exist, there is limited knowledge of what these are in advanced endometrial cancer. Identification of molecular signatures unique to drug resistant endometrial cancer may facilitate identification of novel therapeutic targets to predict and/or reverse resistance to chemotherapy.

Exosomes derived from tumor cell membranes serve as transport vehicles for a variety of tumor derived products including DNA, coding and non-coding RNA and proteins. Exosomes can be identified in peripheral body fluids in large quantities and act at distant sites to facilitate tumor growth and metastasis. They bear direct resemblance to the tumor cells or origin and reflect ongoing alterations in the tumor cell environment. As such, they represent potential peripheral biomarkers of disease and drug resistance. Exosomes can be isolated from the plasma and urine of patients with endometrial carcinoma and bear different miRNA signatures in the presence of active malignancy. Isolation of these exosomes from the peripheral blood of patients undergoing chemotherapy will provide insight into the therapeutic targets critical to overcoming chemotherapy resistance as differential miRNA signatures exist in the tumor of women who respond to chemotherapy.

Presenting Author’s Email: Katherine-Moxley@ouhsc.edu
SHP2 is a protein tyrosine phosphatase (PTP) encoded by the \textit{PTPN11} gene. SHP2 is activated by binding to docking proteins containing bisphosphorylated-tyrosine activation motif (BTAM). SHP2 positively regulates the RAS-ERK1/2 pathway and SRC activation in response to growth factors. We identified paxillin as a direct substrate of SHP2. In cell-derived tumor xenografts and in transgenic mice, we found that SHP2 was required for tumor growth. Gain-of-function mutations that disrupt SHP2 auto-inhibition have been found in various types of human cancer, particularly in juvenile myelomonocytic leukemia (JMML). We and others have demonstrated that cancer-associated SHP2 mutations such as SHP2\textsuperscript{E76K} are oncogenic. Recently, allosteric SHP2 inhibitors targeting the wildtype SHP2 have been discovered. To determine if the allosteric SHP2 inhibitor SHP099 is effective against oncogenic SHP2 mutations, we synthesized SHP099 and analyzed its activities on four common SHP2 N-SH2-domain mutations found in leukemia. We found that SHP2 mutations could affect the sensitivity to SHP099 and identified SHP2\textsuperscript{E69K} as a SHP099-sensitive mutant.

Presenting Author’s Email: Jie-wu@ouhsc.edu
MECHANISM OF RESISTANCE OF CLL PATIENTS TO IDEALISIB THERAPY

Asish Ghosh, PhD

While the use of oral signal inhibitor (ibrutinib, targets Bruton's tyrosine kinase [BTK]; idelalisib, targets PI3Kδ) therapy directed to the B-cell receptor (BCR)-signal has recently been shown to be effective in relapsed/refractory B-cell chronic lymphocytic leukemia (CLL) patients, these responses to BCR inhibitors are limited to partial responses and when patients relapse there is often evidence for more aggressive disease including transformation to lymphomas (Richter's syndrome). In this study, we investigated why the CLL patients responded partially to idelalisib therapy in a clinical trial conducted under the supervision of Dr. Jennifer Brown at the Dana-Farber Cancer Institute, Boston, MA.

CLL B-cells from pre- and post-therapy CLL patients were examined for the activation status of multiple intracellular signal mediators using a phosphokinase array blot. We detected that re-activation of AKT was the most common feature of the post-therapy leukemic B-cells (8 of 12) despite treatment with idelalisib. Further analysis suggests that AKT re-activation was accompanied by increased activating phosphorylation on ERK1/2 in these CLL clones. To delineate the mechanism of AKT re-activation in post-idelalisib-treated CLL B-cells, we used a CLL-like cell line (MEC1) as a model. Indeed, treatment of MEC1 cells with idelalisib showed re-activation of AKT after a transient inhibition (1–2 hours following treatment) of AKT phosphorylation in a time-dependent manner. Further analysis suggests that BCAP and CD19 of the BCR complex recruit increased amounts of PI3Kβ in addition to PI3Kδ but not α- or γ-isoform. Interestingly, combined inhibition of PI3Kδ and PI3Kβ reduced AKT phosphorylation significantly. In consistent with the observations in idelalisib-treated MEC1 cells, primary CLL B-cells from pre- and post-therapy CLL patients also show increased recruitment of PI3Kβ/δ isoforms at the BCR complex but not α or γ isoform. Together, these results suggest that increased recruitment of PI3Kβ to the BCR complex may be, at least in part, responsible for re-activation of AKT in post-therapy CLL B-cells. Thus, combined treatment of CLL patients with idelalisib and a PI3Kβ inhibitor may improve the therapeutic outcome significantly.

Presenting Author's Email: Asish-Ghosh@oushc.edu
DIFFERENT SENSITIVITIES OF PROTEIN TYROSINE KINASE INHIBITORS TOWARDS DRUG-RESISTANT RET MUTATIONS

Xuan Liu¹, Tao Shen¹, Blaine H.M. Mooers², and Jie Wu¹,³
¹Peggy and Charles Stephenson Cancer Center, ²Department of Biochemistry and Molecular Biology, ³Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

The RET protein tyrosine kinase (PTK) is a clinically validated target of therapy in non-small cell lung cancer (NSCLC) and thyroid cancer. Mutations in the targeted PTKs is a common mechanism of drug resistance in cancer therapy with tyrosine kinase inhibitors (TKIs). Mutation-sensitive secondary drugs have been used successfully to overcome acquired drug-resistance to the first line TKIs. Cabozantinib, lenvatinib, vandetanib, and nintedanib are FDA-approved multikinase TKIs with anti-RET activity. Using RET kinase-dependent BaF3/KIF5B-RET cells, we isolated thirteen mutations resistant to one of these TKIs. Cross-analysis of sensitivities of TKIs on the panel of drug-resistant RET mutants and the RETM918T mutant, which is found in medullary thyroid carcinoma (MTC), revealed different TKI resistance-sensitivity profiles. Significantly, the RETM918T mutant was resistant to FDA-approved thyroid cancer drugs cabozantinib, lenvatinib, and vandetanib but did not affect the potency of nintedanib, which is a new RET TKI identified by us. RETL881V was isolated as a vandetanib-resistant mutation. The RETL881V mutation also induced resistance to cabozantinib and lenvatinib but did not affect the nintedanib sensitivity. RETG810A/S were identified as vandetanib-resistant mutations. RETG810 is at a position paralogous to the solvent front mutations EGFRG796S/R, ALKG1202R, ROS1G2032R, NTRK1G595R, and NTRK3G623R that are resistant to the 3rd generation EGFR inhibitor osimertinib, ALK and ROS1 inhibitor crizotinib, and the TRK inhibitor entrectinib. We identified RET TKIs that were effective against the RETG810A or RETG810S mutant. Taken together, we have identified 13 RET mutations that display different resistance-sensitivity profiles against anti-RET TKIs. Moreover, nintedanib is effective in inhibiting the MTC-associated RETM918T. Supported in parts by NIH grant R01CA178456 (to JW) and a PHF Team Science Grant (to JW and BHMM)

Presenting Author’s Email Address: Xuan-liu@ouhsc.edu
ZIP4 PROMOTES PANCREATIC CANCER CHEMORESISTANCE THROUGH ACTIVATING INTEGRIN-ENT1 SIGNALING AXIS BY EMT-TRANSCRIPTION FACTOR ZEB1

M. Liu, Y. Zhang, J. Yang, X. Cui, Z. Li, C. Houchen, M. Li
Department of Medicine, Department of Surgery, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Pancreatic cancer is characterized by a high degree of chemoresistance, which is the major barrier to efficient chemotherapy. However, the underlying molecular mechanism is not well understood. In this study, we aim to investigate whether dysregulated zinc transporter ZIP4 impacts pancreatic cancer chemoresistance and whether targeting the zinc transport pathway has an impact on pancreatic cancer therapy.

Methods: Human pancreatic cancer cells AsPC-1, MIA PaCa-2, and KPC mouse derived cell lines were selected. MTT assay was performed to measure the cell viability and proliferation. The morphological characteristics of pancreatic tumor spheroids was studied through spheroid formation assay. Correlations between ZIP4, integrins and ENT1 were investigated with Western blotting. Orthotopic xenograft model was used for in vivo studies.

Results: We found that ZIP4 could affect both sensitivity and cellular proliferation in response to the chemotherapy both in vitro and in vivo. Silencing of integrin-α3 and integrin-β1 attenuated the function of ZIP4 on pancreatic cancer chemoresistance. ZIP4 upregulates integrin-α3 and integrin-β1 expression through activating EMT-transcription factor ZEB1 which can bind to their promoter regions. ZIP4, ZEB1 and integrins mediate pancreatic cancer chemoresistance through gemcitabine transporter ENT1. ZIP4-ZEB1-integrin-ENT1 signaling axis contributes to gemcitabine resistance which can be activated by ZIP4 in pancreatic cancer cells.

Conclusion: High level of ZIP4 promotes pancreatic cancer chemoresistance through ZEB1-integrin-ENT1 signaling axis and it may serve as a novel therapeutic strategy to overcome pancreatic cancer drug resistance.

Acknowledgement of Funding
This work was supported by NIH grants R01CA138701, R01CA186338-01A1, R01CA203108-01, 1P30CA225520-01.

Email: Mingyang-liu@ouhsc.edu
A WHOLE-GENOME IN VIVO KINOME SCREEN IDENTIFIES IKKβ AS A NOVEL SUPPRESSOR OF THE HUMAN PAPILLOMAVIRUS ONCOPROTEIN HPV 18E6-MEDIATED CELLULAR ABNORMALITIES

Mojgan Padash Barmchi 1, Miranda Thomas 2, Thatte V. Jayashree 2, Bing Zhang 3, Ross L. Cagan 4, and Lawrence Banks 2

1 Department of Biology, University of Oklahoma, Norman, Oklahoma, USA
2 International Centre for Genetic Engineering and Biotechnology, Trieste, Italy
3 Division of Biological Sciences, University of Missouri, Columbia, Missouri, USA
4 Department of Cell, Developmental and Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, New York, USA.

Human Papillomavirus (HPV) is the leading cause of cervical cancer, head and neck cancer as well as the majority of vaginal, vulvar, penile and oropharyngeal cancers. Despite the recent availability of a vaccine, there are still over 250,000 deaths each year worldwide. There is no treatment for HPV cancer in significant part because we do not yet fully understand the cellular and molecular mechanisms of the disease. Taking advantage of the power of fruit fly genetics in addition to high conservation of genes and signaling pathways between flies and human, we recently developed a Drosophila model of HPV18E6 and demonstrated that the mechanism underlying HPVE6-induced cellular abnormalities is conserved between humans and flies. Using a functional screen against Drosophila kinome we identified IKKβ (a regulator of NF-kB) as a suppressor of the HPVE6-induced cellular defects. Reduction in IKKβ suppressed the E6-mediated defects including epithelial morphology, polarity, junctions as well as Magi degradation. We validated these findings in the human cervical cancer cells using an inhibitor of IKKβ. Inhibition of IKKβ blocked the growth of the cervical cancer cells while having a minor effect on the growth of normal cells. We further show that the IKKβ-mediated suppression of Magi degradation is due to hyper phosphorylation of E6 which has previously been shown to block the interaction of E6 with PDZ domain proteins. Additionally, reduction in IKKβ was able to suppress the enhanced defects of HPVE6 caused by the presence of an activated Ras. Altogether our results suggest that IKKβ could be a potential novel therapeutic target for HPV-mediated cancers.

Corresponding author: Mojgan Padash Barmchi, mojgan.padash@ou.edu
ABATED RD3 IN RESIDUAL NEUROBLASTOMA CELLS AFTER INTENSIVE MULTI-MODAL THERAPY PROPEL DISEASE PROGRESSION

Dinesh Babu Somasundaram1 (DineshBabu-Somasundaram@ouhsc.edu), Karthikeyan Subramanian1, Sheeja Aravindan2, Zhongxin Yu3, Terence S. Herman1,2, Natarajan Aravindan1,2,3*

1Department of Radiation Oncology and 3Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. 
2Stephenson Cancer Center, Oklahoma City, OK, USA.

The majority of high-risk neuroblastoma that initially responds to therapy will ultimately relapse. Acquired genetic/molecular rearrangement contributes to tumor relapse and currently, no salvage treatment regimens are known to be curative. Our studies identified the loss of retinal-degeneration-protein-3 (RD3) in progressive disease (PD) and its association with poor clinical outcomes. Herein we investigated the acquisition of RD3-loss after current standard of care (SOC, intensive multimodal therapy) in neuroblastoma. Acquired transcriptional (RNA in situ hybridization, QPCR) and translational (IHC on a custom archived cell micro array, immunoblotting) loss of RD3 with SOC was investigated with bed-to-bench approach utilizing a panel of 15 stage-4 patient derived cell-lines with known therapy status, diagnosis [DX] vs. PD after SOC). Further, RD3-loss in progressive disease, its direct role in the pathogenesis disease progression (cell migration, invasion, tumorosphere formation and metastatic potential) was investigated using mouse model of progressive neuroblastoma and in experimental in vitro and ex vivo settings coupled with gene manipulation strategies. In addition, RD3 status in response to therapy were also affirmed by in silico analysis of independent studies on bed-to-bench and experimental models. Results demonstrated RD3-loss (transcriptional/translational) acquisition with SOC in human PD. Experimental in vitro, in vivo, ex vivo studies affirmed RD3 loss in PD and, further forced RD3-rearrangements in these models defined its functional role in PD pathogenesis. Data-mining experimental studies with salvage therapeutic agents affirmed the acquisition of RD3-loss in resistant cells and in residual tumors. For the first time, these results demonstrate the de novo acquisition of RD3 loss in PD after intensive multi-modal therapy. Defining the criticality of RD3-loss in PD and the defined role of RD3 loss in PD pathogenesis, benefit of targeted reinforcement could lead to improved salvage therapy for high-risk neuroblastoma.

Funding: NIH-COBRE-IP20GM103639-01, OUHSC-COM-Radiation Oncology Research Development Funds
Acquired resistance is a major problem in the treatment of patients with cancer. One mechanism of acquired resistance in tumors is the manipulation of DNA repair pathways, especially the pathways that repair double strand breaks (DSBs). There is a growing body of evidence that demonstrates a connection between factors traditionally associated with transcription and the DSB repair pathways. This is due to the fact that evidence has been gathered demonstrating the association between transcription, double strand breaks, genetic instability, and most recently chromosomal translocations.

During the process of normal transcription RNA:DNA hybrids (R loops) are formed and resolved, causing no harm to the cell. However, unresolved R loops have been associated with DSB formation, genetic instability, and chromosomal translocations. This genetic instability primarily occurs in S-phase, where the replication machinery collides with unresolved R loops. These collisions lead to DSB formation, chromosomal translocations, and eventually tumors; due to the inherent oncogenic potential of free DNA ends. Although, we are beginning to understand how DSBs are formed by unresolved R loops, little is known about how the cell repairs these types of lesions. It has been published that factors involved primarily in transcription are also associated with DNA repair pathways. We have gathered data implicating the transcription termination factor XRN2 in the response and repair of DSBs. XRN2, is 5'-3' RNA endonuclease that degrades RNA and resolving R loops. We found that loss of XRN2 leads to increased DSB formation, sensitivity to ionizing radiation, replication stress, R-loop formation and PARP1 activity. We also found that there is an accumulation of DSB repair factors at the 3’ end of genes that undergo R-loop dependent transcription termination. Although increased DSBs are consistent with increased R-loop formation, increased ionizing radiation and chemotherapy sensitivity is not. Interestingly, we have also observed that the increased radio-sensitivity demonstrated in XRN2 deficient cell is directly related to whether R loops are present. Suggesting that mediating R-loop formation may be a consideration when treating cancer patients with radiation or any chemotherapy that induces DSBs.

Presenting Author’s Email: Julio-Morales@ouhsc.edu
Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Precursor B-cell ALL (pre-B ALL) represents ~85% of these cases. Despite its prevalence and clinical importance, zebrafish pre-B ALL models are lacking. Hyperactive MYC is known to induce *D. rerio* T-cell ALL (T-ALL). One example of this is *rag2:hMYC* transgenic fish, where human MYC (*hMYC*) is regulated by a zebrafish *rag2* promoter. To detect T-ALL in *rag2:hMYC* animals, we added a transgenic fluorescent marker, *lck:GFP*. Unexpectedly, we discovered *rag2:hMYC, lck:GFP* fish also develop a second ALL type. Besides brightly-fluorescent T-ALL, we also found short latency, high incidence dimly-fluorescent GFPlo cancers. Expression analyses of GFPlo cancers using qRT-PCR, RNA *in situ* hybridization (RNA ISH), RNA-Seq, and other techniques confirm they express immature B cell genes, proving they are pre-B ALL. Zebrafish pre-B ALL resembles human pre-B ALL in several ways: (1) Histologic studies and RNA ISH show GFPlo cancers invade lymphoid and non-lymphoid tissues aggressively; (2) Immunoglobulin V(D)J repertoire analyses demonstrate GFPlo cancers are clonal; (3) Cancers are dexamethasone sensitive, like human pre-B ALL. Overall, our findings demonstrate that *hMYC* potently induces zebrafish pre-B ALL that is similar to the human disease, making this the first robust *D. rerio* model of the most important pediatric cancer.

This work was supported in part by NIGMS grant P20 GM103447.

Presenting Author’s Email Address: gpark1@OUHSC.edu
CANCER PREVENTION & CONTROL
1:30 – 2:30 PM  
**SESSION I – PLENARY SESSION**  
**REDUCING CANCER BY REDUCING ADDICTIVENESS OF CIGARETTES**  
Dorothy Hatsukami  
Masonic Cancer Center  
University of Minnesota

2:30 – 3:00 PM  
**SESSION II**  
**TOBACCO REGULATORY SCIENCE**  
Moderator: Theodore Wagener

2:30 – 2:45 PM  
**THE IMPACT OF FLAVORS AND SWEETENERS ON HOOKAH TOBACCO SMOKING**  
Theodore Wagener  
Oklahoma Tobacco Research Center  
The University of Oklahoma Health Sciences Center

2:45 – 3:00 PM  
**HOW PSYCHOPHYSIOLOGY CAN INFORM TOBACCO REGULATORY SCIENCE**  
Glenn Leshner  
College of Journalism  
The University of Oklahoma

3:00 – 3:15 PM  
**ASSESSING YOUTH AND YOUNG ADULT APPEAL FOR, AND ABUSE LIABILITY OF MENTHOL CIGARETTES USING EXPERIMENTAL AND EPIDEMIOLOGICAL APPROACHES**  
Amy Cohn  
Stephenson Cancer Center  
The University of Oklahoma Health Sciences Center

3:15 – 3:30 PM  
**PANEL DISCUSSION AND AUDIENCE Q&A**

3:45 – 4:45 PM  
**SESSION III**  
**DELIBERATION AS COMMUNITY ENGAGEMENT: PROMOTING DIALOGUE ABOUT GENETIC RESEARCH IN THE CHICKASAW NATION**  
Jessica Blanchard, The University of Oklahoma  
Justin Reedy, The University of Oklahoma  
Justin Lund, The University of Oklahoma  
Bobby Sukeah, Chickasaw Nation  
Michael Peercy, Chickasaw Nation  
Christie Byars, Chickasaw Nation
Dorothy K. Hatsukami, Ph.D. is the Forster Family Chair in Cancer Prevention at the Masonic Cancer Center of the University of Minnesota and Professor of Psychiatry. She is the Associate Director of Cancer Prevention and Control at the University of Minnesota Masonic Cancer Center and Director of the Tobacco Research Programs. Her areas of expertise include nicotine addiction and its treatment, including testing medications such as a nicotine vaccine and combination medications in smokers. She has over 400 publications and is currently PI/Co-PI of two multi-project NIH-funded cooperative agreements/P01 that involve assessing the toxicity, appeal and addictiveness of various tobacco products. She has served on numerous scientific advisory boards or councils for the U.S. government including NIDA, SAMSHA, ONDCP, Interagency Committee on Smoking and Health, and the FDA Tobacco Product Scientific Advisory Committee and contributed to Surgeon General Reports and Institute of Medicine reports. She is currently a member of the World Health Organization Study Group on Tobacco Product Regulation.
We are currently living in a tobacco product landscape where the most toxic tobacco products are also the most addictive. Those products include cigarettes and other combusted tobacco products. This is the landscape that leads to over 40 million smokers, about a half-million deaths per year and 16 million smokers who experience smoking related diseases. Smoking is associated with a little less than third of cancer deaths and lung cancer remains the number one cause of cancer mortality. One approach that has the potential to dramatically reduce smoking prevalence and thereby smoking-related morbidity and mortality is to reduce nicotine in these products to minimally addictive levels. This proposal was made over 20 years ago but laid dormant until the Family Smoking Prevention and Tobacco Control Act was passed by U.S. Congress in 2009. This Act gave the Food and Drug Administration jurisdiction over tobacco products and the authority to establish product standards if they demonstrate public health benefit. Since this time the research on the impact of reduced nicotine content cigarettes has burgeoned. The results of these studies show: 1) the dose of nicotine that leads to reduced smoking and dependence and increased quit attempts is less than 0.4 mg/g tobacco; 2) this doses does not lead to compensatory smoking behavior, differences in adverse events compared to other doses of nicotine in cigarettes nor an increase in alcohol or drug use or depression; 3) this dose however does lead to an increase in weight gain; 4) this dose is also less satisfying than higher doses of nicotine in vulnerable populations (e.g., smokers who have a diagnosis of affective disorder, substance use disorders or who are socioeconomically disadvantaged); and 5) this dose is also less satisfying in youth. The results also show that an immediate reduction in nicotine to the lowest level might be more beneficial than a gradual reduction in nicotine dose. Compared to gradual nicotine reduction or continued smoking of normal nicotine content cigarettes, immediate reduction leads to greater decreases in smoking, exposure to toxicants and carcinogens, dependence and greater number of smoke-free days. However, the immediate nicotine reduction approach is associated with more severe withdrawal symptoms and higher rates of study drop-outs and non-compliance with only using the study cigarettes. These findings suggest that if a product standard to lower nicotine is implemented, smokers are likely to seek alternative sources of nicotine. This was observed in another study in which smokers were randomized to very low nicotine content cigarettes vs. normal nicotine content cigarettes. Smokers in the former group demonstrated a greater uptake of alternative nicotine products, particularly
electronic cigarettes. These findings would suggest that if a nicotine product standard was implemented for combusted products, we might see a substantial reduction in smoking prevalence but would likely see an increase in the use of non-combusted tobacco products, therefore changing the landscape of tobacco product use. Despite the uptake in non-combusted products, the potential impact of reducing nicotine to minimally addictive levels in combusted products might be profound. It is estimated that such a standard might save 8.5 million levies by the year 2100.
Impact of Flavors and Sweeteners on Waterpipe Tobacco Smoking Topography, Abuse Liability, Toxicant Exposure, and Intentions for Continued Use

Theodore L. Wagener, PhD1,2 Toral Mehta, PhD1 Eleanor L. S. Leavens, MS1,3 Thomas Eissenberg, PhD4 Alan Shihadeh, PhD5 Jessica J. Hale, MPH1 Kai Ding, PhD1,8 Matthew S. Halquist, PhD4 Evan L. Floyd, PhD1,7 Alayna P. Tackett, PhD1
1Oklahoma Tobacco Research Center, Stephenson Cancer Center; 2Department of Pediatrics, University of Oklahoma Health Sciences Center; 3Department of Psychology, Oklahoma State University; 4Department of Psychology, Virginia Commonwealth University; 5Department of Mechanical Engineering, American University of Beirut; 6Department of Pharmaceutics, Virginia Commonwealth University; 7Department of Occupational and Environmental Health, University of Oklahoma Health Sciences Center; 8Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center

Introduction: Waterpipe tobacco (WT) smoking is proliferating in the US. One possible reason for the increase in WT smoking is the inclusion of flavors and sweeteners in the tobacco. No study has examined what effect the removal of flavors and sweeteners from WT would have on users’ smoking patterns, abuse liability, behavioral intentions for continued use, and toxicant exposure.

Methods: In a randomized crossover design, WP smokers (N=89, 59% male, Mage=24.2 years) completed four smoking sessions, each separated by a 48-hr washout period. Each session used a different WT flavoring preparation [flavored + sweetened (FS); flavored + unsweetened (FU); unflavored + sweetened (US); unflavored + unsweetened (UU)] and included a 10-puff standardized puffing bout followed by a 1-hour ad libitum WT smoking session. Study visits were completed in dyads. Participants completed post-session measures assessing WT abuse liability, behavioral intentions for continued use, exhaled carbon monoxide (eCO) and nicotine boost; waterpipe puff topography was measured continuously throughout the session.

Results: 93% of participants reported that the first time they smoked waterpipe the tobacco was flavored. For all measures of drug liking/satisfaction, the FS tobacco was rated significantly higher than all other unflavored preparations, with the UU tobacco preferred the least (all p<.05). Participants’ intentions for continued use was lowest for the UU preparation, with only 50%, 41%, and 19% of participants reporting that they were ‘likely’ to “try this product again”, “pay to smoke this product at a waterpipe lounge”, or “use this product regularly”, respectively. Significant differences in topography were observed during standardized and ad libitum sessions, with the UU preparation leading to greater total inhaled volume and eCO boost, but lower nicotine boost compared to the FS preparation (all p<.05). Conclusions: The current study
suggests that flavors and sweeteners from waterpipe tobacco significantly influence the product's abuse liability, use topography, users' reported willingness/interest for continued use, and exposure to tobacco toxicants.

**Funding:** Research reported in this publication was supported by NIDA/NIH and FDA Center for Tobacco Products (R03DA041928 and R03DA041928-02S1 to TLW). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. TLW salary is also partially supported by the Oklahoma Tobacco Settlement Endowment Trust.

Presenting Author's Contact: Theodore-Wagener@ouhsc.edu
Tobacco regulatory science can benefit from a media psychology perspective by assessing how individuals cognitively and emotionally process anti-tobacco messages. This perspective proposes that how people pay attention and emotionally respond to various message features not only impact how people think and feel about health messages, but also can inform how they remember important message content and how they form attitudes about the message arguments. Psychophysiology is the systematic study of relationships between psychological and physiological processes, and offers methods for observing the dynamic mental processes that unfold over time as individuals perceive, think, and feel about all forms of stimuli in the environment. These dynamic mental processes are revealed through slight changes in physiological activity due to a strong connection between the human mind, brain, and body. Psychophysiological measures can help identify cognitive and emotional responses to messages and at which point in the message responses occur. Careful application and interpretation of physiological measures can yield the kind of knowledge about health messages that is currently lacking. The primary benefits of psychophysiological measures are that they 1) can assess automatic and controlled responses that individual may not have conscious access to (and thus, cannot report when asked), and 2) provide ways to assess cognitive and emotional changes (i.e., changes in psychological states) during the course of message exposure. Typical psychophysiological measures used in the OU PRIME Lab include ECG, EDA, facial action coding, and eye-tracking. Research examples that from the OU PRIME Lab and its staff will be presented.
Assessing youth and young adult appeal for and abuse liability of menthol cigarettes: using experimental and epidemiological approaches

Amy Cohn

Although the FDA banned characterizing flavors in cigarettes, menthol cigarettes are still available to consumers. Menthol cigarette smoking has increased in young adults (YA; defined here as ages 18-24), while non-menthol smoking has decreased in this age group. Further, a large proportion of new YA smokers initiate with a menthol cigarette. Experimentation with menthol cigarettes is linked to progression to regular smoking and greater nicotine dependence. Menthol’s pleasurable taste and other sensory effects (cooling /soothing sensations in the throat) may contribute to a positive first smoking experience, a potential mechanism linking initiation with uptake and regular smoking. A key unanswered question is whether menthol increases the appeal and reinforcing properties of cigarette smoking beyond nicotine, which may facilitate progression to regular smoking among newer users. Only a handful of controlled investigations have examined the differential rewarding/appealing effects of smoking menthol and non-menthol cigarettes, but most have methodological limitations including small samples and omission of YA smokers. These studies also do not measure, with a sufficient level of accuracy, degree of sequencing, and timing that is needed to address the context-dependent fluctuations in menthol-related appeal and reinforcement in real time. Using evidence from population-based data and ongoing experimental research, Dr. Cohn will present past and ongoing research assessing differential appeal for menthol vs non-menthol cigarettes in younger users and the impact of menthol’s appeal on tobacco use behavior. Together, this research will isolate the unique effects of menthol in cigarette smoking and will help inform prevention communication campaigns and regulatory decisions on potential ban on menthol cigarettes and menthol flavored tobacco products.
Deliberation as Community Engagement: Promoting Dialogue about Genetic Research in the Chickasaw Nation

Bobby Saunkeah, Michael Peercy, Christie Byars, Jessica Blanchard, Erika Blacksher, Justin Reedy, Justin Lund, Paul Spicer

Deliberation is evolving as an area of robust inquiry used to elicit citizen input on a range of topics, including emerging medical practices and health research. The Chickasaw Nation Department of Health and researchers at the University of Oklahoma and the University of Washington, as part of a larger consortium of tribal partners across the U.S., is exploring and piloting community-based deliberative strategies to facilitate more intensive and meaningful dialogue about the role of genetics research in diverse American Indian and Alaska Native tribal contexts.

This panel explores the process of facilitating deliberative forums about genetics research as a means to seek community input about the priorities and concerns related to the possible role of genetics medicine and research in the Chickasaw Nation. Citizens from diverse communities within the Chickasaw Nation convened for two days in September 2018 to deliberate about ethical questions related to genetic research and biobanking. The aim of this particular deliberation was to facilitate intensive discussion and gather informed input from Chickasaw Nation citizens about the potential benefits and risks of tribal involvement with genetic research. Panelists identify a number of methodological strategies for engaging tribal citizens and communities in a deliberative process with the goal of exploring new directions in health research and recommendations for their own communities.

Funding for this work provided to the Center on American Indian and Alaska Native Genomic Research by the National Human Genome Research Institute (RM1HG009042)

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2:42 – 2:54 PM  MODEL BASED OPTIMIZATION OF COMBINATION CHEMO–PHOTODYNAMIC THERAPY WITH FAR-RED LIGHT–ACTIVATABLE PRODRUGS: PROOF OF CONCEPT STUDY IN PRECLINICAL MICE MODELS
Mengjie Li
Department of Pharmaceutical Sciences
The University of Oklahoma Health Sciences Center

2:54 – 3:06 PM  3D MESOSCOPIC FLUORESCENCE TOMOGRAPHY FOR IMAGING MICRO–DISTRIBUTION OF ANTIBODY–PHOTON ABSORBER CONJUGATES DURING PHOTOIMMUNOTHERAPY IN VIVO
Qinggong Tang
Stephenson School of Biomedical Engineering
The University of Oklahoma

3:06 – 3:18 PM  CELASTROL INHIBITS HIGH FAT DIET–INDUCED OBESITY AND INTESTINAL TUMORIGENESIS IN APCMIN/+ MICE BY MODULATING GUT MICROBES AND INFLAMMATION
CV Rao
Department of Internal Medicine, Section of Hematology Oncology
The University of Oklahoma Health Sciences Center

3:18 – 3:30 PM  TOWARDS RAPID AND RELIABLE PROGNOSIS OF DRUG–RESISTANT CANCER CELLS USING SINGLE CELL MASS SPECTROMETRY AND MACHINE LEARNING
Renmeng Liu
Department of Chemistry & Biochemistry
The University of Oklahoma

3:45 – 4:45 PM  SESSION III
Moderators: Kathleen Moore & CV Rao

3:45 – 4:00 PM  SEX MEDIATES THE INNATE AND ADAPTIVE IMMUNE ENVIRONMENT OF METASTATIC COLORECTAL CANCER
Katherine Morris
Department of Surgery
The University of Oklahoma Health Sciences Center

4:00 – 4:15 PM  QUANTITATIVE COMPUTED TOMOGRAPHY IMAGE FEATURE ANALYSIS PREDICTS RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN GYNECOLOGIC CANCERS
Kathleen Essel
Department of Obstetrics & Gynecology
The University of Oklahoma Health Sciences Center

4:15 – 4:30 PM  INVESTIGATION OF POST–IMMUNOTHERAPY RESPONSE RATES IN WOMEN WITH GYNECOLOGIC MALIGNANCIES
Megan Buechel
Department of Obstetrics & Gynecology
The University of Oklahoma Health Sciences Center
**EXPLORATORY ANALYSIS OF SOMATIC BRCA MUTATIONS IN ENDOMETRIAL CANCER AND ITS CLINICAL IMPLICATIONS**


University of Oklahoma Health Sciences Center (1), University of California Los Angeles Medical Center (2), US Oncology, Minneapolis (3), Roswell Park Cancer Institute (4), Sarah Cannon Research Institute (5)

**Objectives**

Germline *BRCA* mutations in ovarian cancer patients are associated with improved response to chemotherapy and survival. With the increased use of molecular profiling, many women with endometrial cancer (EC) have been found to harbor somatic *BRCA* mutations, the significance of which is unknown. The goal of this study is to evaluate the prognostic and predictive features of somatic *BRCA* mutations (*BRCA+*) in EC.

**Methods**

An IRB-approved, retrospective review of patients with molecularly profiled, EC from 4 academic institutions between 2010 – 2018 was performed. Summary statistics were used to describe demographic and clinical characteristics. Analysis included a comparison of response and survival following treatment with platinum-based chemotherapy among *BRCA+* and somatic *BRCA* wild-type (*BRCAwt*) patients.

**Results**

Of the 209 patients included, 15.8% were *BRCA+*. Of these, the median age was 62.5 years and 63% were endometrioid. This was not statistically different from the 176 *BRCAwt* patients, of which the median age was 61.9 years and 56% were endometrioid (all p>0.05). *BRCA+* patients were more likely to have a higher level of tumor mutation burden (TMB) than *BRCAwt* (40% vs 15%, p=0.015). After adjusting for TMB, *BRCA+* is associated with a shorter progression free survival (PFS) for platinum therapy (12 vs 13 mo, p=0.046, Figure 1), but not with overall survival (OS) (19 vs 13 mo, p=0.73).

**Conclusions**

Among EC patients, somatic *BRCA* mutations are relatively uncommon. *BRCA+* patients are more likely to have a higher level of TMB tumors, but no other clinical factors were associated with these mutations. *BRCA+* appears to be a negative predictive biomarker for PFS in EC, but has no impact on OS. These findings suggest that *BRCA+* may not be predictive of therapeutic response to platinum therapy in EC. Data collection continues with obtaining allelic frequency of the somatic *BRCA* mutation to identify those mutations that are more likely to be germline.

Presenting Author's Contact: Wesley-Burkett@ouhsc.edu
Figure 1:

Product-Limit Survival Estimates

Survival Probability

PFS for Platinum Therapy (m)

Somatic BRCA Mutation  No  Yes
APJ PROMOTES METASTASIS AND CHEMORESISTANCE IN OVARIAN CANCER

Deepika Neelakantan1, Samrita Dogra1, Bharat Devapatla1, Pharavee Jaiprasart1, Marie Claire Mukashyaka1, Ralf Janknecht2,6, Shailendra Kumar Dhar Dwivedi3, Resham Bhattacharya3,6, Sanam Husain4, Kai Ding5, Sukyung Woo1,6

1Department of Pharmaceutical Sciences, College of Pharmacy, 2Department of Cell Biology, 3Department of Obstetrics and Gynecology, 4Department of Pathology, College of Medicine, 5Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA, 6Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

High mortality rates in ovarian cancer (OvCa) are due to late stage diagnosis when extensive metastases are present, and the eventual development of resistance to standard chemotherapy. Metastasis in OvCa is supported by a complex tumor microenvironment (TME), and hence TME-targeting therapy in addition to pathways activated in tumor cells, is a potential strategy in ovarian cancer to improve patient survival. Given the tumor-promotional contribution of adipocytes (in the TME) to OvCa tumorigenesis and metastasis, we assessed the role of the multifunctional adipokine apelin/APJ pathway in OvCa tumor progression.

In this study we show that increased apelin receptor APJ expression is detrimental in OvCa, as it correlates with decreased overall survival in ovarian cancer patients. In vitro, using various human ovarian cancer model systems, we show that increased APJ levels enhance various pro-metastatic phenotypes of OvCa cells, including cell adhesion and anoikis resistance; phenotypes that are essential for the non-hematological route of ovarian cancer metastasis. Increased APJ expression and/or activation also increases migration and invasion of tumor cells in vitro, and all these phenotypes are efficiently inhibited by APJ inhibitor ML221. Importantly, APJ significantly increases in vivo OvCa metastasis only in an orthotopic model, suggesting a role for the TME in tumor progression. Notably, APJ increases activation of STAT3, which mediates its pro-metastatic phenotypes in OvCa.

In addition to metastasis, increased chemoresistance significantly contributes to ovarian cancer patient mortality. Our results indicate that APJ increases chemoresistance of OvCa cells to traditional chemotherapeutics including cisplatin and paclitaxel; interestingly, only when the cells are grown in suspension and mimicking the multicellular spheroids formed by OvCa cells in ascites isolated from patients. Our findings thus imply that the APJ pathway is at the crux of OvCa progression, by positively affecting both, metastasis as well as chemoresistance. Hence, this axis presents the potential for a novel therapeutic strategy; both, to curb tumor progression, and increase overall patient survival.

Funding: This work was supported in part by research grants P20GM103639 (SW) from the National Institute of General Medical Sciences, NIH, DHHS, Research Scholar Grant RSG-16-006-01-CCE (SW) from the American Cancer Society, and Gynecology Oncology Drug Development Fund (SW) from Stephenson Cancer Center.

Email: Deepika-neelakantan@ouhsc.edu
Monoclonal ELTD1 Antibody as a Therapy Against Glioblastomas (GBM) in a Mouse G55 Xenograft Model

Michelle Zalles, Jadith Ziegler, Nataliya Smith, Debra Saunders, Rheap A. Towner
Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation, Oklahoma City, OK USA.

Introduction: Glioblastoma multiform (GBM) is a very aggressive form of cancer and an estimated 16,000 patients die of glioblastomas in the US annually. Although high-grade glioblastomas are the most common primary brain tumors found in adults, the therapeutic approaches available do not significantly increase the prognosis for the patients, with the average survival limited to around 14 months. GBM analysis has demonstrated that angiogenesis is not only dramatically upregulated when compared to low-grade gliomas but also plays an essential role in delivering nutrients to the developing tumors. ELTD1 (epidermal growth factor, latrophilin, and 7 transmembrane domain containing protein 1 on chromosome 1) is a biomarker for angiogenesis, and has been found to be highly expressed in human high-grade gliomas by our group. Polyclonal antibody treatment against ELTD1 has proven to be effective as a potential cancer therapy in orthotropic GL261 and human G55 xenograft glioma preclinical models. However, polyclonal antibodies can be subject to batch-to-batch variabilities posing a concern about specificity as a long-term treatment for patients. To overcome these limitations, this study will use an optimized monoclonal antibody against ELTD1 that will have a higher specificity by only binding to one epitope on the antigen.

Methods: Athymic Nude Fox1nu mice were intracerebrally injected with human G55 cells. Morphological magnetic resonance imaging (MRI done on a Bruker Biospec 7.0 Tesla/30 cm horizontal-bore imaging system) was used to monitor and calculate tumor volumes every 3-4 days. Once tumors were detected, 6-7 mm³ in size, they were treated with 2mg/kg of monoclonal anti-ELTD1 antibody or polyclonal anti-ELTD1 antibody (Bioss) via tail-injection. All treatments continued until the tumor volume reached 150 mm³. Perfusion images were performed to assess microvasculature alterations. Images were obtained at tumor detection and before termination. Additionally, molecular targeting against ELTD1 was performed with a molecular probe previously described by our group. Untreated mice were injected via tail-vein with either a non-specific mouse IgG isotype contrast agent (IgG-albumin-Gd-DTPA-biotin; IgG contrast agent), anti-ELTD1 probe with a polyclonal antibody against ELTD1, or an anti-ELTD1 probe with a monoclonal antibody against the external region of ELTD1. Glioma-bearing mice were anesthetized with isoflurane (2-3%) for treatments or anti-ELTD1 probe administration, and for MRI scans. All mice were terminated upon their last MRI imaging session and their tissue was taken for histology. IHC for anti-CD34 antibody (rabbit anti-CD34, 10 μg/mL; #ab81289, Abcam) was performed to assess microvessel density measurements using the Aperio ScanScope Image Analysis System.

Results: The antibody treatment against ELTD1, both polyclonal (p=0.022) and monoclonal (p=0.0022), significantly increased the tumor percent survival compared to untreated control (average survival ~10 days). Additionally, tumor volumes 10 days after tumor detection were found to be significantly lower with the polyclonal anti-ELTD1 treatment (p=0.027) and monoclonal anti-ELTD1 treatment (p=0.0022) compared to untreated animals. MRI perfusion measures the relative cerebral blood flow (CBF), and this can be used to assess the microvasculature alterations associated with tumor angiogenesis. Differences in relative CBF between late and early tumor development demonstrated that the untreated mice had a decrease in relative cerebral blood flow in the tumor regions depicting increased angiogenesis.
while the anti-ELTD1 treated animals had a normalization of perfusion values which demonstrates a decrease of vascularization in the tumor. The polyclonal anti-ELTD1 treatment was significantly more effective in minimizing the decrease in the relative cerebral blood flow (p= <0.001) compared to untreated mice. Additionally, the monoclonal anti-ELTD1 treatment had similar rCBF values to the contralateral region, and the treatment was significantly more effective in normalizing the relative CBF (p=<0.0001) compared to both polyclonal anti-ELTD1 treatment and untreated. CD34+ analysis of the microvasculature demonstrated that the anti-ELTD1 treatment was able to decrease microvasculature density levels compared to control. To determine where our antibody was localizing in vivo, we tracked our molecular probe attached with either non-specific IgG, polyclonal anti-ELTD1, or monoclonal anti-ELTD1 antibody with the use of MRI by calculating T1 relaxation times as well as signal intensity. T1 relaxation is decreased while signal intensity is increased by the presence of our molecular probe. We determined that the T1 relaxation was significantly decreased by the monoclonal anti-ELTD1 attached probe compared to both polyclonal anti-ELTD1 probe (p=0.0098) and non-specific IgG attached probe (p=0.0001). Additionally, signal intensity was significantly increased by the monoclonal anti-ELTD1 probe compared to non-specific IgG (p=0.0069).

**Discussion:** Previous studies demonstrated that the polyclonal anti-ELTD1 treatment was successful in decreasing tumor volumes, increasing overall survival, and decreasing microvasculature density levels compared to untreated. However, our data demonstrated that the monoclonal anti-ELTD1 treatment, which binds onto the external region of ELTD1, was significantly more effective than the polyclonal anti-ELTD1 treatment as well as the untreated control in increasing survival, decreasing tumor volumes, and normalizing microvasculature. Additionally, we demonstrated that the anti-ELTD1 antibody probe had significantly higher specificity for the tumor region. Although there are a lot of unknowns about ELTD1, particularly about its ligand and structure, our data suggests that our monoclonal antibody against ELTD1 is a promising therapeutic against angiogenesis in glioblastomas.

**Funding:** Oklahoma Medical Research Foundation

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**References:**

TARGETING MYOCARDIN-RELATED TRANSCRIPTION FACTOR-A IN PROSTATE CANCER

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Myocardin-related transcription factor (MRTF) -A and -B are transcriptional co-activators of serum response factor (SRF). Previous studies have demonstrated that depletion of MRTFs reduces cell invasion and motility without affecting proliferation in MDA-MB-231 breast carcinoma and B16F2 melanoma cells. However, the role of MRTF in prostate cancer still remains largely unknown. Recently, through bioinformatical analyses of Gene Expression Omnibus (GEO) data sets and published microarray data, we have discovered that the transcript level of MRTF-A, but not MRTF-B, is upregulated in prostate cancer progression and metastasis. Our immunohistochemical analysis of human tissue microarrays has revealed that MRTF-A protein expression is elevated in human prostate tumors and positively correlated with the Gleason grades of the tumor samples. Moreover, MRTF-A protein expression increases in prostate carcinoma tissue from the well-defined mouse model with heterzygous Pten deletion compared with wild-type controls. Based upon these results, we hypothesize that MRTF-A plays a critical role in prostate cancer development. Supporting this hypothesis, we have found that MRTF-A overexpression in prostate epithelial cells induces epithelial-to-mesenchymal transition (EMT), while MRTF-A downregulation in prostate cancer cells reverses EMT. In addition, MRTF-A downregulation abrogates cell proliferation, migration and invasion in prostate cancer cells. The signaling mechanism underlying the novel function of MRTF-A involves the activation of ERK. Treatment with a combination of MRTF-A inhibitor and ERK inhibitor cooperatively abrogates prostate cancer cell proliferation and migration compared with treatment of either drug alone in vitro. Using an in vivo prostate cancer xenograft model, we have demonstrated that the MRTF-A inhibitor significantly suppresses tumor growth, while concurrent administration of the ERK inhibitor enhances the antitumor activity of the MRTF-A inhibitor. Our data reveal a previously unidentified role of MRTF-A in prostate cancer development and support the potential combined therapeutic targeting of MRTF-A and ERK in human prostate cancer.
Diosgenin, a naturally occurring steroidal saponin, prevents colon cancer in animal models of hereditary and sporadic CRC. Colon cancer prevention using Diosgenin

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Colorectal Cancer (CRC) affects more than 1.35 million people worldwide annually. In the US it is anticipated ~140,000 new cases and 50,000 deaths for the year 2017. In spite of existing preventive measures, recent data suggest an increase in the number of CRC incidences in the younger age groups (30 to 55 years) urging the need for better preventives. In the present study we have studied, Diosgenin against colon cancer in APCmin/+ mice and azoxymethane (AOM)-induced rat CRC models. Diosgenin is a steroid saponin with proven diverse medicinal properties, including anti-diabetic, antiobesity and antiinflammatory, and anticancer properties. APCmin/+ mice, a hereditary polyposis mouse model, were bred in-house and starting at 6 weeks age they were given AIN7-6A diets containing diosgenin (0, 500 and 1,000 ppm) for 14 weeks. At 20-wks of age all mice were euthanized and intestines, both small and large, were analyzed for tumors. In the sporadic CRC model, colon tumors were induced in the male F344 rats by two weekly s.c. injections of AOM (15mg/kg BW) followed by diosgenin administration (0 and 1,000ppm) for 38 weeks. Dietary diosgenin showed significant suppression of colon tumor incidence and multiplicity in both models. In APCmin/+ mice both small intestinal polyps (SIP) and colon tumors (CT) were suppressed in a dose-dependent manner with a significant effect in the high-dose treatment. Diosgenin administered female mice had 33% (25±4.1; Mean±SE, p<0.044) and 54% (17.1±3.8; p<0.003) inhibition of SIP as compared to control mice (37.3±5.6); in male mice there was a greater inhibitory effect (p<0.0001) with 53% (14.1±1.8) and 65% (10.7±1.7; p<0.0001) suppression of the SIP at 500 and 1,000 ppm respectively, as compared to control mice (30.4±2.3). Colon tumor multiplicity was also inhibited by 65% (0.45±0.24; p<0.05) and 50% (0.5±0.18; p>0.05) with high dose in both male and female mice as compared to their respective controls (1.3±0.20 and 1.0±0.25). Importantly, diosgenin showed a similar inhibitory effect on AOM-induced colon adenocarcinoma incidence and multiplicity in the rat model. Administration of diosgenin significantly suppressed both invasive and non-invasive colon adenocarcinoma incidence by 60% (p<0.005) and multiplicity by 65% (p<0.0001). HPLC analysis of the intestinal contents of diosgenin suggested that more than 50% reached the colon in its active form. Biomarker analysis suggested that the strong chemopreventive effects are due to the suppression of proliferation (PCNA) and pro-inflammatory proteins (COX-2 and iNOS) with an increase in apoptosis (Casp-3). Based on these results from the preclinical models representing both hereditary and sporadic CRC patients, it is highly imperative to conclude that diosgenin is a potential chemopreventive agent for colon cancer prevention which needs to be further investigated in the clinic. (Endowed Chair Funds from CVR/ASA)
SWEET AND STEALTHY DRUG DELIVERY; HEPAROSAN-BASED SYSTEMS FOR ENHANCING THERAPEUTICS

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Many therapeutics need assistance with delivery to be most effective in the patient. Poly[ethylene glycol] (PEG) polymers are widely used by pharma to enhance the physical, chemical, and/or biological nature of promising drug candidates. PEGylation has resulted in several $Billion/year drugs. PEGylation protects the cargo when in the body and prolongs therapeutic action. For patients, these attributes translate to fewer injections and side-effects. However, PEG’s tissue accumulation and the rising occurrence of immunogenicity (~25 % of the naïve population) are liabilities. Therefore, pharma is interested in PEG alternatives for next-generation medicines.

The University of Oklahoma and Caisson Biotech LLC, an Oklahoma biotech company, are collaborating to develop and commercialize a platform technology, HEPtune™, to add heparosan polymer to therapeutic cargo or secondary delivery platforms (e.g., liposomes, micelles). Heparosan is a natural “self” polysaccharide that is the biosynthetic precursor for heparin, a widely used drug, and heparin sulfate, an extracellular constituent of most cell types. We were inspired by the approach of certain pathogenic bacteria, Pasteurella multocida Type D and Escherichia coli K5, that employ heparosan coatings to evade host defenses. The technology harnesses the Pasteurella heparosan synthase (PmHS1) to chemoenzymatically synthesis sugar polymers with a very narrow size distribution and defined chemical activation that facilitates selective coupling to therapeutics or delivery platforms.

In our experiments in rodents and primates, HEPtune™ extends drug half-life in the bloodstream and has superior attributes over PEGylation including natural degradation pathways (no tissue accumulation) and lack of immunogenicity. Data on next-generation, ‘bio-better’ drug candidates for chemotherapeutic and cancer patient support therapies will be presented.

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MODEL BASED OPTIMIZATION OF COMBINATION CHEMO–PHOTODYNAMIC THERAPY WITH FAR-RED LIGHT–ACTIVATABLE PRODRUGS: PROOF OF CONCEPT STUDY IN PRECLINICAL MICE MODELS

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Background: Photodynamic therapy (PDT) is a clinically approved therapeutic modality to treat certain types of cancers. However, incomplete ablation of tumor is one of the problems of PDT. To improve antitumor efficacy, we developed unique prodrug (folate-polyethylene glycol- phthalocyanine-paclitaxol: FA-2K-Pc-L-PTX) that takes advantages of PDT and site-specific chemotherapy.

In this study, we determined the optimal prodrug-light interval for maximum antitumor efficacy and investigated the mechanisms of tumor damage and the impact of PDT damage to kinetics of paclitaxel in tumor.

Methods: 2 umol/kg prodrug was administered to mice with i.v. bolus and pharmacokinetic (PK) data were determined. Three different illumination time points (0.5, 9 and 48 hr after prodrug administration) were selected. The prodrug was given to the mice followed with illumination at the selected time points. Tumor regression was monitored after the treatment. Quantitative systems pharmacology (QSP) model was used to analyze and predict the experimental data.

Results: The prodrug showed much slower elimination and restricted distribution in comparison to free PTX. According to tumor progression-free survival result, 9 hr post-injection illumination showed best anti-tumor efficacy. Based on our model simulation, we found the best anti-tumor efficacy of 9 hr post-injection treatment was attribute to balanced distribution of prodrug in plasma and cancer cells and a synergistic interaction between PDT damage and PTX retention caused by vasculature occlusion.

Conclusions: The anti-tumor efficacy of our prodrug is greatly influenced by illumination timing presumably because of optimal damage to tumors via both vascular damage and effective cancer cell kill by PDT and released PTX.

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3D MesoSCOPIC FLUORESCENCE TOMOGRAPHY FOR IMAGING MICRO-
DISTRIBUTION OF ANTIBODY–PHOTON ABSORBER CONJUGATES DURING
PHOTOIMMUNOTHERAPY IN VIVO

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As a novel low-side-effect cancer therapy, photo-immunotherapy (PIT) is based on conjugating monoclonal antibody (mAb) with a near-infrared (NIR) phthalocyanine dye IRDye700DX (IR 700). IR700 is not only fluorescent to be used as an imaging agent, but also phototoxic. When illuminating with NIR light, PIT can induce highly-selective cancer cell death while leaving most of tumor blood vessels unharmed, leading to an effect termed super-enhanced permeability and retention (SUPR), which can significantly improve the effectiveness of anti-cancer drug. Currently, the therapeutic effects of PIT are monitored using 2D macroscopic fluorescence reflectance imager, which lacks the resolution and depth information to reveal the 3D distribution of mAb-IR700. In the study, we applied a multi-modal optical imaging approach including high-resolution optical coherence tomography (OCT) and high-sensitivity fluorescence laminar optical tomography (FLOT), to provide 3D tumor micro-structure and micro-distribution of mAb-IR700 in the tumor simultaneously during PIT in situ and in vivo. The multi-wavelength FLOT can also provide the blood vessels morphology of the tumor. Thus, the 3D FLOT reconstructed images allow us to evaluate the IR700 fluorescence distribution change with respect to the blood vessels and at different tumor locations/depths non-invasively, thereby enabling evaluation of the therapeutic effects in vivo and optimization of treatment regimens accordingly. The mAb-IR700 can access more tumor areas after PIT treatment, which can be explained by increased vascular permeability immediately after NIR-PIT. Two-photon microscopy was also used to record the mAb-IR700 on the tumor surface near the blood vessels to verify the results.

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Celastrol inhibits high fat diet-induced obesity and intestinal tumorigenesis in APC^{Min/+} mice by modulating gut microbes and inflammation.

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Obesity and inflammation play a vital role in colorectal cancer (CRC). Anti-obesity agents may be beneficial for CRC prevention. Celastrol is a triterpene bioactive compound derived from Tripterygium wilfordii (TW) plant, which possess anti-obesity and anti-inflammatory properties. In the present study, we tested celastrol for its intestinal tumor inhibitory efficacy, modulation of intestinal microbiome, induction of UCP-1 in inguinal fat, and inflammation under obese conditions using APC^{Min/+} mouse model. For efficacy study, six-week-old male and female C57BL/6J-APC^{Min/+} mice (10 mice/group/gender) were fed high fat diets (HFD; 60% Kcal fat) containing 0 and 150 ppm celastrol and a group of mice with a low-fat diet (LFD; 10% Kcal fat) for 11 weeks. At termination, intestinal tumors were evaluated histologically and serum was assayed for fasting glucose, uric acid, liver enzymes (ALT, AST), triglycerides and cholesterol levels. Untreated and treated intestinal tumors were assayed for apoptosis and inflammatory markers by Real-Time PCR method. Results suggest that administration of LFD showed lower intestinal tumor formation by 52% (p<0.02) in males; 74% (p<0.0009) in females compared to HFD fed animals. Importantly, administration of HFD containing celastrol suppressed the intestinal polyp formation by 92% (p<0.0001) in males and 83.6% (p<0.0002) in females compared to control HFD fed mice. Also, significant inhibition of colonic tumor suppression was observed in (34%) male and (100%) female mice fed with celastrol. HFD fed animals showed 55% high grade adenomas whereas HFD containing celastrol treatment showed 25% high grade adenomas in colon. HFD containing celastrol treatment resulted in significantly reduced body weight gain, p<0.002 compared to HFD alone in both genders with upregulation of UCP1 protein in inguinal fat indicating increased thermogenesis. HFD celastrol treatment significantly reduced fasting glucose and triglycerides levels with an increase in uric acid with no effect on cholesterol, ALT and AST levels compared to control HFD fed mice. A sequence based analysis of fecal microbiota of mice fed with HFD celastrol showed significantly decreased number of inflammation causing microbes belonging to genus Prevotella (84%), Dorea (77%), Allobaculum (74%), and Aneroplasma (100%) and increased number of beneficial microbes belonging to genus Bifidobacterium (100%), Akkermansia (99.9%), Mucispirillum (94%) and Coprococcus (97%) compared to control HFD fecal samples. Celastrol treatment altered mRNA expression of IFN-γ, Ccl6, TGFβ1, and Aimp1. This is first study to report the chemopreventive properties of celastrol against the small intestinal and colonic neoplasia, modulation of gut microbiome and inflammation in APC^{Min/+} mice. (Stephenson Cancer Center Grant)
Towards Rapid and Reliable Prognosis of Drug-resistant Cancer Cells Using Single Cell Mass Spectrometry and Machine Learning

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Drug resistance, a phenomenon that renders tumor evasion of anticancer agents, is regarded as the major reason for chemotherapeutic failures. Unfortunately, drug resistance cannot be monitored or evaluated using common molecular imaging techniques, such as positron emission tomography, until accomplishing one or two chemo-treatment cycles in modern clinical practice, resulting in ineffective treatment accompanied by serious toxicity for the patients. In addition, different tumor cells within the same histological region may respond differently to chemo-treatment due to intratumor heterogeneity. However, conventional studies of drug resistance based on cell populations lack the ability to uncover biological information masked by such tumor cell heterogeneity. Herein, it is imperative to study drug-resistant cell phenotypes by interrogating and evaluating individual cells using single-cell based methodologies.

On the other hand, cell adhesion-mediated drug resistance (CAM-DR) was reported for myelogenous leukemia cells upon adhering to extracellular matrix (ECM), which coexists with those leukemic cells in the bone marrow, through integrin-ECM interaction. Despite the achievements of illustrating related biological mechanisms, limited effort was contributed to predict such drug-resistant phenotype prior to any chemo-treatment. Limited studies in this area are likely due to a variety of factors, including 1) the lack of rapid and sensitive single cell analytical approaches that can simultaneously unveil phenotypic discrimination and intratumor heterogeneity, 2) the shortage of methods for systematic metabolomic analysis of single cells to reveal cellular metabolic profiles associated with different phenotypes, and 3) the absence of advanced data mining methods towards rapid and reliable prediction.

To address those issues, we used the Single-probe single cell mass spectrometry (SCMS) technique to conduct metabolic analysis at single cell level (i.e., single cell metabolomics) of cultured chronic myelogenous leukemia (CML) cells and obtain metabolic information from individual cells. Data analysis was conducted using machine leaning (ML) algorithms to mine the complex metabolomic datasets and unveil hidden biological patterns by performing clustering, regression, and prediction. A series of ML models were constructed and evaluated in terms of predictive accuracy with experimental validation. To the best of our knowledge, it is the first time to combine SCMS experiments with ML models for single cell metabolomics studies. Our method combines SCMS experiments and ML models for the first time, and can be potentially applied for future clinical prognosis of drug-resistant phenotypes prior to chemotherapy on patient derived samples.
SEX MEDIATES THE INNATE AND ADAPTIVE IMMUNE ENVIRONMENT OF METASTATIC COLORECTAL CANCER

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Background Women with colorectal cancer (CRC) have a significant survival advantage compared to men. The effect of sex on the tumor microenvironment (TME) is unclear, despite the importance of immune response in CRC. We hypothesized that a difference in immune response could contribute to women’s survival advantage. Using an immune competent mouse model of metastatic CRC, we examined T cells, macrophages, and cytokine production systemically and within the TME.

Methods Age/sex matched C57/BL6J mice were used to compare the immune response to $10^5$ MC38 cells injected IP (n=6/sex, control and 8-9/sex, tumor). TME and serum chemotactic and inflammatory cytokines were measured by multiplex bead-based arrays. FACS was used to identify cell populations and phenotypes. We used 2-tailed Student t-tests or Mann-Whitney tests to compare means as appropriate and log-rank testing to compare survival.

Results Female tumor-bearing mice lived longer than males and showed increased TME immune cell populations and activity. CD8+ and CD4+ T cells were elevated compared to males and females had more Th2 cells (IL-4+CD4+ T cells) in the lymphocyte population. CD8, CD4, and Th2 populations correlated positively with survival. Males had increased serum levels of several chemotactic cytokines, including GCSF, and inflammation-associated cytokines, including IL-6 and TNF-α. Within the TME, however, males had lower local cytokine levels than females, suggesting a stronger, more localized immune response in the female TME. Tumors from the females had elevated IL-10+ macrophages, which correlated with prolonged survival.

Conclusions These data demonstrate survival-associated differences in the immune response of males and females to metastatic CRC. Decreased circulating GCSF and elevated TME GCSF within females was accompanied by increased immune cell populations, with a phenotypic shift toward Th2-axis phenotypes. Overall T cell infiltration was increased, suggesting that sex-dependent differences in immune response to CRC could affect response to immunotherapies. Key differences in the immune response to CRC were correlated with survival in this model. The differences observed were in both innate and adaptive cells, and across the cytokine milieu, suggesting a multifaceted shift across the tumor niche.
Quantitative computed tomography image feature analysis predicts response to immune checkpoint inhibitors in gynecologic cancers

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Objectives: To investigate the role of applying quantitative image (QI) feature analysis computed from computed tomography (CT) images for early prediction of tumor response to immune checkpoint inhibitors (ICPI) amongst patients with recurrent gynecologic cancer.

Methods: We conducted a retrospective review of 56 patients with gynecologic cancer at a single institution who received an ICPI for management of recurrent disease. Each patient had CT images prior to and after the initiation of therapy. A computer-aided detection scheme was applied to segment metastatic tumors previously tracked by radiologists on CT images and image features were computed. A QI feature pool was built and a features selection method was applied to select optimal features; an equal-weighted fusion method was used to generate a new quantitative imaging marker for each pool to predict 6-month progression-free survival (6PFS). The prediction accuracy between quantitative imaging markers and the response evaluation criteria in solid tumors version 1.1 (RECIST) criteria and immune RECIST criteria (iRECIST) were also compared. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were assessed by RECIST criteria.

Results: Of the 56 patients identified, 29 patients (51.8%) had ovarian cancer, 16 patients (28.6%) had cervical cancer, and 11 patients (19.6%) had uterine cancer. Thirty-eight patients (67.9%) received a programmed death 1 (PD-1) inhibitor, 11 patients (19.6%) received a programmed death-ligand 1 (PD-L1) inhibitor, 5 patients (8.9%) received a combination of PD-1 inhibitor and cytotoxic lymphocyte antigen-4 (CTLA-4) inhibitor, and 1 patient (1.8%) received anti-cell immunoglobulin and ITIM domain protein (TIGIT) and 1 patient (1.8%) received a GITR-agonist resulting in 1 CR, 9 PR, 9 SD, and 20 PD.

The area under the receiver operating characteristic curve (AUC) is 0.95 when using QI feature analysis to predict 6PFS and 0.81 when using RECIST criteria. The QI feature analysis resulted in a prediction accuracy level of 92.3% versus 61.5% when using RECIST criteria versus 70.9% when using iRECIST criteria.

Conclusions: Quantitative CT image feature analysis accurately predicts response to ICPI in patients with recurrent gynecologic cancer. This technology is a promising tool to predict the clinical benefit of ICPIs early in the course of treatment of gynecologic cancers.
INVESTIGATION OF POST-IMMUNOTHERAPY RESPONSE RATES IN WOMEN WITH GYNECOLOGIC MALIGNANCIES

M. Buechel, K. Essel, K. Ding, K. Moore

OBJECTIVES: The use of novel targeted agents and immunotherapeutics in gynecologic oncology patients challenges our traditional paradigm of how to assess disease response rates. Historically patients have worse PFS with each subsequent regimen of treatment. Therefore, in other solid tumors a progression free survival ratio has been proposed as a marker of improved response. If the ratio is <1 then there is an improvement in PFS with the subsequent regimen and therefore an improvement of predicted response. In addition, we hypothesize that use of immunotherapy alters a patient’s response rates to subsequent therapies by altering either the immune profile of the tumor or immune response of the patient. Our objective was to look at the PFS ratios of pre and post immunotherapy treatments in patients with gynecologic malignancies.

METHODS: A retrospective analysis of patients of all gynecologic oncology patients that were treated with immunotherapy from 6/2015-3/2018 was performed. Demographic, clinical, and pathologic data were collected and analyzed with appropriate statistical methods. The two PFS ratios (pre-immunotherapy to immunotherapy ratio and immunotherapy to post-immunotherapy ratio) were summarized using PROC ICLIFETEST. The difference between the two PFS ratios were assessed by using PROC PHREG for clustered censored data after reciprocal transformation of the ratios so that they became right-censored.

RESULTS: A total of 56 patients were included in our analysis. Patients carried a diagnosis of ovarian (52%), cervical (29%), and uterine (20%) malignancies with a median age of 52 years old. Patients had a median number of 2 previous lines of therapy. Majority of the patients were treated with a cytotoxic regimen pre-immunotherapy and only 52% of patients received any treatment post-immunotherapy. The median PFS for patients pre-immunotherapy was 6.5 months (95% CI: 3.6 – 8.9). The median PFS on immunotherapy was 3.6 months (95% CI: 2.8 – 7.2) which showed a pre-immunotherapy PFS ratio of 1.28 (95% CI= 0.69, 2.02). The median PFS for post-immunotherapy was 7.4 months (95% CI: 4.2 – 9.4) with a PFS ratio of 0.48 (95% CI: 0.26-0.88).

CONCLUSIONS: Interestingly, patients had a higher PFS post-immunotherapy compared to both their pre-immunotherapy PFS and immunotherapy PFS. The ratio of response was not statistically significant likely secondary to our small sample size. However, this warrants further investigation of both the utility of the PFS ratio as an endpoint in early clinical trials. In addition, if response rates are improved post-immunotherapy further investigation into why this phenomenon occurs should be investigated as this may guide our utilization of immunotherapy of patients with gynecologic malignancies.
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DNA MUTATION ANALYSIS IN ENDOMETRIAL CANCERS WITH AND WITHOUT POL E MUTATIONS
Rosemary Zuna, The University of Oklahoma HSC
Glycoproteins are incredibly important proteins, making up a large percentage of the proteome and taking part in many physiological events including cell-cell interactions, cellular differentiation, protein folding and trafficking, signal transduction, secretion, immune response and cancer development. In protein glycosylation, oligosaccharides are covalently attached to the polypeptide through a highly specific enzymatic process. The assortment of glycan structures possesses the same protein backbone but different oligosaccharide components and site of glycosylation, that give rise to a greater variation. N-linked glycosylation is the most abundant type of glycan attachment in proteins. One of the enzymes that catalyzes this process is N-glycosyltransferase (NGT), which recognizes the consensus sequence, −Asn-X-Ser/Thr−, within the protein and catalyzes the glycosidic bond formation between the sugar donor and the sidechain amide nitrogen of the asparagine residue. The attachment of the sugar moiety is believed to influence the physiochemical and biological properties of proteins by affecting their folding, modulating interactions with other biomolecules and modifying their functions in cellular level. Importantly, alterations in protein structures are associated with many physiological and pathological events such as cell growth, migration and differentiation. Consequently, aberrant glycosylation occurring in cancer cells may influence the progression and cancer metastasis. Interestingly, there are a number of N-glycosylated proteins that have been implicated as biomarkers for cancer diagnosis and prognosis.

Therefore, we have performed in vitro glycosylation to evaluate the effects of N-glycosylation on protein structure, dynamics and interactions. We are specifically interested in determining the effects of glycosylation on membrane glycoproteins because these are key components in many cancers and other disease states. For the preliminary in vitro studies of N-glycosylation, WALP peptides engineered with a single glycosylation site were used, as these simple peptides have been shown to be effective models for characterizing membrane proteins. WALP peptide and gamma-sarcoglycan protein have been used to demonstrate the successful glycosylation of membrane proteins. In the present study, several other membrane proteins including syndecan and T-cell receptor will be used to understand the functional influence of N-glycosylation in protein folding and cancer development. The work presented here will outline our strategy for in vitro glycosylation of membrane proteins incorporated into lipid environments that ensure that the protein remains folded in a native confirmation while providing conditions that allow the glycosylating enzyme to retain its activity.

ACKNOWLEDGEMENT: This work was supported by the start-up funds of Dr. Gabriel A. Cook provided by the Department of Chemistry, the College of Arts and Sciences and Oklahoma State University.

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EVERYDAY DISCRIMINATION INDIRECTLY INFLUENCES SMOKING CESSATION THROUGH POST–QUIT SELF–EFFICACY

Adam C. Alexander, PhD\textsuperscript{1}, Emily T. Hébert, DrPH\textsuperscript{1}, Michael S. Businelle, PhD\textsuperscript{1,2}, Darla E. Kendzor, PhD\textsuperscript{1,2}

\textsuperscript{1}Oklahoma Tobacco Research Center, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States
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Introduction: Although studies have shown an association between discrimination and current smoking, the influence of discrimination on smoking cessation is an understudied area in tobacco research. The current study evaluated the influence of everyday discrimination on smoking cessation and examined self-efficacy as a potential mediator of this association.

Methods: Participants were 146 socioeconomically disadvantaged adults enrolled in a smoking cessation program at an urban safety-net hospital. Participants completed a self-report measure of perceived discrimination one week before a scheduled quit attempt and self-efficacy for quitting was assessed on the scheduled quit date. Biochemically-verified 7-day point prevalence abstinence was assessed weekly, through the fourth week post-quit. Structural equation modeling was used to evaluate the indirect effect of perceived discrimination on smoking cessation via self-efficacy for quitting.

Results: Analyses indicated significant indirect effects of discrimination on smoking cessation through self-efficacy at Weeks 1 (\(\beta = .09\ SE = .04, p = .02\)) and 4 (\(\beta = .06\ SE = .03, p = .04\)). A higher frequency of discrimination was associated with lower post-quit self-efficacy, and low self-efficacy increased the likelihood of non-abstinence at 1 and 4 weeks after the scheduled quit attempt. The direct association between discrimination and smoking cessation did not reach statistical significance.

Conclusions: Findings suggest that perceiving discrimination reduces the likelihood of smoking cessation via diminished self-efficacy. Future research is needed to identify intervention strategies to reduce the frequency of discrimination experiences and attenuate the negative impact of discrimination and low self-efficacy on smoking cessation.

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ABCG2 EXPRESSION IN PRE-, MID- AND POST- MIGRATORY CONTEXTS IN GBM: ROLE IN TREATMENT RESISTANCE?

Anish Babu,¹ Xue Cai,³ Hannah Homburg,³ Sima Asfa,³ Young-Tae Kim,⁴ James D. Battiste,¹,² Stephenson Cancer Center,¹ and Departments of Neurology² and Neurosurgery,³ University of Oklahoma Health Science Center, Oklahoma City, OK, USA, UT Arlington, Arlington Texas⁴

Introduction: Therapy resistance is a fundamental problem limiting survival benefits in patients with glioblastoma multiforme (GBM), a deadly form of brain cancer. Treating GBM is a major challenge because the cells diffusely migrate in the brain and are often resistant to therapies causing inevitable tumor recurrence. Overexpression of ATP binding Cassette (ABC) transporters are among the initial molecular indicators of emergence of treatment resistance in migrating glioma stem cells. Moreover, recent studies suggest that the high expression levels of a candidate ABC transporter molecule, ABCG2 (ATP binding Cassette G superfamily 2), is associated with multi-therapy resistance in cancer. In this study, we seek to determine the expression level and cellular localization of ABCG2 expression in pre-, mid- and post migratory phases of GBM cells in vitro. Our goal is to identify new strategies to overcome treatment resistance.

Methods: A combination of a microfluidic device (emulating brain white matter tracts) and standard cell-based analysis (immunostaining, RT-PCR, western blot) are utilized to study the expression of ABCG2. Established GBM cell lines such as U87, G55, U251, LN229 are investigated on 2D monolayer platform and 3D microchannels for ABCG2 expression and its role in treatment resistance.

Results: Differential expression of ABCG2 is observed in pre-, mid- and post migratory GBM cells. Migrating cells are monitored using 3D microchannels and are being isolated and analyzed for induction of ABCG2 mRNA and protein expression. The ABCG2 expression level is then correlated with drug efflux activation using Doxorubicin (an ABCG2 substrate) as model drug in cells under pre-, mid- and post migratory phases. Radiation therapy sensitivity and chemosensitivity in migrating cells via 3D microchannels are being compared to pre- and post-migratory GBM cells to establish an experimental therapeutic strategy.

Conclusions: Microfluidic device is a suitable platform for studying cells under migration in confined 3D spaces. Our initial data suggests that ABCG2 is highly expressed in drug and radiation resistant GBM cell lines. The correlation between ABCG2 expression levels and treatment resistance are being investigated. We expect to extend our studies in patient derived cell lines and in vivo GBM models where new therapy strategies will be tested.

Funding Resources: This study is supported by NIH-COBRE Grant # P20GM103639 from NIGMS.
THE INFLUENCE OF INSOMNIA SYMPTOMS ON THE LIKELIHOOD OF SMOKING CESSATION

Jocelyn M. Barton, Joseph Waring, Emily T. Hébert, Adam Alexander, Michael S. Businelle, & Darla E. Kendzor
The University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma Tobacco Research Center

Significance
Sleep disturbance is associated with smoking, and also as a symptom of tobacco withdrawal. There is evidence that those with sleep problems are at greater risk of relapse after quitting tobacco. However, little is known about how insomnia symptoms experienced during a cessation attempt affect long-term cessation outcomes.

Methods
Participants were tobacco users interested in quitting who engaged in cessation interventions at a tobacco cessation research clinic. Participants were enrolled in an observational study (treatment as usual; TAU), or in a study on the effects of providing small financial incentives for tobacco abstinence. All participants were encouraged to complete 6 weekly counseling sessions, and were offered 12 weeks of pharmacotherapy. Participants included in analysis attended at least one, and up to eight, follow-up visits after baseline. Nicotine replacement therapy (patches, lozenges, and gum) and counseling were offered free of charge to all participants. Abstinence was verified through participant self-report and biochemical analysis. Insomnia symptoms were measured using the Insomnia Severity Index (ISI), a 7-item measure of sleep disturbance (range = 0 – 28).

Results
The majority of participants (N = 166) were female (62%), white (59%), had a mean age of 50.57 years (SD = 12.33), and had completed an average of 12 years of education (SD = 2.44). At quit day (QD), participants reported an average ISI of 11.43 (SD = 7.35), and 33% (n = 40) reported ISI scores placing them in the clinically significant range of insomnia symptoms. Results indicate higher post-quit ISI (measured on QD, 4- and 12- weeks post-quit) predicted higher likelihood of tobacco use at 26 weeks post-quit (QD: n = 117; β = .06, p = .028; 4 weeks: n = 117; β = .082, p = .014; 12 weeks: n = 119; β = .07, p = .038). This effect remained after controlling for age, race, sex, education level, and cigarettes/day pre-quit, and when controlling for type of cessation intervention (TAU vs. small financial incentives).

Conclusion
Consistent with previous findings, sleep disturbance is associated with greater difficulties quitting tobacco. Importantly, a brief measure of sleep disturbance measured from QD through 3 months post-quit was able to predict tobacco use at 6 months, over and above other potential predictors. To date only one study has been published investigating the addition of an insomnia intervention along with tobacco cessation. Results are discussed in terms of insomnia interventions as an appropriately timed adjunct to tobacco cessation efforts.

FUNDING: This research was funded by Oklahoma Tobacco Settlement Endowment Trust grant 092-016-0002
INTRODUCTION: A large number of studies have addressed adolescent smoking, but few have focused on tobacco retailer density near schools and even fewer on tobacco retailer proximity to schools. Recent studies have shown contrasting results on the association of tobacco retailer density near schools and smoking prevalence among students. Some studies found an association between tobacco retailer density near schools and smoking prevalence among students while others found no association. In the few studies that have been conducted on tobacco retailer proximity to schools, the studies have agreed that the proximity from schools to the nearest tobacco retailer had no association with student smoking. However, none of these studies focused specifically on retailer distance to schools and the likelihood of illegal sales to minors. For this project, we used cluster analysis to determine if there were clusters of sales to minors and we used Euclidean distance from a school to a tobacco retailer to determine association with their likelihood of selling to a minor.

METHODS: In this analysis, we used the SMHSA Synar Program, which requires states to have laws prohibiting the sale and distribution of tobacco products to minors. States randomly select tobacco retailers for monitoring their sales to minors through undercover compliance check inspections. Local partners, some with minors, attempt to buy various types of US Food & Drug Administration (FDA)-regulated tobacco products from each retailer under inspection. The data are publically available online through the FDA. We downloaded all retailers (1,402) from Oklahoma in calendar year 2016 and geocoded them using the ESRI® world geocoder. We then pulled the publicly available Oklahoma school locations (1,813) from the National Center for Education Statistics. We ran spatial autocorrelation to determine if selling to a minor was random in Oklahoma using ESRI® ArcMAP 10.6 using an alpha level of 0.05. We then determined the distance from the nearest tobacco retailer who had either sold or not sold to minors and examined specific distances.

RESULTS: Of the 1,402 retailers inspected in 2016, 277 (20%) sold tobacco products to minors. We ran a High/Low Clustering (Getis-Ord General G) Global analysis that showed significant clustering (p-value <.00001). Using Local Indicators of Spatial Associations (LISA) with an Optimized Hot Spot Analysis (Optimized Getis-Ord Gi*), we observed two significant hot spots in south central Oklahoma Western Oklahoma. Among tobacco retailers that sold to a minor, the average distance from each school was 12,044 meters (SD 13,638), compared to 4,402 meters (SD 6,548) among retailers who did not sell...
to a minor. There was a significant difference even after controlling for rural and urban area.

**CONCLUSIONS:** Based on 2016 compliance checks, we observed clusters of tobacco retailers selling to minors in Oklahoma. Moreover, tobacco retailers closer to schools are less likely to sell to minors.

**Funding**

Research was also supported by the National Cancer Institute Cancer Center Support Grant P30CA225520 awarded to the University of Oklahoma Stephenson Cancer Center and used The Stephenson Cancer Center Biostatistics and Research Design Shared Resource (JC). SM supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number U5GM104938. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Deliberation as Community Engagement: Promoting Dialogue about Genetic Research in the Chickasaw Nation

Bobby Saunkeah, Michael Peercy, Christie Byars, Jessica Blanchard, Erika Blacksher, Justin Reedy, Justin Lund, Paul Spicer

Deliberation is evolving as an area of robust inquiry into ways to elicit citizen input on a range of topics, including emerging medical practices and health research. The Chickasaw Nation Department of Health and researchers at the University of Oklahoma and the University of Washington, as part of a larger consortium of tribal partners across the U.S., is exploring and piloting community-based deliberative strategies to facilitate more intensive and meaningful dialogue about the role of genetics research in diverse American Indian and Alaska Native tribal contexts. Central to the work of this larger consortium of tribal partners is an exploration of a range of approaches to promoting deliberation on health research and the possible value of genomics to American Indian and Alaska Native communities.

This poster explores the process of facilitating deliberative forums about the potential benefits and risks of genetics research as a means to seek community input about the priorities and concerns related to the possible role of genetics medicine and research in the Chickasaw Nation. Citizens from diverse communities within the Chickasaw Nation convened for two days in September 2018 to deliberate about ethical questions related to genetic research and biobanking. The aim of this particular deliberation was to facilitate intensive discussion and gather informed input from Chickasaw Nation citizens about the potential benefits and risks of tribal involvement with genetic research. This poster identifies a number of methodological strategies for engaging tribal citizens and communities in a deliberative process focused exclusively on their own questions with the goal of exploring new directions in health research and recommendations for their own communities.

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Exosome microRNA contents are altered and contribute to pre-invasive breast cancer progression

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Background: The progression of breast cancer involves the transformation of normal mammary epithelial cells to ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC). This process is initiated by genetic alterations and characterized by changes to gene expression programs and microenvironmental alterations. However, the specific drivers of DCIS progression to IBC are not well understood nor has an indicator of progression been identified. Exosomes are small secretory vesicles that can contribute to cancer progression by transferring oncogenic factors, such as microRNAs (miRNAs), to surrounding cells in the tumor microenvironment, and enter the circulation to act at distant sites. MiRNAs are short noncoding RNAs that regulate the expression of a target messenger RNA (mRNA). Altered regulation by miRNAs is implicated in cancer progression. In this study, we sought to characterize the exosome miRNAs in the MCF10 isogenic model of breast cancer progression in order to identify potential drivers of breast cancer and to examine the functional role of exosomes in this process.

Methods: Exosomes were isolated from the conditioned media of the MCF10 isogenic cell line model of breast cancer progression representing the following stages: normal, benign proliferative, carcinoma in situ, and invasive carcinoma. RNA was extracted from the exosomes and next generation RNA sequencing was performed. Exosome miRNA expression was validated in breast cancer cell lines and in plasma exosomes collected from a mouse-intraductal transplantation (MIND) model implanted with MCF10DCIS.com (DCIS) cells that can mimic human DCIS progression in vivo. Scratch-wound healing and invasion assays were performed to determine the migratory and invasive activity of DCIS cells when treated with exosomes from invasive cells.

Results: Comparisons were made between differentially expressed miRNAs among each condition (fold change >1.5; Kruskal-Wallis p<0.05). Twenty-nine miRNAs were differentially expressed among invasive and DCIS exosomes. The expression of 5 oncogenic miRNAs (miR-30c-5p, -210, -182-5p, -200c-3p, and -200b-3p) were consistently increased, while 2 tumor suppressive miRNAs (miR-423-5p and -92b-3p) were consistently decreased with invasive progression. Exosome miRNA expression was confirmed in breast cancer cell lines and mouse plasma exosomes. Migration and invasion of DCIS cells was significantly enhanced when treated with exosomes from invasive cells.

Conclusion: This work demonstrates that the microRNA contents of exosomes change upon malignant transformation to invasive breast cancer and indicates that certain exosome microRNAs are consistently up- or down-regulated in DCIS exosomes. This work also shows that exosomes from invasive cells promote invasive activity of DCIS cells and may contribute to breast cancer progression.
SMOKING CESSATION TREATMENT FOR PEOPLE LIVING WITH HIV: A NEED FOR ENHANCED STRATEGIES

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Background: With the availability and effectiveness of antiretroviral therapy, people living with HIV (PLWH) now live longer and face disproportionally high risks of both AIDS-defining and non-AIDS-defining cancers. Tobacco-related morbidity and non-AIDS-defining cancers are now the leading non-AIDS causes of death among PLWH. The Ask-Advise-Connect (AAC) project was implemented to link smokers visiting 13 safety-net healthcare system clinics, including a single HIV-specific treatment clinic, with the Texas Quitline.

Objective: This analysis reports on: 1) the proportion of identified HIV+ smokers enrolled in treatment and 2) the abstinence rates at the 6-month follow-up assessment.

Method: AAC was implemented from April 2013 through February 2016 in 13 community clinics, one of which specialized in HIV/AIDS treatment and care. Patients were asked if they smoked and those who reported current smoking were given brief advice to quit and offered to be “connected” to the Quitline. That is, the names and phone numbers of smokers who agreed to be connected were immediately sent to the Quitline through an automated link within the electronic health record. Within 48 hours of receiving patients’ contact information, Quitline staff proactively called all participants to offer enrollment in the standard proactive, 5-call tobacco cessation treatment program.

Results: The smoking status of 5,825 unique HIV+ patients was recorded during the 34-month implementation period. The smoking prevalence was 46% (2,675/5,825). Approximately 32% of HIV+ smokers (867/2675) agreed to be connected to the Quitline. Among those who agreed to be connected, 44% (385/867) talked with the Quitline. Among those who talked with the Quitline, 75.1% (289/385) enrolled in treatment. Among smokers who enrolled in treatment, 74% (214/289) agreed at the time of treatment enrollment to be contacted for follow-up at 6 months. Among those who agreed to be contacted for follow-up, self-reported abstinence was 18.7% (40/214) and biochemically confirmed abstinence was 4.2% (9/214).

Conclusions: AAC resulted in Quitline treatment enrollment rates and 6-month abstinence rates comparable to those observed in non-HIV low-income smokers at the other 12 clinics. However, given the vulnerability of this
population, enhanced strategies tailored to the unique needs of HIV+ smokers are needed to facilitate cessation. Specifically, interventions are needed to motivate HIV+ smokers to quit, such as raising their awareness of how smoking significantly affects the health of PLWH given their immunocompromised status. Furthermore, cessation treatment programs need to address the complex characteristics of this heterogeneous population, such as the diversity of sexual orientations, other substance use or co-dependence, lack of social support, chronic stressors (e.g., due to stigmatization), or other mental health issues. Interventions targeting provider level and system level factors are also needed.

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TUMOR LYSIS SYNDROME IN GYNECOLOGIC CANCERS: THE IMPORTANCE OF IMMEDIATE DIAGNOSIS AND TREATMENT

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Objectives: To describe the incidences, trends, common clinical and laboratory findings, treatment strategies and outcomes associated with tumor lysis syndrome (TLS) in women with gynecologic cancer (GOC).

Methods: A retrospective multi-institutional cohort study of women with gynecologic malignancy that received inpatient treatment of acute TLS was assembled. Patient data was collected from two large academic sites in different states. Cases were included if women with new or established GOC presented with elevated serum uric acid and was managed with intravenous Rasburicase, a uric oxidase inhibitor. Descriptive analysis of patient characteristics, clinical factors, laboratory findings, treatment and outcome data was performed.

Results: From institution A, pharmacy records identified 1,134 inpatients from 2008-2018 receiving an inpatient dose of Rasburicase were screened. Of those, 344 (30.34\%) were women and of those, 307 women had a known malignancy, 15 were found to have GOC reflecting an approximate 5\% proportion of women with TLS. From institution B, an informatics agency queried the medical record system from the dates of 2014-2018 using the patient inclusion criteria and three additional patients were identified, totaling N=18 patients meeting inclusion criteria.

High-grade gynecologic malignancies were found in nearly all cases, n=17, 94.4\%. The most common sites were ovarian (n=8, 53.3\%) and uterine (n=6, 35.3\%). The majority of patients were Caucasian (n=11, 61.1\%) with median age at admission of 60 (range: 35-71), and mean BMI of 39.9. A majority (n=12, 70.6\%) of TLS diagnosis was made at the same time of GOC diagnosis, the remainder were made at the time of recurrence. TLS was diagnosed following chemotherapy in n=7 (38.89\%) of cases; six treated with Taxol and, interestingly, two of the seven cases, 28.6\%. were treated with a CD47 inhibitor. One case was associated with major surgery and radiation. Chief complaints included electrolyte and renal issues (n=11, 73.3\%). Mean peak serum creatinine, potassium, uric acid, and phosphorus levels were 5.11mg/dL, 5.66mEq/L, 14.16mg/dL, and 6.78mg/dL and the mean serum calcium nadir was 8.33mg/dL. On average, 2 doses of Rasburicase were given by hospital day(d) 2 of a median 9 d(range: 4-16d) admission. Full laboratory recovery occurred in 6 (40\%) cases and the remaining 9 were placed on hospice during their admission with 3 (20\%) deaths occurring as inpatients. Median OS is 29 (range: 2-398)d following diagnosis of TLS and median time to death, in those that died was 21 (range: 3-87)d.
Conclusions: TLS, though rare in solid tumors, can be associated with GOC. Early recognition of unique presenting symptoms, laboratory findings and subsequent urgent treatment may help with electrolyte recovery; however, TLS associated with GOC may herald a rapidly deteriorating state with significant associated mortality.

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LEUKEMIA INITIATING CELLS IN A MYC-DRIVEN PRE-B-ALL ZEBRAFISH MODEL

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. ALL is characterized by the malignant transformation and proliferation of bone marrow lymphoid progenitors, and can develop in lymphoblasts of either the B or T cell lineage. Precursor-B cell ALL (pre-B ALL) is the most common ALL subtype in children and adults, and the most prevalent childhood cancer overall, representing over 25% of all pediatric malignancy. A major challenge for approximately 20% of pre-B ALL patients is relapse, which has a much worse prognosis than de novo pre-B ALL. One reason relapses are thought to occur is because therapy failed to eliminate leukemia initiating cells (LIC). LIC have unique self-renewal properties that can, theoretically, re-grow an entire cancer from a single cell. Unfortunately, LIC biology is poorly understood, limiting our ability to identify new therapies that might target LIC to prevent pre-B ALL relapses.

We recently discovered the first highly penetrant zebrafish pre-B ALL model; a human MYC transgene (hMYC) regulated by the D. rerio rag2 promoter induces pre-B ALL in these fish. We are investigating LIC in zebrafish pre-B ALL using allo-transplantation. Our data indicate pre-B ALL LIC exist and can engraft into immunosuppressed recipient fish. We have also identified a flow cytometric “side population” that may contain pre-B ALL LIC. No zebrafish markers to evaluate if side population cells contain LIC are known, so to test this functionally, we are allo-transplanting pre-B ALL side population cells into irradiated recipients to test self-renewal. Overall, our data suggest D. rerio hMYC-induced pre-B ALL may be a powerful model to study pre-B ALL LIC. After identifying LIC, we seek to define LIC gene expression profiles, using single cell technologies to answer fundamental questions about the biology of this crucial, yet rare, population of leukemia cells.
APPLICATION OF MICROFLUIDIC DEVICES FOR STUDYING GLIOBLASTOMA

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Introduction: Glioblastoma multiforme (GBM) is the most aggressive primary brain cancer in adults with a very poor prognosis and low survival rate in patients. Because of its heterogeneity and extraordinary ability to migrate, infiltrate and invade, GBM is difficult to cure and frequently recur. We use microfluidic devices to mimic the in vivo microenvironment for studying the cellular and molecular characteristics of GBM to better understand the cause and progression of the disease, in order to identify new therapeutic targets for the treatment.

Methods: Two polydimethylsiloxane (PDMS) microfluidic devices are used in the studies: a collection microfluidic channel (2.5 cm long and 4 mm wide) and a “flower design” (central cell seeding chamber connected with 6 collection wells through tapered microchannels of varied dimensions). Using commercially available GBM cell lines (G55) and patients-derived GBM cell lines, we performed measurement of cell migration velocity, assessment of the effects of radiation therapies, and cell sorting to characterize the genomic and proteomic features of patient-derived GBM cells.

Results: The migration speed of 13 patients-derived GBM cells inside the microchannels at a defined time points was assayed to determine the relationship between the migration speed and malignancy. Radiation treatment reduced the migrating speed and the cell viability of the cells inside the channels. However, the reduction of viability was less than cells grown in traditional adherent cell culture indicating that migrating cells have a greater resistance to radiation. The fast migrating cells from one of the patients-derived cell lines were collected with the “flower design” for analyzing their genomic and proteomic profiles compared to none migrating or “pre-migratory” cells.

Conclusions: Microfluidic devices which mimicking the in vivo microenvironment of the GBM cancer are very useful tools for studies of migration and invasion of individual GBM cells, and for assessment of treatment efficacy. They can also be used to separate and collect GBM cells with quickly migrating phenotypes, and characterize their molecular features to discover the mechanisms by which the GBM cells act.

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INTRODUCTION: Spatial epidemiology is the study of geographic variation of diseases. It is crucial to understand the underlying spatial factors such as potential environmental exposures, including tobacco and multiple cancers, asbestos exposure and mesothelioma, aflatoxin and liver cancer, benzene and acute myeloid leukemia, and air pollution and lung cancer. Moreover, distance to care has been shown to be a critical factor in completion of care and survival. Therefore, geocoding, the method for converting textual address information to spatial coordinates, is integral to conducting spatial epidemiologic research.

METHODS: For this project, 29,800 cancer cases from the University of Oklahoma Cancer Registry (2005-2017) were geocoded using the Texas A&M geocoding toolbox. This toolbox allows users to access the Texas A&M geocoder without having to transfer records outside of a secure server at the University of Oklahoma Health Sciences Center.

RESULTS: Over 95% of the cases were geocoded successfully. Among those successfully geocoded, 39% were geocoded to the parcel level, 36% to a street segment, 21% to ZIP code and 4% to ZIP code tabulation area (ZCTA). OU Medicine now has the ability to investigate geospatial factors, which are critical for future analysis. As a next step, we will develop maps that include estimates of distance to treatment for breast cancer as an example of the potential of the improved spatial data quality.

CONCLUSIONS: While these are excellent results, we aim re-geocode those not coded to a parcel level. Particularly we would like to increase the accuracy for the addresses that resulted in ambiguous (N=191), unmatchable (N=852), street segment (N=10,276), ZIP code (N=5,941) and ZCTA (N=1,151) based geocodes. With the addition of geospatial information to the University of Oklahoma cancer registry, researchers interested in spatial epidemiologic studies have a valuable resource for future research.
PATTERNS OF OPIOID USE IN GYNECOLOGIC ONCOLOGY SURGICAL AND CANCER SURVEILLANCE PATIENTS

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Objectives: Describe current opioid prescribing patterns, utilization of supportive and pain services and patient concerns in surgical and surveillance patients from a large gynecologic oncology (GO) practice.

Methods: Questionnaires were distributed to patients identified as post-operative or surveillance GO patients. Operative patients were dichotomized as having low/usual use (LU) and high/unusual use (HU) of opioids. LU patients did not require additional opioid refills and were not using opioids at time of 2-week follow-up (f/u) visit. HU were those requiring opioid refills or still requiring opioids at 2-week f/u. Answers correlated to baseline and clinical demographics were tested for significance using T- and chi-squared testing for univariate analysis for association, with a p<0.05.

Results: 130 participants met inclusion criteria and 79 (60.9%) participated totaling 35 post-operative patients and 44 surveillance patients.

Of the post-operative group, on average 37 opioid tablets were prescribed at discharge with 8 unused tablets in those no longer requiring opioids; equating to 21.6% over-prescribing. There were 25 (71.4%) LU patients identified (median follow up 13d). The remaining were (28.6%) HU patients (median follow up 16d). Three HU patients (30%) reported requiring both a refill and continued need and were characterized as unusually high use UHU. There was no significant difference in age (P=0.24), BMI (p=0.13), mood disorder (p=0.25), operative complexity (p=0.49), hospital stay (p=0.23) and presence of cancer diagnosis (p=0.74) in those that with LU versus HU of opioids. Those with HU were more likely to have an opioid listed as a home med (P<0.01) and those patients with UHU were more likely to have benign disease (P<0.01) compared all else.

The surveillance cohort (median age 61, median surveillance 19.8 m) had majority uterine (40.9%, n=18) followed by ovarian (27.3%, n=12), cervix (18.1%, n=8) and vulvar (13.6%, n=6) cancers. In all, 77.2% reported receiving opioids during cancer treatments and only 8.8% (n=3) were still receiving opioids at time of study, two of which receive supportive and/or palliative care services. A third (n=15) of all surveillance patients were referred to supportive care services with 86.7% referral completion rate (median 3 visits).
In all, only 5 women expressed concern about having unused opioids at home but 15.2% (n=12) expressed interest in returning unused opioids. The majority cited concern for younger children in the home.

**Conclusions:** A variety of services provided by GO provide complex settings for opioid use optimization. GO patients undergoing surgery are generally low-risk; home opioid use is a predictor for UHU of post-operative opioids. Cancer diagnosis does not increase post-operative narcotic use. Utilization of ancillary services is inversely related to low chronic opioid usage in cancer surveillance patients.

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MECHANISMS OF DNA REPLICATION REGULATION DURING EMBRYONIC DEVELOPMENT

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Eukaryotic replication origins follow a specific pattern of initiation termed the replication-timing program. Clusters of origins within large genomic domains activate together and each domain follows a temporal order of initiation throughout S phase. Deregulated DNA replication contributes to human developmental disorders and cancer progression, but we know little about how DNA replication is coordinated with changes in transcription and chromatin structure. We have developed the zebrafish into a model system to study how modifications in replication timing coincide with the extensive alterations in the cell cycle, transcription and chromatin organization that occur in the developing embryo.

Rif1 has previously been shown to mediate DNA replication timing by suppressing activation of late-replicating origins; in addition, Rif1 has also been linked to heterochromatin organization and gene silencing. The broader role of Rif1 in establishing the replication timing program and chromatin structure during early vertebrate development remains unknown. We have performed RNA sequencing and whole-genome replication timing analyses on Rif1 mutant and wild-type zebrafish embryos isolated at multiple developmental stages. These analyses show that Rif1 loss causes general effects on replication timing in the developing zebrafish embryo as well as additional roles for Rif1 in zygotic genome activation and sex determination.

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MASS SPECTROMETRY ANALYSIS OF NON-ADHERENT CANCER CELLS BY SINGLE-PROBE

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Cell lysates, the traditional method of analyzing intracellular content, take information from a large population of cells. This masks the heterogeneity between the cells, so to find the differences between each individual cell single-cell analysis must be performed. The current method employed within the Yang lab is Single-probe mass spectrometry. The Single-probe is a multifunctional device with a ~10 μm tip meant to puncture individual cells. It couples easily with a mass spectrometer for analysis of intracellular compounds such as cellular metabolites or drug compounds. However, this method has the drawback that is primarily used on adherent cells which is not representative of patient cell samples.

To adapt the Single-probe method to be used on non-adherent cells, an Integrated Cell Manipulation Platform was used with the Single-probe and coupled with mass spectrometer. Within the Integrated Cell Manipulation platform two Eppendorf Cell Manipulation systems were used to manipulate the Single-probe and the cell-selection probe for the capture and transfer of the single cells. The capture of the cells was monitored from below with a Nikon Dxxx inverted microscope (TE-DH100W) while the cells were kept alive by a Tokai Hit Thermoplate system. This was coupled with an LTQ Orbitrap XL for analysis of the intracellular content. This method and instrumentation has been used to detect the intracellular contents of the human leukemia cell line, K562, both treated and untreated.

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POTENTIALLY REDUCED TOBACCO PRODUCT USE AMONG AMERICAN INDIAN SMOKELESS TOBACCO USERS: IMPACT ON SMOKELESS TOBACCO CESSATION BEHAVIORS AND TOBACCO EXPOSURE BIOMARKERS.

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Objectives: American Indians/Alaska Native (AI/AN) adults consume smokeless tobacco (SLT) products more frequently than other populations. Adults in the US, including AI/ANs, increasingly use potentially reduced exposure tobacco products (PREPs), such as, electronic cigarettes and Snus, as an alternative to more harmful products. However, few studies have evaluated the prevalence of PREPs use among SLT users or whether PREPs use influences SLT cessation behaviors or nicotine dependence. No studies have examined PREPs use among AI/AN SLT users. This is an important area of research for AI/ANs since they have a higher prevalence of cigarette and SLT consumption and tobacco-related morbidity and mortality, including cancer mortality. To address this gap, this study was devised to explore associations between current PREPs use and SLT-related measures, including SLT-cessation attempts and nicotine dependence, in a sample of adult AI SLT users.

Methods: We collected survey and tobacco biomarker data in a sample of 299 adult AI SLT users at Cherokee Nation healthcare facilities and events. We used multivariate logistic and linear regression analyses to determine associations between PREPs use and SLT-related characteristics.

Results: In this sample of AI SLT users, PREPs users were younger, less likely to be married or living with a partner, less likely to report a chronic medical condition, and more likely to report other tobacco use, including cigarettes, cigars, cigarillos, hookahs, and dissolvable tobacco when compared to non-PREPs users (all p<0.05). Among individuals with annual incomes less than or equal to $30,000, PREPs users were less likely to report having a desire to quit SLT than PREPs non-users (p=0.02), while among those with higher incomes ($30,001+), the point estimate for this relationship was inverted with PREPS users being more likely than non-users to report a desire to quit SLT at near statistical significance (p=0.08). PREPs use was not significantly associated (p>0.05) with planning to quit SLT, past 12 months SLT quit attempts, number of SLT cans/pouches used per week, cotinine levels, or Fagerström Test for Nicotine Dependence-SLT scale score.
Conclusions: In this sample of ALs SLT users, our results suggest PREPs use has a negative association with a desire to quit SLT among low-income ALs. There was no statistically significant difference between PREPs users and non-users on other SLT cessation behaviors or nicotine dependence. Additionally, PREPs users were more likely to use multiple tobacco products. These findings indicate that PREPS use may not be a useful aid in SLT cessation in this population. However, additional research would be needed to determine if PREPS use might lower SLT users’ exposure to carcinogens or other harmful toxicants.

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Prostate cancer (PCa) is a complex heterogeneous disease, with the majority of cases remaining indolent and 10% of cases progressing to lethality. While some of this clinical heterogeneity can be explained by traditional clinicopathological factors, molecular profiling studies signal an extraordinary genomic variability, which may lead to diverse clinical outcomes. The identification of molecular subclasses of PCa has the potential to guide the prediction of clinical outcomes, the discovery and design of innovative prognostic biomarkers, and the development of novel therapeutics. To this end, we investigated genes associated with TMEFF2, an androgen-regulated tumor suppressor gene with exceptionally heterogeneous expression in PCa. Low levels of TMEFF2 mRNA significantly (p<0.0001) correlate with reduced disease-free survival (DFS) in patients from the Memorial Sloan Kettering Cancer Center (MSKCC) dataset. Using RNA interference, we identified a panel of 11 TMEFF2 regulated cell cycle related genes (TMCC11), with strong prognostic value. TMCC11 expression stratified radical prostatectomy (RP) patients on the risk of recurrence, served as an independent indicator of poor prognosis, and improved the prognostic value of standard clinicopathological markers in four geographically different patient cohorts (n= 834 samples). The prognostic ability of TMCC11 panel exceeded previously published oncogenic gene signatures (p=0.00017). This study provides evidence that the TMCC11 gene signature is a robust prognostic marker for PCa, reveals the value of using highly heterogeneously expressed genes, like TMEFF2, as guides to discover prognostic indicators, and suggests the possibility that low TMEFF2 expression marks a distinct subclass of PCa.

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USING CONTENT ANALYSIS OF REDDIT TO UNDERSTAND PATTERNS AND PERCEPTIONS OF JUUL USE AMONG YOUTH

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Background: JUUL is an electronic cigarette (EC), which currently makes up approximately 67% of the market. In the past year, sales of JUUL have increased over 600% and 73% of sales are presumed to be attributed to its popularity among youth. However, little research examines youth perceptions of JUUL. The aim of the current study was to examine posts on Reddit specific to JUUL and youth to better understand perceptions of JUUL use.

Methods: The current study obtained all submissions and comments posted on Reddit from January 2015 to May 2017 with the character string “juul” (n=16,068) and removed posts that did not refer to JUUL the EC (n = 4,561). A final dataset with 11,507 posts was uploaded into NVivo 11 for further analysis. Posts were then minimized to only those including youth-related terms (college, high school, kids, students, underage, teenagers, young, or youth) for a final sample of 364. Then, posts were examined for frequencies of topics of interest using NVivo (flavors, references to youth, reasons for use, health-related posts, and polarity).

Results: 364 posts were included for a quantitative content analysis. Posts included a variety of reasons for using JUUL but four were most prominent: (1) popularity of JUUL (34.2%), (2) using it to quit smoking (23.3%), (3) to feel a buzz (20.2%), and (4) the stealth/discreetness of the product (11.4%). The mentioned primary barrier to use was age restrictions (34.9%), followed by price (18.8%), and lack of availability (16.1%). The posters were mixed age ranges but most were deemed as being familiar with the product with as much as 20.6% clearly reporting current use. One-fifth of the sample also reported current dual use of other products such as other ECs (20.3%) and combustible cigarettes (21.7%). The most commonly reported flavor choices were mango and mint. Posts tended to use positive language (83.9%) when discussing JUUL and were more likely to refer to its perceived health-related benefits, such as helping one to quit smoking (15.1%), than its perceived negative health consequences (3.8%), such as disease risk or nausea.
Conclusions: Reddit posters’ perceptions of JUUL use indicate the strong influence of social norms. Fortunately, age restrictions may continue to be a barrier to use. Additionally, because many mention using JUUL to quit combustible cigarettes, there may be a potential for harm reduction. The perceptions of health-related benefit and the high level of nicotine buzz are most likely responsible for its growing popularity but as the market share grows, this information may inform electronic cigarette regulations.

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Glioblastoma (GBM) is a highly aggressive brain cancer. The standard course of treatment is a combination of radiation and chemotherapy, typically Temozolomide. Even with the dual treatment of chemotherapy and radiation, the 5-year survival rate of patients with GBM is between 4-7%. Therefore, there is an urgent need to develop novel therapies to increase the survivorship of GBM patients. A possible cause of the low survival rate for GBM patients is the presence of motile neoplastic cells. Motile cells have been shown to be resilient against chemotherapy and radiation. They often seed to favorable sites and continue to grow unchecked.

XRN2 is upregulated in GBMs as compared to normal and other brain cancer types. XRN2 is a 5’-3’ exonuclease that resolve naturally occurring DNA:RNA hybrids (R loops) that arise during transcription, especially transcription termination. Increasing amount of evidence support the role of R loops in DNA damage response (DDR). Preliminary data suggest that XRN2 acts as a protectant against ionizing radiation (IR). Loss of XRN2 led to increasing double-stranded breaks, DSBs and sensitivity to IR. Our preliminary data have shown that XRN2 is required for cancer cell motility in two GBM cell lines, U87 and U251. In addition, loss of XRN2 sensitizes cells to Cisplatin, a common chemotherapy drug.

Based on these observations we propose that XRN2 may contribute to glioblastoma progression by acting as a chemo- and radio-therapy protectant and a driver of cancer cell motility and/or invasion. To elucidate the mechanism of XRN2-mediated cancer progression, we conducted RNA-Seq on GBM cells with and without XRN2 expression. From this survey we will determine which of XRN2-mediated targets are required for DNA damage repair and/or metastasis. To effectively treat cancer patients and yet maintain a good quality of life, it is imperative to target biological mechanisms unique to cancer cells. By discovering novel relationships we may find new lynchpins to effectively treat glioblastoma.

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Oral cavity cancer is a common type of cancer with over 350,000 new cases estimated worldwide in 2018, and remains a significant national health challenge. Although advancements have been made in diagnosis and surgical treatment of oral cancer, survival rates for oral squamous cell carcinoma patients have not improved in the last 30 years, and only 40 to 50% of patients reach 5 year survival. This study aims to better understand clinical characteristics and treatment trends in oral cavity cancers.

For the analysis of tumor characteristics and treatment patterns, oral cavity squamous cell carcinoma cases diagnosed between 2004 and 2015 were selected from the National Cancer Database. Using both univariate analysis and multivariable regression models we examined tumor traits (e.g.- nodal status, tumor size, or location), sociodemographic characteristics (e.g.- race, age, insurance), and treatment (e.g.- sequence and type) in oral cavity cancer.
APELIN/APJ ANTAGONIST INHIBITS OMENTAL METASTASIS OF OVARIAN CANCER CELLS

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Abstract: Ovarian cancer (OvCa) metastasis is mainly confined to the peritoneal cavity with predilection for omentum, an organ primarily composed of adipocytes. Adipocytes produce multiple adipokines including apelin which provide a milieu that promotes initial homing of tumor cells to omentum. Apelin and its receptor APJ mediates glucose/energy metabolism and angiogenesis. The study objective is to assess the functional role of apelin/APJ pathway in omental metastasis of OvCa and associated benefits from antagonizing this pathway as a novel treatment strategy against OvCa metastasis. Mouse adipocyte cell line 3T3-L1 was used to obtain adipocyte-derived conditioned media (AdipoCM). We showed that mature adipocytes increased apelin expression about 2.5-fold higher than pre-adipocytes, and secreted 1 ng/mL apelin in AdipoCM. In the presence of Adipo CM, human OvCa cells with high APJ expression (OVCAR-5APJ and OVCAR-8) showed increased migration (~3.5-fold) and invasion (~4-fold). We observed a 1.5-fold increase in OVCAR-5APJ cell adhesion to mouse omentum ex vivo. Furthermore, high-APJ expressing OvCa cells showed 2.75-fold increase in ‘homing’ to the omentum in vivo. These apelin-induced pro-metastatic effects were reversed by apelin-specific antagonist (F13A) in a dose-dependent manner. Together, our studies demonstrate that apelin-derived from fat cells promotes OvCa pro-metastatic phenotypes in a paracrine manner. Inhibiting the apelin/APJ pathway using F13A could present as a novel therapeutic in OvCa metastasis.

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CARE COORDINATION FOR CHEROKEE NATION CANCER PATIENTS: PERSPECTIVES OF KEY STAKEHOLDERS

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The rapidly growing number of cancer survivors in the United States poses challenges for Tribal health care delivery. The post-acute phase of cancer treatment is a largely neglected area of cancer trajectory research, especially when undertaken from a primary care perspective and there is sparse literature on this topic for American Indian or Alaska Native populations. As a first step in developing an intervention to facilitate cancer care coordination between oncology and primary care, the proposed study guided by the Care Coordination Model, will provide insight into the current care coordination process from the perspective of: 1) cancer survivors; 2) primary care providers (PCP) within the Cherokee Nation Health System; and 2) the corresponding oncology care providers that patients are referred to for specialty care. Specifically, the study aims to: 1) Identify the perceptions, knowledge, and practices regarding care coordination of adult cancer survivors receiving care through the Cherokee Nation Health System in a sample of cancer survivors, primary care providers and oncology care providers; 2) Identify barriers and facilitators of transitions from primary care to oncology care and back to primary care in current clinical practice; 3) Describe key aspects of communication about the care transition; and 4) In collaboration with key stakeholders, identify potential strategies for reducing barriers and facilitating cancer care coordination. As it is necessary to understand impediments to high quality care before intervening, this study will employ a qualitative descriptive design to gather information about cancer care coordination in Cherokee Nation patients. Key stakeholders (cancer survivors, PCPs, Oncology providers) engaged with care coordination for cancer patients within the Cherokee Nation Health System will be interviewed individually or in small groups. After data are analyzed, the results will be used to develop potential strategies for improving care delivery experiences for providers and survivors. This study will provide critically needed information that will underpin the development of future interventions to improve cancer care coordination in the Cherokee Nation and other Tribal settings resulting in high-quality referrals and transitions of care between the oncology and primary care settings.

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EXECUTIVE FUNCTIONS, EMOTIONAL VOICE-TONE SENSITIVITY, AND CANCER TREATMENT ADHERENCE

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This project will focus on the correlation between the ability to recognize the voice-tone of verbal directives and adherence to cancer treatment. In the treatment of gynecologic cancer, a critical treatment-adherence component consists of heeding verbal directives issued by healthcare providers to instigate (e.g., “go on a diet”) or to impede (e.g., “quit smoking”) treatment-relevant behaviors. Whether a patient heeds or ignores these directives has a major impact on treatment adherence and outcomes; thus, finding out why some patients heed and others ignore these verbal directives is most important. In addition to understanding what they mean, heeding verbal directives requires sensing their voice tone (lenient, stern, worried), which conveys the emotional disposition of the healthcare provider and requires patient empathy. If the patient cannot sense and recognize its voice tone, a stern “quit smoking!” directive could have little or no effect on the patient’s smoking behavior. Adhering to treatment-related verbal directives is most precarious in information- or response-conflict conditions (e.g., trying to diet at a restaurant), that activate executive functions and interfere with emotional voice-tone recognition. In gynecologic cancer patients, this project will measure the ability to recognize the emotional voice-tone (lenient or stern) of simple verbal directives used to instigate (e.g., “go!”) or impede (e.g., “quit!”) behaviors. At three time points along the treatment, emotional voice-tone recognition will be assessed in the absence and in the presence of conflicting information that requires activating each of four executive functions: inhibitory control, selective attention, cognitive flexibility, and working memory. Recognition accuracy is expected to decrease as the executive function demands increase. Objective measures of treatment adherence (pill count, rate of prescription refills, patient self-report, patient’s clinical response, and miscellaneous indices) and self-efficacy will be obtained to determine if they correlate with the ability to recognize the emotional voice-tone in the midst of executive function demands. Since treatment non-adherence entails ignoring treatment-relevant verbal directives, a significant correlation is expected. In addition to being ecologically valid, the research results could help understand individual differences on the ability to adhere to verbal directives, and develop treatment plans that take into account the patient’s ability to process verbal directives.

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A Hybrid CompuCell3D Model of Cancer Migration in a Metastatic Remodeling Extracellular Matrix

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One of the leading causes of cancer mortality is the acquired ability of malignant cancer cells to metastasize uncontrollably from a localized tumor to other parts of the body. Central to the metastatic migration is the mutual interaction between the cancer cell and the surrounding tumor microenvironment, particularly the extracellular matrix (ECM). During the early stage of metastatic invasion, remodeling enzymes including matrix metalloproteinases (MMPs) and lysyl oxidase (LOX) are secreted by cancer cells to degrade and crosslink collagen fibers in the ECM. Such structural alterations to collagen fibers induce changes in the overall physical and biomechanical properties of the ECM. However, questions regarding the underlying mechanism of how these changes facilitate the directional motility of cancer cells through the network of collagen fibers in the ECM remain unanswered. Employing a multiscale modeling approach, a hybrid discrete-continuous computational model is developed via the open-source software CompuCell3D to address the complex interplay between metastatic cancer cells and the ECM while the ECM undergoes chemical and physical remodeling. In this work, cancer cells are treated as discrete agents in a cellular Potts model while ECM components including collagen fibers and remodeling enzymes are modeled as a continuous system of coupled partial differential equations describing their concentrations. Results obtained from the model suggest that ECM fiber concentration is potentially a regulator of cell motility. The computational model of cancer migration addresses the influential role of remodeling enzymes MMPs and LOX and provides fundamental understanding of how ECM remodeling can affect the overall migration efficiency. Future extensions to models of this kind could potentially guide patient-specific and tissue-specific therapies by accounting for drug actions on inhibiting the effects of MMPs and LOX or altering the remodeling rate of the ECM to slow down metastasis.

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THE DEVELOPMENT OF CACFP BEST PRACTICE MENUS IN AMERICAN INDIAN EARLY CARE AND EDUCATION PROGRAMS

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Background. Excess weight in childhood tends to persist into adulthood, resulting in a higher risk for developing other health problems such as heart disease, diabetes, and other diseases. Overweight and obesity status at a young age (i.e., childhood and adolescence) has been linked with increased incidence rates of various cancers in adulthood including but not limited to endometrial and ovarian cancers, colorectal cancer, gastric cancers, and pancreatic cancer.

In Oklahoma, over 30% of low-income, American Indian (AI) children aged 2- to 4-years-old were classified as overweight or obese in 2009, which is higher than the national average of 27%. The majority of U.S. children spend 35+ hours per week in early care and education (ECE) programs and typically eat two-thirds of their daily nutrient needs in care. Barriers may exist which keep ECEs from adhering to the recommended best practices, preventing children from receiving optimal nutrition.

Study purpose. The purpose of this project is to determine the nutritional quality of menus and identify barriers preventing AI ECEs from complying to the best practices. A best practice menu will be developed in collaboration with tribal communities to address identified barriers.

Methods. Two tribally-affiliated ECEs have been recruited from the larger project - Wellness Across Traditional Community Health (WATCH). Compliance with federal recommendations and best practices will be determined for current menus. Focus group meetings with the food preparers will be held in December 2018 at the ECEs in order to assess current food and nutrition practices, assess menu goals, and to identify current barriers preventing the food preparers from adhering to the CACFP meal patterns and best practices. Once barriers and concerns have been identified, a comprehensive CACFP best practice menu will be developed for implementation within these ECEs.

Results. We anticipate finding that certain barriers such as the proximity of grocery stores, the frequency of food vendor delivery, and/or the infrastructure of the ECE (e.g., limited space and lack of supplies) will hinder the quality and availability of healthy foods in tribal ECE program menus and, therefore, inhibit the ECEs from following CACFP best practices. Regardless of substitutions that the ECEs may make to cater to their identified barriers, we anticipate that CACFP compliance scores will increase following menu modification.
**Implications.** Enhancing the ECE environment through menu modification would be instrumental in improving the health behaviors of young AI children. Through identification and understanding of barriers, plausible and tailored interventions could be implemented such as partnerships with supply chains, vendors, local grocers, and potentially farmers to provide long-term success for healthier nutrition in these ECE programs.

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PADDA, A NOVEL ASSAY, DETECTS HIGH LEVELS OF DNA DAMAGE IN ORAL EPITHELIUM OF ELECTRONIC CIGARETTE USERS

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**Background:** The use of electronic cigarettes (e-cigs) has skyrocketed among adolescents and young adults. E-cigs are promoted as safer than combustible cigarettes but their long term effects on human health are still unknown. E-cig aerosols contain significantly lower number of chemicals than tobacco smoke, however they also contain known carcinogens, reactive oxygen species (ROS), and unique chemicals poorly studied. *In vitro* and animal studies revealed that e-cig aerosols increases DNA damage and reduces DNA repair. There have been no studies assessing e-cig-induced DNA damage in human subjects. This reflects, at least in part, technical limitations that make it quite challenging to measure the *in vivo* steady-state levels of DNA damage, particularly for relatively low levels of genotoxic exposure. Our lab has previously developed and validated a novel quantitative primer anchored DNA damage detection assay (q-PADDA) to quantify *in vivo* DNA damage. We have also reported that, in an *in vitro* setting, q-PADDA has high sensitivity to detect e-cig-induced DNA damage. Here, we take advantage of this assay to start assessing the potential long-term impact of e-cig use on human health.

**Aim:** To determine whether e-cig users have higher levels of DNA damage on oral epithelial cells than non-users.

**Methods:** Ethics Committee approval was obtained. Participants were recruited through internet ads, leaflets, flyers and word-of-mouth. After written informed consent, a total of 35 individuals were included in this study: 20 exclusive e-cigarette users and 15 individuals reporting no e-cig or tobacco use. Self-report of tobacco use was biochemically confirmed by salivary cotinine and by measuring exhaled carbon monoxide (CO). Oral mucosa samples were collected by cytobrush and used for DNA extraction and damage quantification. DNA damage was quantified by q-PADDA within p53, the most frequently mutated gene in human cancer. Plasma nicotine levels were analyzed by liquid chromatography–mass spectrometry. Data was analyzed by Student’s t test

**Results:** The study including participants using high and low voltage e-cig devices. E-cig users (33 ± 8) and non-users (33 ± 7) had similar age distribution. We observed that oral epithelial cells collected from e-cig users have significantly higher levels of DNA damage in both transcribed and non-transcribed DNA strands of the p53 gene when compared to never users.
Conclusion: Our work is the first study to measure DNA damage in e-cig users. Our study shows for the first time that e-cig users have significant levels of DNA damage in their oral mucosa epithelium. These data has major clinical implications and suggest that e-cig users might have an increased cancer risk. Further studies are urgently needed to expand these kind of studies and to characterize the molecular mechanisms underlying e-cig induced DNA damage which may leads to cancer.

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Objectives: With legalization of medical marijuana (MM) in Oklahoma and across the nation there is increasing pressure by providers to make recommendations. In the field of oncology, MM has a special place of interest with its potential for symptom management and palliation. However, the paucity of high quality evidence on MM and the lack of standardized training in professional schools may leave practitioners ill prepared for their patient's request. The specific aims of this study were to survey current oncology professionals at the Stephenson Cancer Center in Oklahoma City to assess attitudes, comfort, and interest of oncology professionals with regard to recommending MM as part of their oncology practice.

Methods: This is a cross-sectional survey of all oncology providers at the Stephenson Cancer Center (SCC) in Oklahoma City, OK. An electronic voluntary survey study was distributed to all medical and surgical adult and pediatric oncologists, palliative and supportive care cancer specialists, as well as physician extenders (PA/NP) and pharmacist affiliated with SCC. All survey data was collected using a REDCap survey tool. Relationships between categorical variables were assessed using Fisher's exact test.

Results: We identified 119 possible participants and had a response rate of (34%) n=41. A majority of oncology providers do have an interest in prescribing MM (70.7%) compared to having no interest or being unsure (30.3%). Even though there was a high interest in MM most felt they had insufficient knowledge to recommend MM (76.9%). Only (7.5%) of oncology providers felt they had a comprehensive knowledge of the new laws and (35%) of provider had no or limited knowledge of the laws. Providers in general are looking to SCC, University of Oklahoma or OK Medical Board to provide guidance in recommending MM. Most, (82%) of providers felt that there has been a modest to significant increase in patient interest in being prescribed MM since the passing of the new laws.

Potential areas of interest in symptom management for MM include poor appetite, nausea, chronic pain, and poor sleep. Within context of the opioid crisis, nearly half (45%) of respondents felt that MM could reduce polypharmacy and (69%) felt MM could be beneficial in decreasing opioid dependency in oncology treatments.

Conclusions: This study supported the fact that many providers were interested in prescribing or recommending MM. In the limited time since the new law changes providers are seeing a higher demand from patient requesting to be treated with MM. However providers feel ill prepared to counsel their patients appropriately. Most providers receive information from high quality peer
reviewed journals however there is relatively small amount of high quality evidence on the use of MM in the treatment of common medical issues associated with cancer and oncology treatments. Providers are looking to their programs and governing bodies to fill in the knowledge gaps. This study addresses the need for further high quality studies to guide the treatment of oncology related issues.
Noise Power Analyses of CMOS and CCD X-ray Detectors

Bradley Gregory, Muhammad Ghani, Hong Liu

The goal of this study was to investigate and compare the normalized noise power spectra (NNPS) of two x-ray detectors, CCD and CMOS based, with different dosages and binning techniques. NPS are important characteristics that model the noise density of detectors as a function of spatial frequency. A phase sensitive prototype was used to acquire images for NPS calculations. The prototype utilizes a microfocus x-ray tube and detector aligned on an optical rail. NNPS have so far been calculated for a x-ray flat panel detector with dosages of 0.38, 0.96, and 1.44 mGy with 1x1 pixel binning, as well as a 0.38 mGy dose with 2x2 binning. The source-to-object distance (SOD) was 68.58 cm while the source-to-image distance (SID) was 172.72 cm, resulting in a magnification of 2.5. A 5 cm thick uniform compressed breast-mimicking phantom was used for the experiments. The pixel pitches of the CMOS and CCD detectors are 50 μm and 22 μm, respectively. Preliminary results confirm the conventional wisdom that higher dosage reduces noise. Furthermore, the 2x2 binning experiment yielded a normalized NNPS that was very similar to the 1x1 experiment with the same dose, and perhaps even yielded slightly less noise. Further study will be required with different dosages to examine the effect of 2x2 binning on the NNPS in more detail. Experiments will also be conducted with a CCD camera, to compare its NNPS with that of the CMOS flat panel detector. The results will help to better understand how new x-ray imaging detectors’ NPS, and therefore their quantum efficiency (DQE), compare to those using older technology.

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IMPACT OF FINANCIAL ASSISTANCE PROGRAMS ON TIME TO COMPLETION OF THERAPY IN WOMEN RECEIVING CHEMORADIATION FOR CERVICAL CANCER

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Objective: To evaluate how social services programs improve outcomes amongst patients with cervical cancer undergoing chemoradiation.

Methods: This is a single institution, retrospective analysis of all patients receiving chemoradiation for squamous cell, adenocarcinoma, or adenosquamous cancer of the cervix from January 1, 2015-July 31, 2018. Demographic, clinical, and social services utilization data were collected. Descriptive statistics, univariate and multivariate analyses were performed. Kaplan-Meier curves were used to estimate progression free (PFS) and overall survival (OS).

Results: Of the 116 patients who met inclusion criteria, 106 (91.45%) completed therapy in ≤63 days. The median household income among patients was $45,782 ($19,771-$96,222). Patients, on average, used 1.24 services, including registration for disability and Medicaid, assistance with medication costs, financial assistance, access to emergency funds, access to low cost or free lodging, and transportation. Only disability registration was associated with improved time to completion of therapy (p<0.001), however registration for federally funded breast and cervical cancer Medicaid demonstrated a trend toward ability to complete therapy in ≤63 days (p=0.06). When compared to high-income patients who did not require assistance, low-income patients (those whose household income was less than the median) who received assistance from the cancer center did not experience a significantly different median PFS or median OS (11.2 vs 12.1 mo, p=0.495 and 16.2 vs 15.3mo, p=0.098). Low-income patients receiving assistance were also able to complete therapy in a similar timeframe as their higher income counterparts (56.5 vs 50 days, p=0.11).

Conclusions: In a rural state with a single academic cancer center, our data demonstrate that we may be able to overcome barriers to care with social and financial assistance programs. Identifying individual patient’s needs prior to therapy may allow for continued improvement in therapy compliance and patient outcomes.

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TARGETED PHOTOTHERMAL ABLATION OF BREAST CANCER COMBINED WITH IMMUNOSTIMULATION

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The anionic aminophospholipid phosphatidylserine (Ptd-L-Ser) is actively sequestered to the inner leaflet of the plasma membrane of healthy cells. In a tumor, this tightly regulated Ptd-L-Ser membrane asymmetry breaks down, and Ptd-L-Ser is expressed on the outer leaflet of cancerous cells and the tumor vascular endothelium. The presence of Ptd-L-Ser solely within the tumor serves as a tumor specific antigen which can be used in targeted therapeutics. We employ the natural ligand of Ptd-L-Ser, annexin V (ANXA5), in a protein-nanoparticle conjugate to sensitize tumors to photothermal ablation. The targeted ablation of the tumor in conjunction with the anti-CTLA-4 monoclonal antibody immunotherapy generates a powerful in situ cancer vaccine creating a robust systemic immune response rejecting tumor metastasis. Anti-CTLA-4 is an immune checkpoint inhibitor.

Mice with orthotopic syngeneic EMT6 breast tumors (d ≥ 5 mm) were administered an intravenous systemic dose of the conjugate of single-walled carbon nanotubes and ANXA5, which localized to tumor vasculature. Tumors were then irradiated with near-infrared light (980 nm) for 175 s at a power density of 1 W cm². Mice additionally received three doses of 200 μg of the immunostimulant anti-CTLA-4. The low energy NIR laser does not harm healthy tissue but rapidly generates temperatures near 60° C within the tumor. This temperature is sufficient to instantly destroy cancerous cells. The addition of anti-CTLA-4 immunotherapy in conjunction with this targeted photothermal ablation modality resulted in a significant synergistic increase (p < 0.001) in helper T cells (CD4+) and cytotoxic/suppressor (CD8+) in the spleen when compared to photothermal or immunostimulatory monotherapy. This increase in tumor effector cells led to tumor rejection. The combination of immunostimulation and targeted photothermal therapy led to significant increases in animal survival with more than half of all animals found to be tumor free at the conclusion of the study (120 days), at which time all of the animals in the control groups had died.

Sources of funding: Oklahoma Center for the Advancement of Science and Technology; Jean Wheeler and Baxter Abbott Sparks Breast Cancer Research Fund at the University of Oklahoma Foundation
The MYC oncogene is commonly dysregulated in cancer and has well established links to several kinds of lymphoid leukemia. MYC is hyperactive in many and diverse leukemias, so pathways that cooperate with MYC are putative targets for many human lymphocyte cancers, as well as other malignancies. Zebrafish provide a genetically-tractable model organism to study leukemia that possess conserved oncogenic pathways and anatomic structures, with identical types of lymphocytes as in humans. The first zebrafish cancer model was created 15 years ago by expressing murine Myc (mMyc) under the control of a zebrafish rag2 promoter, which potently induced T cell acute lymphoblastic leukemia (T-ALL). Subsequent mMyc and human MYC (hMYC) transgenic models further enhanced our understanding of T-ALL. Recently, we discovered that double-transgenic fish (rag2:hMYC, lck:eGFP) develop B cell ALL (B-ALL) in addition to T-ALL. While lck is highly expressed by T cells, in fact, other adaptive lymphoid (B cells), innate lymphoid (ILCs and NK cells), and even myeloid cells also express lck. Thus, we can use lck:eGFP fish (with or without hMYC) to study many leukocyte populations prior to the onset of ALL. We hypothesize that MYC, when regulated by the rag2 promoter, alters the development of multiple lymphoid cell types in terms of their quantity, identity, and gene expression patterns even before B- or T-ALL occur. To test this, we are quantifying B and T cells at different developmental stages from primary (thymus and marrow) and secondary (spleen) lymphoid organs. We are comparing double-transgenic rag2:hMYC, lck:eGFP fish at early pre-leukemic stages to wild-type (WT) single-transgenic lck:eGFP fish by flow cytometry, FACS, qRT-PCR, and RNA sequencing. Our results suggest that lymphoid hyperplasia exists in all pre-leukemic hMYC fish, including hyperplasia of thymic B cells, a rare population in WT fish. The ultimate goal of this project is to identify molecular mechanisms that allow MYC-induced lymphoid hyperplasia to advance to outright B- and T-ALL. Doing so will reveal key pathways that cooperate with MYC in ALL transformation, serving as new therapeutic targets.

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TOBACCO ADVERTISING EXPOSURE AND SMOKING AMONG INDIVIDUALS PARTICIPATING IN A SMOKING CESATION PROGRAM: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

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Significance: Research has demonstrated a causal relationship between tobacco advertising and tobacco use. However, the assessment of exposure to tobacco advertising has been limited by recall bias and indirect estimates of exposure such as brand recognition. The purpose of this study was to examine the association between daily tobacco advertising exposure reported via ecological momentary assessment (EMA) and smoking among individuals undergoing a quit attempt.

Methods: Participants were socioeconomically disadvantaged adults participating in a clinic-based smoking cessation program. Participants were prompted to complete 5 daily EMAs each day from 1 week pre-quit to 4 weeks post-quit. Daily EMAs evaluated smoking, mood, environmental context, and exposure to tobacco advertising. Generalized linear mixed models were conducted to evaluate the relationship between same-day tobacco advertising exposure and smoking in the pre- and post-quit periods. Models were adjusted for gender, age, race, education level, treatment group, and heaviness of smoking at baseline.

Results: Participants (N=106) were primarily female (64.2%), white (59.4%), and 48.2 years old (SD=13.2). On average, participants saw a total of 16.4 (SD = 25.9) tobacco ads during the study period. A majority of ads (41.5%) were seen at the point of sale (POS, i.e., convenience store, supermarket, or gas station). The odds of smoking in a given day increased by a factor of 2.3 (95% CI =1.2, 4.2) for each tobacco ad viewed in the pre-quit period, and by a factor of 1.2 (95% CI=1.04, 1.4) in the post-quit period. For ads seen at the POS, the odds of smoking increased by a factor of 3.1 (95% CI = 1.9, 5.2) for each ad viewed during post-quit, but the relationship was not significant for POS ad exposure pre-quit.

Conclusion: Exposure to tobacco advertising is associated with daily smoking among individuals participating in tobacco cessation treatment. In particular, ads seen at the POS are associated with smoking lapse during the post-quit period. Smoking cessation interventions may benefit from educating patients about the importance of avoiding tobacco retail outlets or coping with ad-driven cues to smoke.

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TWO WEEKS OF HI-FIVE EXERCISE AND DIET PREHABILITATION IMPROVES PHYSICAL FUNCTION BEFORE PANCREATICODUODENECTOMY: RESULTS OF A PILOT RCT

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Introduction: Sarcopenia (low muscle mass & function) predicts worse outcomes in pancreatic cancer (PanC), including 63% higher 3-year mortality. Pancreaticoduodenectomy (PD) is the only chance at PanC cure, but skeletal muscle catabolism initiated by PanC is compounded by PD surgery and hospitalization; post-operative sarcopenic frailty threatens the quality of an extended life. In esophageal, colorectal, and bladder cancers, exercise & nutrition before surgery (‘prehab’) mitigates post-op functional decline. PanC prehab studies target patients starting months of neo-adjuvant chemo; 1-2 weeks to surgery is assumed insufficient time to benefit. But we hypothesized that optimally-dosed prehab could improve muscle mass and function in only 2 weeks, even amidst PanC sarcopenia, and gains could sustain post-operatively. Toward this goal, we developed HI-FiVE-PD ‘bolus-dosed’ prehab.

Purpose: We aim to quantify pre-operative changes in physical function after 2 weeks of HI-FiVE-PD in PanC.

Materials/Methods: Patients with PanC and related diagnoses scheduled for PD in 2 weeks were enrolled in this 2-arm pilot RCT if cleared for exercise, independent with household mobility (ECOG PS 0-2) and not exercising regularly. After baseline testing (V1), each met with a dietitian for high protein counseling, and a physical therapist for HI-FiVE-PD home exercise instruction. Prescriptions were personalized, but the only distinction between Groups (GR) was Resistance (S). GR S (Resistance) & N (No resistance) both received endurance & arm/leg exercise, protein supplement, exercise equipment, daily adherence log, and 1-2 phone calls over the 2-wk intervention. Measures of physical function [Handgrip Strength (HGS), Gait Speed (GS), Sit-to-Stands (StS)] were repeated 1-2 days pre-op (V2), by a masked assessor. Pooled performance was compared from V1 to V2, by paired t-test. Change was compared between GR S&N by 2-samples t-test.
Results: 32 participants (67.2 ± 10.6 yrs; 47% female; 3.1% black, 3.1% Amer Indian, 3.1% Hispanic) were included. Physical function did not differ between GR S & N at baseline (V1). In pooled analyses, V1-V2 change was significant for HGS (mean 2.2 ± 2.8 kg; Range -2.0, 8.2; p=0.002) & StS (-1.0 ± 1.6 s; -4.3, 1.8; p=0.003). GS approached significance (0.1 ± 0.1 m/s; -0.2, 0.4; p=0.059). At V2, StS change trended toward clinical benefit for resistance (-1.3 ± 1.3 s GR S vs -0.5 ± 2.0 s GR N).

Discussion: Physical function improved before PD, with only 2-weeks of HI-FiVE prehab, in a cancer known for muscle catabolism. We plan mechanistic analyses to test sarcopenia markers as mediators & moderators of this improvement, and a larger study for full-power between-groups comparisons of sustained post-op benefit in QOL, function, complications, and survival, to isolate the impact of resistance training (S) in the HI-FiVE-PD prescription. Pilot results suggest that patients with resectable tumors who are refused PD for “borderline fitness” could be fitO for surgery with 2 wks of optimal prehab.

Acknowledgement of Funding: Presbyterian Health Foundation Clinical Scientist Development Award (PI: Hile, Mentor: Li), TSET

Key words: Pancreatic cancer, sarcopenia, physical function, prehabilitation, exercise, nutrition
**THE IMPACT OF TIME TO SURGERY ON PATHOLOGIC STAGING OF INVASIVE BREAST CANCER**

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Upstaging, defined as an increase in tumor size or nodal involvement at the time of pathologic staging, has been shown to increase cancer morbidity and mortality. A review of current literature suggests that larger or palpable tumor, higher histological grade, presence of a palpable mass, use of core needle biopsy rather than vacuum-assisted biopsy, and pleomorphic calcifications are all factors consistently and significantly associated with breast tumor upstaging. However, existing studies focus heavily on the upstaging of DCIS, and the influence of other factors such as surgical delay on upstaging have not been explored.

The average time to surgical intervention from initial tumor biopsy among breast cancer patients has been steadily increasing since the 1990s. This increase in time to surgery (TTS) is present across all racial groups and among patients with all insurance types. While no clinical guideline exists regarding an acceptable interval between breast cancer diagnosis and surgical treatment, prolonged delays in TTS can have negative prognostic significance for patients with breast cancer.

We analyzed the prevalence of upstaging among women diagnosed with clinical stage I breast cancer between 2010 and 2015 using the National Cancer Database. Adjusted logistic regression models were used to examine the relationship between socioeconomic and clinical factors and pathologic upstaging (stage group, tumor size, and node involvement). Multivariable analysis revealed a significant association between increasing TTS and pathologic upstaging of breast tumors.

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ADHERENCE TO EXERCISE & DIET PREHABILITATION IN PANCREATICODUODENECTOMY: RESULTS FROM A FEASIBILITY RCT SUGGEST A CRITICAL WINDOW FOR BEHAVIORAL CHANGE

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Introduction: Pancreatic cancer (PanC) 5-year survival is 8.5%, and incidence & death rates are rising. Surgical resection is the only cure, but post-operative complications threaten quality & quantity of life in 40-70% of survivors after pancreaticoduodenectomy (PD). Pre-operative rehabilitation ('prehab') may improve outcomes, but there is no standard prescription in PanC, and behavioral approaches require adherence for efficacy. We designed ‘bolus-dosed’ prehab with High-Frequency High-Volume Exercise (HI-FiVE) for the 2-week window to PD.

Purpose: To quantify adherence to HI-FiVE-PD exercise & protein prescriptions, in a 2-arm feasibility RCT. We anticipated lower exercise adherence in PanC than is published in less lethal cancers.

Materials/Methods: PanC survivors were eligible if scheduled for PD in ~2 wks, independent with household mobility (ECOG PS = 0-2), and cleared by the surgeon for HI-FiVE. Nutrition intervention was personalized counseling for 1.3-1.5 g of daily protein/kg of body weight, using whey protein supplement in Wk 1 & immune drinks in Week 2. After randomization, survivors met with a physical therapist for individual instruction in moderate intensity daily home exercise of endurance training, plus 8 arm/leg exercises. Intervention differed by group only in the specifics of arm/leg exercise; Group S used Resistance, and Group N performed Active motion. Participants in both groups received protein supplement, exercise equipment, a daily adherence log, and 1-2 phone calls; phone data supplemented daily adherence logs when necessary. Adherence (%) was calculated for Exercise as: days performed / total days in intervention period, and for Protein as: whey scoops (alt: immune drinks) consumed / total scoops (drinks) prescribed, and transformed to a 3-category scale: 75-100% = Full, 50-74% = Moderate (Mod), <50% = Minimal (Min) for correlations by Kendall’s Tau. Dichotomous categories (Full vs Mod/Min) were used to compare between-groups by Fisher’s Exact Test (SPSS).

Results: Pooled exercise adherence data for 40 PanC participants (66.6 ± 12.0 yrs, 45% female, 87.3% white/ 6.4% Amer Indian/ 4.3% black, 2% Hispanic) as Full/Mod/Min = 75.0% / 10.0% / 15.0% for Endurance; 80% / 7.5% / 12.5% Min for Arm/leg Exercise. Adherence to Resistive Arm/leg Ex (Gr S, n=22), was
81.8% / 9.1% / 9.1%, and did not differ \((p=0.528)\) from Gr N Active Arm/leg Ex. Pooled protein adherence = 50.0% Full / 26.5% Mod / 23.5% Min to Week 1 whey; 72.2% / 13.9% / 13.9% to Week 2 drinks; and did not differ by S or N Group \((p=1.0 \text{ whey}; p=0.72 \text{ drinks})\). Exercise adherence and protein adherence did not correlate \((\tau=0.014-0.194; p>0.05)\).

**Discussion:** Exercise adherence was higher than anticipated in resectable PanC. Co-survivor support, home program, and brief pre-op window were facilitators. Caregiver status was a barrier. Adherence to whey protein was lower, but some survivors increased protein through whole foods, a more sustainable approach. PanC survivors are motivated to make short-term behavioral change before PD.

**Acknowledgement of Funding:** Presbyterian Health Foundation Clinical Scientist Development Award (PI: Hile, Mentor: Li), TSET

**Key words:** Pancreatic cancer, prehabilitation, exercise, nutrition, adherence
CHEROKEE NATION HEALTH ANALYTICS CORE

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Cherokee Nation and the University of Oklahoma Health Sciences Center (OUHSC) are collaborating on a National Institutes of Health-funded Native American Research Center for Health (NARCH) grant. The Cherokee Nation and OUHSC have partnered since the year 2000 to develop the capacity of Cherokee Nation to reduce health disparities, support the cancer surveillance system through data linkages, and support clinical service delivery. The age-adjusted cancer incidence among Oklahoma American Indians (584.5 per 100,000) was higher than the Oklahoma white population (442.0 per 100,000), and US white (466.5 per 100,000) and American Indian (295.8 per 100,000) populations from 2011-2015.

The Cherokee Nation Cancer Registry (CNCR) is the first and only tribally-operated population-based Surveillance Epidemiology and End Results (SEER) cancer registry in the US. The CNCR is used to monitor incidence and mortality of cancer among American Indians in the Cherokee Nation and provides opportunities for research. However, like most registries, CNCR lacks important behavioral risk factors, comorbidities, and detailed treatment and follow-up data. The NARCH project aims to build research capacity at Cherokee Nation through development of the Cherokee Nation Health Analytics Core (CNHAC) and a pilot research project on breast cancer patterns of care and outcomes by diabetes status among American Indians.

The CNHAC staff will conduct a data linkage between the Cherokee Nation Cancer Registry (CNCR) and the Cherokee Nation electronic medical record (EMR) to examine health behaviors, disease status, and cancer outcomes for future research studies. Through ongoing linkages with the Oklahoma Central Cancer Registry and planned linkages with the EMR, we will be able to evaluate breast cancer patterns of care among American Indians in Cherokee Nation and evaluate whether the prognosis of breast cancer in women with type 2 diabetes is worse than women without this condition.

We have worked to establish infrastructure for the CNHAC, including the hiring of three staff members at Cherokee Nation. We have also developed policies and procedures for accessing and linking databases across Cherokee Nation. We are working closely with Cherokee Nation Information Technology and the Governing Board to ensure data security and patient confidentiality are maintained. In addition, we have developed an initial cancer report for the
Cherokee Nation community including information on incidence, survival, and stage of cancer at diagnosis using data from the CNCR. As next steps, we plan to conduct the linkage between CNCR and the EMR. In the future, we will continue validating linkages and data completeness and conduct feasibility studies to better understand what research questions can be addressed using the registry and EMR linkages. We will also continue building a comprehensive data repository and capacity for research and explore other comorbidities and cancers to address health disparities.

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It is estimated that more than 3 million people in the United States are diagnosed with nonmelanoma skin cancer each year. These common cancers are often highly curable, especially when diagnosed early and appropriately. In order to ensure the appropriate diagnosis, it is important that the current literature remain updated on cutaneous findings that can mimic skin cancers. Squamous cell carcinoma (SCC) is known to be difficult to differentiate histologically from a variety of other entities including inverted follicular keratosis, warty dyskeratoma, epitheliomatous hyperplasia, hypertrophic lichen planus, verruca vulgaris, and some metastatic carcinomas (Tan et al., 2013).

We present a 63 year old Caucasian man with Darier’s disease who was referred to our Mohs surgery clinic with a diagnosis of a large SCC on his nasal sidewall. Darier’s disease is an autosomal dominant disorder caused by a mutation of the ATP2A2 gene which encodes SERCA2. Clinical findings associated with Darier’s disease include hyperkeratotic papules, acrokeratosis verruciformis of Hopf, palmar keratosis, red and white alternating bands of the nails, v-nicking of the nails, and cobblestoning of the oral and anogenital mucosa. The biopsy performed on the nasal side wall was read by a dermatopathologist as “atypical squamous proliferation with acantholysis, indicating superficially invasive carcinoma”. Prior to proceeding with Mohs surgery, the pathology was again reviewed and was noted to have areas of suprabasilar acantholysis with dyskeratosis, corps ronds and columns of parakeratosis (grains), histologic findings consistent with Darier’s disease. A large surgery and nasal reconstruction was avoided for the patient.

This case highlights the importance of having sufficient clinical information when interpreting skin biopsies. This is not the first time patients with Darier disease have been misdiagnosed with a skin cancer. A recent case report published in Ophthalmic Plastic & Reconstructive Surgery described Darier’s disease mimicking basal cell carcinoma of the eyelid (Russel et al., 2009). Of note, there are case reports of patients with Darier disease developing nonmelanoma skin cancer, and these patients should still undergo appropriate skin checks, biopsies, and skin cancer treatments as clinically indicated (Matsui et al., 2009).

Citations


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PERIPHERAL AND CENTRAL EFFECTS OF IGF-1: ROLE IN CANCER AND COGNITION

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A decline in circulating levels of insulin-like growth factor-1 (IGF-1) is closely associated with reduced cognitive function with age, as well as increased propensity to develop neurodegenerative disorders. Early-life IGF-1 deficiency increases lifespan in rodent models, in-part by reducing cancer incidence. Yet, the effects of IGF-1 on healthspan, age-related pathology and/or lifespan remain controversial. In this study, we investigated the central and peripheral effects of circulating IGF-1 deficiency later in life (5 and 15 months) on pathological outcomes, cognitive performance through assessment of learning and memory correlates, and tissue mitochondrial function. We reduced circulating levels of IGF-1 via AAV-Cre mediated knockdown of liver IGF-1 in \textit{Igf}\textsuperscript{-/-} mice. Cognitive function was evaluated using the radial arm water maze and Barnes maze. Our results indicate that early-life IGF-1 deficiency reduced cancer risk and increased lifespan in females whereas no effect was observed in males. More importantly, IGF-1 deficiency impaired cognitive performance in male mice. These behavioral data correlated with decreased brain ATP levels and reduced hippocampal mitochondrial OXPHOS coupling efficiency while no differences were observed on muscle mitochondrial function albeit fat metabolism was increased. These data indicate that peripheral effects of IGF-1 mediates cancer risk and progression with age, while in the central nervous system IGF-1 is critical for spatial learning and hippocampal mitochondrial function.

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A MECHANISM FOR EPIGENETIC CONTROL OF DNA REPLICATION

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DNA replication origins in hyperacetylated euchromatin fire preferentially during early S-phase. However, how acetylation controls DNA replication timing is unknown. TICRR is an essential protein required for the initiation of DNA replication. Here, we report that TICRR physically interacts with the acetyl-histone binding Bromodomain and Extra-terminal (BET) proteins BRD2 and BRD4. Abrogation of this interaction impairs TICRR binding to acetylated chromatin and disrupts normal S-phase progression. Our data reveal a novel function for BET proteins and establish the TICRR-BET interaction as a potential mechanism for epigenetic control of DNA replication.

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Background and Aim: Are electronic cigarettes (ECs) safer than combustible tobacco? No one knows the answer yet. ECs are devices that deliver an aerosol from a heated mixture of propylene glycol, vegetable glycerin, and flavors with or without nicotine. Short-term EC studies are mostly limited and inconclusive. Despite unknown long-term health effects, the use of ECs has increased alarmingly over the past decade. ECs aerosols contain unique chemicals in addition to other chemicals similar to those found in tobacco smoke. Tobacco smoking during cancer treatment has been associated with increased drug resistance and reduced overall survival rate. The awareness of the dangers of cigarette smoking and the paucity of studies evaluating the safety of ECs pose a dilemma for cancer patients who might be considering switching to ECs during chemotherapy. Here, we sought to examine the effects of EC aerosol extracts exposure on cell survival in oral cancer cells during cisplatin treatment.

Methods: EC aerosol extracts were collected from two brands of ECs as previously described. Mainstream tobacco smoke (MS) extract was used as a positive control. To evaluate clonogenic survival after cisplatin treatment, oral cancer cells were exposed for 48 h to EC aerosol extracts at nicotine doses comparable to those observed in EC users. Next, cells were treated with both EC aerosol extracts and cisplatin (or vehicle-control) for another 48 h. After treatment, cells were counted and seeded in 6-well plates and colony formation was assessed two weeks later. Colonies were fixed with methanol followed by staining with 0.5% crystal violet in 25% methanol and counted manually. Only colonies with at least 50 cells were counted. Data were analyzed by Student’s t-tests and one-way analysis of variance (ANOVA).

Results: After cisplatin treatment, cells exposed to EC aerosol extracts showed a significant increase in clonogenic survival fraction compared to vehicle-control treated cells. Furthermore, cells exposed to EC aerosol extracts formed visibly larger colonies. An increase in clonogenic survival was also observed in MS extract-treated cells.

Conclusions: Collectively, our data suggest that short-term exposure to EC aerosol can induce cisplatin resistance in oral cancer cells, thus allowing the cells to survive and form colonies. These findings are particularly important in paving the way to understanding whether ECs are a safer alternative for oral cancer patients undergoing chemotherapy.
Grant support: This work was supported by the Oklahoma Tobacco Research Center, NIH/NCI (R33, R01), OCAST, and the Presbyterian Health Foundation. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.
A PARTNERSHIP TO OPTIMIZE SMOKING CESSATION WITHIN DIABETES CARE
AT THE CHEROKEE NATION

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Overview: The Cherokee Nation and University of Oklahoma Health Sciences Center (OUHSC) have partnered together on a National Institutes of Health-funded Native American Research Center for Health (NARCH) grant to examine the complex relationship between smoking and type 2 diabetes (T2D) among American Indians (AIs) in an effort to design and pilot test a tailored smoking cessation intervention.

Background: AIs suffer a disproportionate burden of commercial tobacco-related disease and have the highest T2D prevalence of any racial group. The harms of smoking are particularly profound among individuals with T2D who continue to smoke, with an accelerated progression of microvascular and macrovascular complications and an increased risk of several types of cancers. Smoking cessation is recommended as a standard treatment of T2D; however, patients with T2D and their providers are often inundated with other challenging lifestyle changes and disease management strategies. Due to the large number of competing lifestyle changes recommended at diagnosis, smokers with T2D may benefit from a tailored smoking cessation intervention that integrates tobacco education within the context of T2D care (e.g. diabetes-specific information on risks, addressing concerns of weight gain, coordinating lifestyle changes simultaneously or sequentially). Through a mixed-methods study, we will identify the perceived risks of smoking and facilitators and barriers to smoking cessation among Cherokee Nation patients with T2D as reported by both patients and providers. We will then determine the feasibility, acceptability, and potential effectiveness of a tailored smoking cessation intervention coordinated within T2D care.

Study Design: Using a mixed-methods study design, we will conduct surveys and semi-structured interviews with both providers and patients to understand barriers to cessation using the Capability, Opportunity, Motivation, and Behavior (COM-B) model with the Behavior Change Wheel. Based on community input and the COM-B framework, we will select the most appropriate and evidence-based intervention component(s) that will address the primary barriers identified. To evaluate feasibility and adherence to the protocol, we will use mobile-based real-time ecological momentary assessments (EMA) throughout the study. Daily assessments will capture urges to smoke, stress, motivation, exposure to secondhand smoke and other triggers, and abstinence or relapse.
Expected Outcomes: With the results from the pilot study, we expect to better understand the feasibility and acceptability of the designed intervention in this study population as well as the benefits or challenges with using the mobile technology in this setting. We hope to gather evidence of potential health systems changes that will allow Cherokee Nation to optimize smoking cessation within their diabetes management program.

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Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system. The prognosis for GBM continues to be poor with a median overall survival between 14 and 22 months from initial diagnosis. Current treatment consists of maximum safe surgical resection, concurrent radiation therapy and chemotherapy (temozolomide) followed by adjuvant temozolomide which extends median overall survival to about 14.5 months, with a 5-year survival rate of less than 10%. Over the last half-decade rapid advances in nanotechnology have spawned a new generation of engineered nanoparticles with promising antineoplastic activity. Employing one such nanoparticle, single-walled carbon nanotubes (6,5-chiral enrichment ≥ 99.7%), in conjunction with several clinically relevant treatment modalities, we hypothesize that there is a synergistic antineoplastic activity of SWCNTs with chemotherapy in the U251, U87 and LN222 models of GBM. Here, we present data evaluating the use of SWCNTs and temozolomide therapy to increase tumor cell kill, prevent tumor cell migration, and sensitize tumor cells to ionizing radiation.
CHARLSON COMORBIDITY INDEX AS PREDICTOR OF POOR SURGICAL OUTCOMES IN PATIENTS UNDERGOING MINIMALLY INVASIVE Hysterectomy BY GYNECOLOGIC ONCOLOGISTS

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Objective: To determine whether the validated Charlson comorbidity index (CCI) and other preoperative assessments are predictive in poor surgical outcomes in women undergoing minimally invasive hysterectomy by gynecologic oncologists.

Methods: Patients undergoing minimally invasive (MIS) hysterectomy for both benign and gynecologic cancer indications between January 2008 and July 2018 were reviewed. The CCI, performance status, body mass index (BMI) were pre-operative measures of interest. Post-operative complications were defined as conversion to laparotomy, viscus injury, prolonged admission, 30-day readmission, reoperation, ICU stay or death, and post-operative infections and/or venous thrombotic events (VTE). Factors were tested for significant differences between patients with and without complications using T and chi-squared testing for univariate analysis for association, with a p<0.05.

Results: The study included 206 patients, 49 of which had surgical or post-operative complications. Baseline characteristics were not statistically different. In all patients, regardless of post-operative diagnosis (benign vs. malignant), the CCI was higher among patients with complications (p=0.04). The optimal cutoff point for CCI was 6, based on the Youden index; a CCI of \( \geq 6 \) indicated a higher risk of post-operative complication. In a logistic regression model with both CCI and performance status as covariates, CCI was significantly associated with post-operative complication (0.036), however performance status was not (0.93). CCI and hospital stay were positively correlated; a 1-unit increase in CCI was associated with a 7.8% increase in hospital stay (p<0.001).

For patients in whom malignancy was diagnosed (79.6%), CCI was higher among patients with post-operative complication (0.045). The optimal cutoff point was again 6; a CCI of \( \geq 6 \) indicated a higher risk of post-operative complication. In a logistic regression model with CCI and performance status as co-variates, CCI was significantly associated with post-operative complication (p=0.03), but performance status was not
A 1-unit increase in Charlson score was associated with a 0.3% increase in hospital stay (p<0.001).

Conclusions: Gynecologic oncologists frequently serve as referents for women with gynecologic malignancy but also for complex surgical candidates with possible benign disease. A CCI of ≥ 6 indicates a higher risk of post-operative complication in patients undergoing MIS independent of the presence of malignancy. CCI is also associated with an increase in hospital stay. The frequently utilized performance status does not indicate a higher risk of post-operative complications. Integration of CCI as a pre-operative counseling tool for gynecologic oncology patients undergoing planned minimally invasive surgery should be routinely considered.

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Impact of Flavors and Sweeteners on Waterpipe Tobacco Smoking Topography, Abuse Liability, Toxicant Exposure, and Intentions for Continued Use

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Introduction: Waterpipe tobacco (WT) smoking is proliferating in the US. One possible reason for the increase in WT smoking is the inclusion of flavors and sweeteners in the tobacco. No study has examined what effect the removal of flavors and sweeteners from WT would have on users’ smoking patterns, abuse liability, behavioral intentions for continued use, and toxicant exposure.

Methods: In a randomized crossover design, WP smokers (N=89, 59% male, M_age=24.2 years) completed four smoking sessions, each separated by a 48-hr washout period. Each session used a different WT flavoring preparation [flavored + sweetened (FS); flavored + unsweetened (FU); unflavored + sweetened (US); unflavored + unsweetened (UU)] and included a 10-puff standardized puffing bout followed by a 1-hour ad libitum WT smoking session. Study visits were completed in dyads. Participants completed post-session measures assessing WT abuse liability, behavioral intentions for continued use, exhaled carbon monoxide (eCO) and nicotine boost; waterpipe puff topography was measured continuously throughout the session. Results: 93% of participants reported that the first time they smoked waterpipe the tobacco was flavored. For all measures of drug liking/satisfaction, the FS tobacco was rated significantly higher than all other unflavored preparations, with the UU tobacco preferred the least (all p<.05). Participants’ intentions for continued use were lowest for the UU preparation, with only 50%, 41%, and 19% of participants reporting that they were ‘likely’ to “try this product again”, “pay to smoke this product at a waterpipe lounge”, or “use this product regularly”, respectively. Significant differences in puff topography were observed during standardized and ad libitum sessions, with the UU preparation leading to greater total inhaled volume and eCO boost, but lower nicotine boost compared to the FS preparation (all p<.05). Conclusions: The current study suggests that flavors and sweeteners from waterpipe tobacco significantly influence the product’s abuse liability, users’ reported willingness/interest for continued use, puff topography, and exposure to tobacco toxicants.
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THE EFFECT OF A UNIVERSITY-WIDE BAN OF ELECTRONIC CIGARETTES ON TOBACCO USE PATTERNS

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INTRODUCTION: Electronic cigarettes (ECs) have increased in popularity since they entered the market, particularly among college students. Many college campuses implement EC use bans within smoke-free policies, but there are concerns individuals will begin to use other tobacco products in the wake of these bans. However, the effects of these regulations are unknown. The current study examined changes in tobacco use patterns and perceived product harmfulness following a university-wide ban of ECs.

METHODS: Participants were 1,727 undergraduate students (Mage = 19.48, SD = 2.06; 66.7% women) attending a large Midwestern university. Participants self-selected to participate via the university’s online research pool system. Self-report measures were administered through an online questionnaire assessing demographics, smoking/vaping prevalence, and perceived product harmfulness. Data were collected in the fall semesters of: 2013 (pre-ban), 2014, 2015, and 2016 (post-ban). Participants were grouped by tobacco use status (never users vs. triers vs. occasional users vs. daily users).

RESULTS: Results suggested the proportion of never EC users significantly decreased from pre-ban to 3 years post-ban ($p = .004$). During the same time, the proportion of daily users remained relatively stable while the proportion of EC triers increased significantly. Alternatively, for all other tobacco products, the proportion of never users increased significantly while daily use either decreased or remained stable (all $p < .05$). Perceived absolute harmfulness of ECs and cigarettes increased each year following the ban (all $p < .001$).

DISCUSSION: The current study is one of the first to examine use patterns of ECs following a campus-wide ban. Results suggest the ban did not result in significant decreases in EC daily use but did result in decreases in other tobacco use. This pattern of results demonstrates institutional bans of all tobacco products including ECs have a positive public health impact. Future directions include following up on the ban to observe if the findings from this study are maintained long-term.

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Investigation of Anti-Cancer BH3-Mimetic Drugs ABT-199 and A-1210477 as Leads for Developing Anti-Apoptotic Small Molecules

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Downregulation of apoptosis is a critical component of oncogenesis and therapy resistance. However, anti-cancer therapies also induce significant off-target cell death. The intrinsic pathway of apoptosis is governed by the Bcl-2 family of proteins, composed of pro-survival (Bcl-2, Mcl-1, Bcl-XL, etc.), pro-death (BAX, BAK), and BH3-only proteins (tBID, BIM, NOXA, etc). When pro-survival proteins are inhibited they can no longer prevent pro-death proteins from forming pores in the mitochondrial outer membrane (MOM), irreversibly committing the cell to death. Pro-survival proteins are often upregulated in tumor cells, making them attractive drug targets. Venetoclax (ABT-199) is an efficacious anti-cancer drug that inhibits Bcl-2 by mimicking its BH3-only protein ligands. Other BH3-mimetics targeting Bcl-XL or Mcl-1 are in clinical trials. However, since excessive cell death is implicated in pathologies such as neurodegeneration, there is need for apoptosis-mitigating drugs, which could also potentially prevent off-target apoptosis from anti-cancer therapies. Pro-survival and pro-apoptotic proteins share a conserved BH3-binding pocket essential for their function. Therefore, we use existing BH3-mimetic Bcl-2 and Mcl-1 inhibitors—ABT-199 and A-1210477, respectively—as leading compounds to develop small molecules that target BAK via their BH3-binding pockets. We use an in-vitro fluorescence-based assay to measure these drugs’ ability to impede BAK’s ability to permeabilize MOM-mimicking membranes. Our results suggest that these BH3-mimetics can inhibit BAK’s membrane-permeabilizing activity in the absence of Bcl-2 or Mcl-1, albeit at higher concentrations than required for inhibiting the pro-survival proteins. We suspect that these drugs compete with tBID for BAK’s BH3-binding groove. Therefore, we use Rosetta-based docking software to identify BAK mutations that can nullify ABT-199 and A-1210477’s, but not tBID’s, ability to bind with BAK. Future directions include testing these mutants in a membrane permeabilization assay and verifying the predicted binding sites for the compounds using crosslinking and co-crystallization/structure determination of the BAK-compound complexes.

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Preferences for Electronic Nicotine Delivery Systems among Young Adults: Results from an Online Discrete Choice Experiment

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Objective: To examine the impacts of flavor, device types, and health warning messages on young adult preferences for electronic nicotine delivery systems (ENDS).

Methods: In May 2016, using an online panel, we conducted an online discrete choice experiment (DCE) among a convenience sample of 400 young adults aged 18-24. We gave each study participant 9 choice sets and asked them to choose from either two hypothetical ENDS products or not using any ENDS. If the participants had ever used ENDS, they were given an additional choice of their most-used ENDS products. To measure participants’ willingness-to-pay (WTP), prices of devices and refills, varying at different levels, were also provided along with three attributes: flavor, device types, and health warning messages. Participants’ tobacco use history and their related behaviors following the experiment were also surveyed. The impacts of flavor, device types, and health warning messages on participants’ probability of choosing ENDS were examined using conditional logit regressions, while controlling for individuals’ socio-demographic characteristics and current smoking status.

Results:

We document that fruit/sweet/beverage and menthol flavors significantly increased the probability of choosing ENDS among young adult ENDS ever users. Higher prices of devices and refills also significantly decreased the probability of choosing ENDS. The effect of refill prices on ENDS use is more pronounced than the impact of device prices. The results further indicate a marginal WTP of $13 for fruit/sweet/beverage flavors and a marginal WTP of $6.42 for menthol flavor. Device types and health warning messages did not significantly influence ENDS choices among young adult ENDS never users.

Conclusions and Relevance: Flavors (i.e. menthol and fruit/sweet/beverage flavors) and device and refill prices are the main factors that influence the probability of choosing ENDS among young adults. Restricting flavors in ENDS and increasing device and refill prices may decrease the probability of choosing ENDS among young adult ever-users.

Keywords: Electronic Nicotine Delivery Systems (ENDS); Survey Research
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PHASE SENSITIVE X-RAY IMAGING IN BI-RADS TYPE 3 AND 4 BREASTS AND EVALUATING ITS PERFORMANCE IN CANCER DETECTION USING CDMAM PHANTOM

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Objective: Full filed digital mammography is widely accepted as first line screening tool for breast cancer detection. Phantoms such as contrast detail for mammography (CDMAM) or ACR accreditation phantom are generally used for image quality control of the physical and technical aspects of mammography. The aim of this study was to compare the performances and image qualities of conventional and phase sensitive x-ray imaging modalities, in relatively thick dense breasts under same Average Glandular Dose (AGD) using CDMAM phantom.

Method: CDMAM phantom with slabs of 70-30 glandular to adipose tissue ratio mimicking a 5 cm compressed breast was used in this study. We utilized the conventional mammography prototype, operating at 40 kVp, 300 μA and compared it with image of same object by phase contrast imaging prototype, operating at 90 kVp, 300 μA and M=2.5 with similar glandular dose of 1.6 mGy in both cases. Imaging systems were both consist of microfocus x-ray source and flat panel detector with pixel size of 50 μm. Visual observation study was conducted to quantitively analyze two systems’ performances.

Results: Phase contrast imaging system showed considerably higher correct observation ratio. The CD curves showed that both the contrast and spatial resolutions were higher for the phase contrast imaging. Additionally, image quality figure (IGF) was lower in phase contrast imaging which it results in higher Figure of Merit (FOM) for this technique.

Conclusion: Phase contrast imaging system can be imaging modality of choice for early cancer detection in breast screening, specifically, when the target population is women with relatively large breasts and/or with highly glandular breast tissue (BI-RADS type 3 and 4).

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QUITLINE TREATMENT ENROLLMENT, DOSE, AND CESSATION OUTCOMES AMONG SAFETY NET PATIENTS LINKED WITH TREATMENT VIA ASK–ADVISE–CONNECT: DIFFERENTIAL EFFICACY AMONG SPANISH– VS. ENGLISH–SPEAKING SMOKERS

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Most quitlines offer treatment in Spanish. However, little is known about the long-term efficacy of quitline-delivered treatment among Spanish-speaking smokers. This study is a secondary analysis of a 34-month implementation trial evaluating Ask-Advise-Connect (AAC) – an electronic health record (EHR)-based approach designed to facilitate enrollment in quitline-delivered treatment – in 13 community clinics serving low-income, racially/ethnically diverse patients in Houston, TX. Our goal was to compare treatment engagement, counseling dose received, and smoking abstinence among individuals who received treatment in Spanish versus English. Clinic staff were trained to Ask all patients about their smoking status, Advise all smokers to quit, and offer to immediately Connect smokers with treatment through a link within the EHR. Quitline treatment consisted of up to 5 proactive counseling calls. Outcomes included treatment engagement (i.e., enrollment in treatment), treatment dose (i.e., number of counseling calls completed), and biochemically confirmed, self-reported abstinence six months after enrollment.

The smoking status of 218,915 unique patients was assessed and recorded in the EHR. The preferred language for 95.2% of patients assessed was Spanish (n=102,146) or English (n=106,312). Among Spanish speakers, smoking prevalence was 8.4% (8,602/102,146). Among English speakers, smoking prevalence was 29.4% (31,264/106,312). The proportion of Spanish-speaking smokers who enrolled in treatment was 10.7% (924/8,602), and 78.5% of these individuals (725/924) agreed to be contacted for the 6-month follow-up. The proportion of English-speaking smokers who enrolled in treatment was 12.1% (3,785/31,264), and 78.1% of these individuals (2,957/3,785) agreed to be contacted for follow-up. Outcomes were examined among the subset of individuals who agreed to be contacted for follow-up. Among those who received treatment in Spanish, the median number of counseling calls completed was 2.26. Among those who received treatment in English, the
median number of counseling calls completed was 1.20. Among those who received treatment in Spanish, self-reported 7-day point prevalence abstinence was 25.1% (182/725), and biochemically confirmed abstinence was 7.6% (55/725). Among those who received treatment in English, self-reported abstinence was 14.5% (429/2,957) and biochemically confirmed abstinence was 3.7% (110/2,957). Those who received treatment in Spanish were twice as likely to be abstinent at 6 months (self-report: OR: 1.98; 95% CI: 1.62, 2.40; biochemically confirmed: OR: 2.13; 95% CI: 1.52, 2.97).

Findings indicate that streamlined, automated approaches such as AAC have great potential to engage Spanish-speaking smokers in treatment. Once engaged, Spanish speakers completed more counseling calls and were twice as likely to be abstinent at 6 months. It is also notable that large discrepancies were observed between self-report and biochemically confirmed abstinence.

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Functions of the Ska3 Protein in Kinetochore Stability and Mitotic Progression

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In mitosis proper chromosome alignment, occurring during metaphase, is crucial for avoiding defects in the resulting daughter cells that could result in cell death or cancer. Kinetochores are specializations on mitotic chromosomes important in moving chromosomes on mitotic spindle microtubules and in signaling the mitotic spindle checkpoint. The spindle checkpoint regulates progression through mitosis by detecting improper alignment of chromosomes and delaying the onset of anaphase until proper alignment is achieved. The Spindle and Kinetochore Associated (Ska) complex is a hexomeric kinetochore complex composed of two copies of three proteins called Ska1, Ska2 and Ska3. The Ska complex appears to play roles in both chromosome movement and cell cycle regulation in mitosis. Previous work has shown that Ska1 has a microtubule binding domain within its c-terminus. There is also evidence to suggest that Ska3 contains a domain that enhances the Skal-mediated binding of microtubules by the Ska complex. However it is unknown how Ska3 enhances Ska complex binding to microtubules nor have the exact locations of possible microtubule binding domains on Ska3 been clearly mapped. Through sequence alignment and homology modeling with the crystal structure of the Ska1 microtubule binding domain, we have identified a possible location of the proposed Ska3 microtubule binding domain in a section of Ska3 for which the structure has not been determined. The predicted location of the Ska3 microtubule binding domain is located within a region of the Ska3 protein that, based on the published crystal structure of the Ska complex and protein sequence position, would put it near the Ska1 microtubule binding domain. This potential Ska3 microtubule binding domain may help facilitate Ska complex binding to spindle microtubules to promote chromosome alignment and mitotic progression from metaphase to anaphase. In addition, our group has found evidence that Ska3 interacts with Protein Phosphatase 2A (PP2A), a phosphatase that plays a large role in countering the spindle checkpoint when chromosomes are fully aligned. Through sequence analysis we have identified a possible PP2A binding motif that was recently identified in proteins that bind the B56 subunit of PP2A. The location of this motif would be consistent with results from studies which indicate that this region of Ska3 is critical for rescuing normal mitotic progression when Ska3 is depleted by RNAi. We have also identified two motifs in the Ska3 protein sequence, a KEN-box and a D-box, which are often found in proteins that interact with Cell division cycle protein 20 (Cdc20), an important regulator of mitotic progression. Based on
these observations, we propose a model in which Ska3 binding microtubules stabilizes their interactions with kinetochores, while also putting the Ska3 c-terminus in position to interact with PP2A and Cdc20 in order to facilitate removal of inhibitory phosphorylations on Cdc20, allowing Cdc20 to promote mitotic progression from metaphase to anaphase.

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FACTORS ASSOCIATED WITH DUAL USE OF ELECTRONIC CIGARETTES AMONG ADULT AMERICAN INDIANS WHO SMOKE: A CHEROKEE NATION COHORT STUDY

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Significance: American Indians (AI) have a higher prevalence of smoking, higher prevalence of electronic cigarette (EC) use, and higher cancer mortality than most other racial groups, particularly in Oklahoma. However, AI are rarely included in studies of EC use among smokers. As many individuals who smoke also use ECs to reduce harms from cigarettes, understanding correlates of using both products by AI merits greater attention.

Methods: In Oklahoma in 2016, 375 AI who smoke and were ages 18 years and older completed a survey collecting demographic information, personal and family history of cancer, perceptions of EC harm and benefits, measures of smoking and dependence, other tobacco use, and EC use by spouse or partner. We defined dual users as using EC within 30 days and every day or some days (n = 44; 12%), and compared dual users to EC never users ECs (n = 137; 37%).

Results: Dual users were younger than never users (median 36 vs 46 years, respectively; p = .01) but did not differ significantly by sex, education or income. Dual users did not differ significantly from never users in self-reported general health status, personal history of cancer or other smoking related medical conditions. Dual users more often reported history of depression (56% vs 29%; p < .01) and a family history of cancer (lung, head, neck, other) marginally more often than did never users (58% vs 41%, p = 0.05). While no significant differences were noted for perceived harms of smoking or secondhand smoke, low perceived harm of ECs was more frequent among dual users than never users (64% vs 24%; p < .01) as well as secondhand vapor (77% vs 29%; p < .01). Dual users agreed more often that ECs help to quit smoking (75% vs 16%; p < .01) and are less harmful than smoking (70% vs 17%; p < .01). Only 9% of dual users did not know or were uncertain about EC harms or benefits, compared to 29% of never users for harms (p < .01) and 38% for benefits (p < .01). Differences between groups were not significant for cigarette consumption, salivary cotinine levels, or smoking dependence scales, but dual users reported a likelihood to quit smoking more often than never users (86% vs 65%; p = .01), and more often tried to quit in past 12 months (55% vs 32%; p = .01). Dual users
significantly ($p \leq .01$) more often ever tried snus (36% vs 10%), cigars (68% vs 46%), cigarillos (82% vs 56%), and hookah (50% vs 14%) but no differences in ever use of other smokeless tobacco. Among persons living with a spouse/partner, dual and never users did not differ in spouse/partner smoking, but dual users much more frequently lived with a spouse/partner who uses ECs (45% vs 6%; $p < .01$).

Conclusions: EC use is a potential, albeit unproven, harm reduction strategy for people who smoke. The American Cancer Society strongly discourages dual use of EC and cigarettes. This exploratory study of AI found several significant associations with dual EC and cigarette use, but cigarette consumption was similar between groups. It remains to be determined whether ECs will have a role in smoking cessation or reducing cancer health disparities among AI.

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**JUUL Perceived Drug Effects and Preferences Between Emerging Adults, Young Adults, and Older Adults**

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**Objective:** JUUL, a small, rechargeable, closed-system e-cigarette has recently become a market leader, with growing popularity among emerging and young adults. However, little is known about their attitudes toward the product, reasons for use, perceived drug effects, dependence, and patterns of use. The present study examined these among emerging adults (EA: 18-24 years), young adults (YA: 25-29 years), and older adults (OA: 30+).

**Methods:** Participants were (N = 949) adult ever JUUL users, who completed online surveys via Amazon Mechanical Turk. Questionnaires examined current JUUL use, preferences, and perceptions. For analyses, age groups were divided into EA, YA, and OA.

**Results:** Frequency of JUUL use differed by age groups, with EAs having the greatest percentage of nondaily users (37%) and OAs with the greatest percentage of experimenters (69%). There were no significant differences in the percentages of daily users between age groups (10.3% of EAs, 11.3% of YAs, 10% of OAs). EA (54%) and YAs (52.8%) had a greater preference for fruity/sweet flavors (e.g., Mango, Fruit Medley, Crème Brulee) compared to OAs and OAs reported greater preference for traditional flavors (e.g., Cool Mint and Virginia Tobacco; 59.3%; p = .003) compared to EA (46%) and YAs (47.2%). Compared to OAs, EAs reported greater dizziness (p = .003), lightheadedness (p = .001), nausea (p < .001), coughing/choking (p = .006), rush/buzz (p = .001), and difficulty inhaling (p < .001) when using JUUL. EAs also reported greater perceived rush/buzz (p = .02) than YAs. No differences between groups were observed in JUUL dependence and reasons for first use.

**Discussion:** In this sample, EAs reported greater non-daily use and experiencing greater positive and negative drug effects from JUUL use compared to OA and YAs. EA and YAs also reported greater preference for fruity/dessert flavors, while OAs preferred more traditional tobacco flavors.
EAs may experience and use the JUUL differently than YAs and OAs, therefore preventive efforts should be tailored specifically to this age range.

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A NOVEL PROMISING BIOMARKER TO ASSESS CERVICAL CANCER RISK

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Background: Cervical cancer is the 4th most common female cancer, accounting for 500,000 new cases and 200,000 deaths across the world. 99% of cervical cancer is due to infection by human papillomavirus (HPV). The factors leading to HPV integration and induced carcinogenesis are not entirely clear, but high DNA damage levels have been proposed to play a role in HPV integration. Chronic HPV infection increases DNA damage and reduces DNA repair, leading to even higher DNA damage levels. Recently, we showed that the levels of nuclear DNA (nDNA) damage are a potential biomarker predictive of cancer risk. Mitochondrial DNA (mtDNA) damage has been reported to be more persistent than nDNA damage. We have previously demonstrated a good correlation between mtDNA and nDNA damage. Herein, we performed a pilot study to assess whether the levels of mtDNA damage can be used as a potential tool to screen cancer risk.

Aims: (1) To measure determine whether the amount of mtDNA damage differs between cervical samples with distinct pathologies. (2) To determine whether the number of mtDNA lesions correlates with the grade of cervical dysplasia.

Methods: Ethics Committee approval and written informed consent was obtained from all participants. Samples from 25 patients were collected from the endocervix during a pelvic exam in the Dysplasia Clinic. Samples for DNA damage studies were collected by cytobrush and DNA extracted as previously reported. Demographic and risk factor data were collected through detailed questionnaires. Clinicopathologic data was abstracted from the medical chart. The amount of mtDNA damage was quantified by a long-run real-time PCR-based DNA-damage quantification (LORDQ) assay. Data were analyzed by Student’s t-tests. Logistic regression analysis was done modeling the probability of having present pathology risk.

Results: Histopathological reports indicated that 9 cervical samples were normal (CO) and 16 had cervical dysplasia. Dysplasia samples were as follows: 9 low-grade squamous intraepithelial lesions (LSILs or C1) and 7 high-grade squamous intraepithelial lesions (HSILs or C2/3). The amount of mtDNA lesions per 10,000 bases were increased two fold in LSILs or C1 cases and three fold in HSILs or C2/3 cases when compared to CO. Regression analysis showed no
significant correlation between age, race, smoking and drinking status compared with pathology risk.

Conclusion: Our data shows that mtDNA damage is the lowest in patients without cervical dysplasia and increases progressively with higher grades of dysplasia and correspondent cancer risk. This pilot study shows the feasibility of the approach and stresses the potential of using mtDNA damage to predict cervical cancer risk. Measuring mtDNA damage detection by LORDQ is less time consuming and more cost-effective than the measurement of nDNA damage. Larger population studies are urgently needed to fully assess the potential of this approach for cervical cancer risk.

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During radiation therapy, photon beam positioning must be well characterized to accurately measure the delivered dose to the tissue. In this study, we investigate the feasibility of using X-ray Acoustic Computer Tomography (XACT) for real-time dosimetry and image guided radiation therapy. We have developed a simulation workflow to detect acoustic waves induced by pulsed x-ray illuminations on breast and prostate digital phantoms and used these to determine the deposited dose into the samples. Dose distributions from breast and prostate CT images were combined with treatment planning software and converted into initial pressures using the formula for X-ray Acoustic (XA) pressure. The acoustic waves were then allowed to propagate in silico via the k-wave toolbox, at which point they were detected and used to reconstruct images of the dose distribution. The prostate simulations feature a 2D planar detector array and the breast simulations feature a 3D cup detector array. A 3D back projection algorithm was used to image reconstruction in both cases. The reconstructed XACT image reveals the beam position and radiation field shape during dose delivery. XACT reconstructed images for both prostate and breast imaging demonstrate the feasibility of XACT as a viable dosimetry tool.
Mitosis accurately divides the replicated genome into two daughter cells. In mitosis, centrosomes become spindle poles from where microtubules emanate and capture sister kinetochores. Formation and maintenance of the bipolar spindle is critical to ensure proper chromosome segregation at anaphase. Mitotic cells with more than two spindle poles are termed multipolar, and these cells usually segregate chromosomes inaccurately in more than two daughter cells. Multipolarity greatly compromises the fidelity of chromosome segregation at anaphase. In vertebrate cells, a centrosome is composed of a pair of centrioles surrounded by various proteins that form pericentriolar matrix (PCM). Multipolar mitoses are often caused by centrosome over duplication, failure to cluster extra centrosomes or PCM fragmentation during mitosis. Malignant cells with extra centrosomes often cluster the extra centrosomes into two poles to maintain bipolar spindle and avoid massive chromosomal instability. Among many PCM proteins only a few have clearly defined functions. It is still unclear which proteins help maintain spindle pole integrity during mitosis. Multipolarity can either drive tumorigenesis or can cause cell cycle arrest and cell death in cancer cells depending on context. Cancer cells often employ various mechanisms to avoid multipolarity and promote survival. While multipolar mitosis is central to the cancer biology, the sources of multipolarity, as well as how cancer cells avoid multipolarity, are poorly understood. Therefore, identification of such sources and a comprehensive understanding of the underlying causes of multipolarity may aid in cancer treatments.

Using a bioinformatics approach to identify functions of poorly characterized gene products based on known functions or depletion phenotypes of co-expressed genes, we have characterized previously unknown function(s) of a cancer testis antigen, chondrosarcoma associated gene 1 (CSAG1). CSAG1 is often overexpressed in melanomas, centrain lung cancers, and head and neck cancers. We report that CSAG1 is a novel centrosomal protein and its depletion in HeLa cells results in multipolar mitotic exit. CSAG1 depletion neither alters the centrosome number nor affects centrosome clustering. A GFP-tagged version of CSAG1 localizes to the centrosomes in interphase and is enhanced at poles during mitosis. We have found that extra poles in CSAG1-depleted cells do not contain centrioles but consist of aggregates of PCM components. Our data reveals that the PCM fragments during subtle mitotic delays in absence of CSAG1. Localization data along with irregular distribution of PCM and eventual fragmentation observed in cells lacking CSAG1 indicates that CSAG1 strengthens PCM integrity during mitosis. We also find that cells lacking normal p53 function are more susceptible to
multipolar mitosis when depleted of CSAG1. Our study suggests that CSAG1 could be a new example of oncogene addiction in a p53 null background and thus a potential target in cancer therapy.

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**CHD1 — A NOVEL EPIGENETIC REGULATOR IN MYELOID MALIGNANCIES WITH A ROLE IN DNA REPAIR**

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Myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML) are clonal hematopoietic disorders resulting from genetic alterations in hematopoietic stem cells. These myeloid disorders are clinically heterogeneous and biologically complex. Despite major advances in understanding the genetic and molecular landscape of MDS/AML, along with the introduction of newer and targeted therapies, the cure rates in AML are still only about 60% in children, and much lower in adults. Exploiting the genetic tractability of the zebrafish (Danio rerio) vertebrate model, we are investigating the role of a novel epigenetic regulator, Chromodomain helicase DNA binding protein-1 (CHD1) in hematopoiesis and its misregulation leading to MDS and AML. CHD1 is located at chromosome 5q21, which lies within the most frequent breakpoints seen with the deletion of the long arm of chromosome 5 [del (5q)] in patients with MDS and AML. In addition to del (5q), we found that CHD1 levels are significantly lower in bone marrow cells of patients with other forms of MDS, relative to normal controls. Using CRISPR/Cas9-mediated targeted mutagenesis in zebrafish, we created chd1 homozygous mutant fish. We confirmed a marked decrease in chd1 gene expression in these mutant fish. Chd1 homozygous mutants are viable and fertile as adults, with no significant developmental or hematopoietic phenotypes observed during embryogenesis. As CHD1 can act as a tumor suppressor and is linked to the DNA damage response, we hypothesized that chd1 mutant zebrafish would be more sensitive to DNA damaging agents. Indeed, we found that chd1 mutants have increased sensitivity to ionizing radiation as evidenced by elevated brain cell death measured by whole mount imaging of live embryos and immunofluorescence for activated Caspase 3, a marker of apoptosis. We also generated chd1het; tp53het zebrafish to test whether chd1 haploinsufficiency could accelerate tumor rates in tp53 mutant fish. Single heterozygotes chd1het or tp53het usually do not form tumors at one year of age, but chd1het; tp53het double heterozygous zebrafish showed substantial tumor growth by one year of age. Taken together, our data suggest that CHD1 may play a key role in protecting genomic integrity, explaining why diminished CHD1 levels could contribute to the pathogenesis of MDS and AML. This genetic interaction may be especially crucial in patients with combined del (5q) and TP53 alterations, and could contribute to the increased severity seen in this group. Our findings suggest these and other CHD1-deficient patients may be resistant to standard therapies due to
attenuated DNA damage responses, allowing their AML to survive DNA damage caused by conventional anti-cancer treatments.

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The impact of provider’s feeding behaviors training on providers’ feeding behaviors in rural tribally-affiliated early care and education centers

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Introduction
Cancer is the second leading cause of death in the United States and results in approximately 17% of Native American (NA) deaths. Obesity is strongly associated with some cancers and obesity prevention is recommended to begin before the age of 5. Establishing healthy eating habits early impacts lifelong dietary intake, which has implications for many health outcomes, including cancer. With children spending more time in childcare, teachers establish the daytime meal environment through their feeding practices. The purpose of this study was to evaluate the impact of an intervention to increase healthy feeding practices in a NA community in Oklahoma.

Methods
Nine tribally affiliated early childhood education (ECE) centers across four communities in Osage Nation participated in the Food Resource Equity and Sustainability for Health (FRESH) study. In addition to community, center, and classroom components, teachers at five intervention sites attended a 1.5 hour healthy feeding practice training. One table in one classroom at each ECE center consisting of 2-5-year-old children was observed during lunch, before and 1 month after the intervention. The Mealtime Observation in Child Care (MOCC) was adapted from previously validated tools to identify provider behaviors during meals and organize teacher behaviors into eight subscales based on the Academy of Nutrition and Dietetics best practice guidelines. Descriptive statistics and Shapiro-Wilk Test for Normality were calculated. Independent t-tests were calculated for the delta (post-pre) of each subscale and overall score.

Results
There was an average of 5.4±SD children and 1.6±SD teachers observed during pre and post, respectively. Mean MOCC scores at baseline for the intervention and control sites were 6.46±0.75 and 6.05±0.88, respectively. The max possible score is 10. Mean MOCC scores following the training for the intervention and control sites were 6.40±1.03 and 7.50±0.26, respectively.
Conclusion

Control sites showed greater improvements in desired teacher feeding practices than the intervention sites. Possible explanation for this unanticipated effect was that greater provider burden placed on intervention sites for the overall FRESH curriculum decreased their capacity to change feeding practices in addition to other classroom changes. In spite of insignificant findings, further research is warranted due to the sample size limitations.

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CELLULAR AND SUB-CELLULAR LANDSCAPE OF RD3 IN HUMAN TISSUES: BASIS FOR ITS “TUMOR SUPPRESSOR” RELEVANCE

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The 195-amino-acid-long human Retinal Degeneration Protein 3 (RD3) is critical in the regulation of guanylate cyclase (GC) signaling and photoreceptor cell survival. Recently, we identified significant loss of RD3 in high-risk neuroblastoma and the influential role of RD3 in tumor progression. However, the functional characterization of RD3 in tumor systems has been hampered by the dearth of information on its localization in normal tissue and by the lack of antibodies suitable for staining FFPE tissue, primarily due to the inaccessibility of the epitopes. In this study, we validated a custom-synthesized RD3 antibody and investigated the expression/localization of RD3 in assorted human tissues. RD3 specific labeling was characterized by defining (i) RD3 labeling in panel of neuroblastoma cells with known RD3 levels, (ii) immunoblotting specificity in a panel of normal human tissues including retina, (iii) Ab neutralizing experiments (immunoblotting, IHC) with antigen peptide (compared with scrambled peptide), (iv) gene manipulation approach by silencing or re-expressing RD3 in RD3 expressing or null cells and, (v) by comparing the immunostaining in retina with commercially available antibodies. We observed stratified expression of RD3 in different cell types and subcellular location of retina. We demonstrated extensive positive RD3 immunoreactivity in various normal tissues and particularly strong dot-like perinuclear staining in the lining epithelial cells, suggesting that RD3 may play an important role in the normal functioning of epithelial cells. RD3 expression is limited in the CNS. While neuroblastoma is often RD3-positive, the adrenal medulla, where many neuroblastomas originate, is RD3-negative. Meta-analysis of RD3 transcriptional expression across normal tissues confirmed tissue-specific RD3 mRNA levels. Our results revealed the tissue-specific expression/localization profile of RD3 for the first time.

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NON-INVASIVE TESTING OF BLADDER CANCER PATIENT CELLS AT THE SINGLE-CELL LEVEL

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Single cell analysis has the potential to revolutionize personalized chemotherapeutic regimens by exploring heterogeneity on the single-cell level. Single-cell techniques are limited by the small sampling volume of an individual cell (~a few picoliters of solution), which makes analysis challenging. Another major issue for cellular analysis is extensive sample pretreatment that perturbs the cellular environment and alters metabolites. Our group developed a bioanalytical method, known as the integrated cell manipulation platform, capable of extracting information from an individual cell in solution for real-time analysis.

The integrated cell manipulation platform contains an inverted microscope to monitor suspension cells, a ThermoPlate to maintain the cells at 37°C, and glass cell-selection device coupled to a CellTram Vario with spatial movement controlled using an Eppendorf TransferMan Cell Manipulation System. This platform is coupled with the Single-probe mass spectrometry technique developed by our group, which has previously shown success in the exploration of adherent cell line models. An internal standard (15N-gemcitabine) was added into the sampling solvent for quantification of the anti-cancer compound, gemcitabine, inside individual cells derived from the urine of bladder cancer patients. In collaboration with the OUHSC, patients’ urine specimen were collected 1 hour post-infusion. The sample was spun down to isolate the cells and resuspended in PBS for analysis. Once a cell was selected, the mineral-oil level in the glass device was changed to secure the cell to the tip of the probe. The glass probe was raised in the z-direction until it formed a junction with the Single-probe tip, causing microscale lysis to occur.

Using this technique, over 30 cells were analyzed from different patients, and the amount of gemcitabine was found in healthy cells, cancer cells, and urine. Gemcitabine’s inactive metabolite, dFdU, could also be seen in these samples, which indicates the feasibility of using this technology to explore the efficacy of chemotherapy treatments for individual patients in the future.

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**Significance:** Introduced to the market in 2015, JUUL, a small, rechargeable, closed-system e-cigarette (EC) has been gaining in popularity, now with 70% of the current market. While news about JUUL has been widespread in the press, only a handful of studies have examined it. Past research shows that JUUL is highly recognizable and prominent on social media. However, little is known about users’ harm perceptions of the product and how they describe it using positive and negative words. The current study examined harm perceptions of JUUL among users and examined how the product was described.

**Method:** Survey participants (N=979; M_age=33.2) who reported ever using JUUL were recruited from Amazon’s Mechanical Turk. Survey items included use status, harm perceptions of JUUL and other tobacco products, and a checklist of positive and negative words that they chose to describe JUUL.

**Results:** The majority of participants reported only trying JUUL once or twice (triers; 60%), while 29% reported regular non-daily use, and 10% reported daily use. Paired samples t-tests revealed that participants perceived JUUL to be significantly less harmful than combustible cigarettes, cig-a-likes, smokeless chewing tobacco, snus, hookah, cigars, and cigarillos (all \( p < .001 \)). Participants did not perceive JUUL to be less harmful than tank (\( p = .051 \)) or mod systems (\( p = .67 \)). Analysis of Variance revealed a significant association between JUUL use status and JUUL harm perceptions \( [F(2, 834) = 9.34, p = .02] \) such that daily users perceived JUUL as the least harmful followed by non-daily users, and triers. Participants overwhelmingly described JUUL with positive word associations such as “trendy” (43%) and “cool” (38%) and described JUUL less with negative word associations such as “disgusting” (4%) and “gross” (4%).

**Conclusion:** JUUL users and triers perceived JUUL to be significantly less harmful than most tobacco products except tank and mod system ECs. The greater the use, the less harm was perceived, and the majority viewed JUUL in a very positive way. This suggests that the propensity for JUUL’s popularity may be driven by lesser harm perceptions and positive views about the product.

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Keywords: JUUL, e-cigarettes, harm perceptions

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ENGAGING AMERICAN INDIAN STUDENTS IN ONCOLOGY RESEARCH AND HEALTH PROFESSIONS EDUCATION: A REVIEW OF THE LITERATURE

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Background: American Indian/Alaska Native (AI/AN) students face significant challenges in navigating the educational pipeline. As a result, AI/ANs are underrepresented among health care professionals relative to population demographics. Alaskan non-Hispanic Whites and 36.1% higher than US all races. To address Al education, training and cancer-related healthcare needs, our long-term goal is to increase the number of AI/AN students who successfully progress through the higher education pipeline and become cancer healthcare providers and researchers. We recognize that the proposed program should be grounded in best practices for developing, implementing, and evaluating educational programs. Our primary goal was to conduct a narrative literature review to identify and summarize best practices for developing oncology-focused research and training experiences for AI/AN undergraduate, graduate and professional students. A secondary goal was to identify methodological limitations and areas for future research related to rigorous educational program evaluation.

Methods: Published literature was searched using databases relevant to oncology (PubMed, Web of Science) and sociology (PsychINFO, SocIndex). The bibliographies of identified relevant papers were searched for additional references by title. Search terms involved three general areas: target population (e.g., American Indian), training area (e.g., oncology), and educational program (e.g., undergraduate).

Results: 107 original publications and 33 review papers that were relevant to the project goals have been identified. Key areas of program development and implementation include advertising and recruitment; a diverse didactic curriculum, research immersion experiences, ongoing career development support, mentoring, and culture-specific enrichment. Important areas for program evaluation relate to measures of reaction, knowledge, practice and long-term outcomes.

Conclusions: Successful programs address barriers related to perceived lack of abilities, lack of AI/AN role models, limited culture-specific enrichment, and limited mentoring and ongoing career development support. Program directors should work with local tribal and community leaders to create bicultural programs. Opportunities to improve the rigor of educational program evaluation include using measures beyond self-reported reaction and knowledge to focus on educational program enrollment and completion and long-term career outcomes. Methodologic challenges include identifying relevant control groups for comparison and the use of experimental designs.

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SEX DIFFERENCES IN THE EFFECTS OF DAILY STRESS ON SMOKING BEHAVIOR: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

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Introduction: Research has demonstrated that stress can impact smoking behavior. Further, women and men may experience stress differently. Thus, specific stressors could influence smoking behavior differently in men and women. The aim of the present study was to determine if sex and exposure to specific stressor types interact to effect smoking lapse in adults who are trying to quit smoking.

Method: Participants were recruited from a smoking cessation clinic as part of a randomized controlled trial to compare a smoking cessation smart-phone application to standard treatment. Through the app, all participants completed ecological momentary assessments (EMA) 5 times per day for 5 weeks (1 week pre-, and 4 weeks post-quit). EMAs assessed two types of stress (e.g., family/relationships, work/school), as well as daily smoking status (coded: 1=smoked, 0=did not smoke). A generalized linear mixed model analysis with a logistic binomial outcome assessed the effects of daily stressors on smoking status, controlling for age, race, education, baseline score on the Heavy Smoking Index (HSI; a brief measure of nicotine dependence) , and treatment group (app vs. standard care). We also explored how these stressors interacted with sex to effect smoking.

Results: Participants were 106 adults (48.2 [13.2] years old, 58.3% white, 63.0% female). On average, participants completed 12.1 [1.9] years of education, and had a score of 3.6 [1.4] on the HSI. Results indicated that endorsing exposure to family stress (OR=1.5; 95% CI=1.1–2.1) increased the likelihood of smoking within a day, while exposure to work/school stress significantly decreased the likelihood of smoking within a day (OR=0.3; 95% CI=0.2–0.5). Further, a significant interaction was found between experiencing family stress and sex, such that women, but not men, who reported experiencing family stress within a day were more likely to smoke on those days (OR=0.5; 95% CI=0.3–1.0). There was no significant interaction between work/school stress and sex.

Discussion: Mobile applications can be used to assess daily stressors that may increase risk for smoking lapse or relapse. These findings may suggest that mobile apps could be tailored to the individual, targeting the types of stress that are more likely to influence smoking lapse/relapse (i.e., family/relationship stress).

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High-grade serous ovarian cancer is the most lethal form of ovarian cancer due to development of resistance to chemotherapy and a high recurrence rate. Since more than 95% of high grade serous ovarian cancers harbor TP53 gene mutations, we hypothesized that upregulation of p53 protein with a repurposed drug mebendazole (MBZ) in combination with reactivation of the mutant p53 protein using the PRIMA1MET drug will synergistically inhibit ovarian cancer cell line growth in a p53-dependent manner. First, the combination indices of these drugs were examined using the Chou-Talalay method in different endogenous and exogenous p53 mutant (MES-OV R282W, ES2 S241F, SKOV3 R273H, SKOV3 R248W), p53 null (SKOV3) and p53WT (A2780) ovarian cancer cell lines. The mechanism of drug combination was evaluated by immunoblotting of proteins involved in the intrinsic and extrinsic apoptosis pathways and measurement of soluble/assembled tubulins and reactive oxygen species (ROS). In vivo validation of drug combination is currently being performed using an intraperitoneal tumor model of MES-OV GFP/Luc cells in athymic nude mice. The p53 missense mutant cells (IC50-1.5 µM) were significantly more sensitive to MBZ compared to p53 null cells (IC50-7.8 µM). The combination index of MBZ and PRIMA1MET indicated synergism (CI= 0.3 to 0.7) in all cell lines except for the SKOV3 R248W p53, which exhibited nearly additive drug combination effects (CI= 0.90 to 1.10). The average dose reduction index (DRI) of this drug combination was 8.5 fold less than the single dose. The p53 protein was increased in both PRIMA1MET and combination treated group and p21 protein was increased in MBZ and combined treated groups. Increased levels of cleaved caspase 9, 3 and cleaved PARP confirmed that this drug combination induced intrinsic apoptosis. Moreover, decreased tubulin polymerization in the MBZ and combination treated groups confirmed that MBZ affects microtubule assembly known to lead to mitotic arrest and cell death. In conclusion, the combination of MBZ and PRIMA1met exerted a synergistic effect and induced intrinsic apoptosis by modulating microtubule assembly and apoptotic proteins in ovarian cancer cells with different p53 mutations. The drug combination may have a potential benefit to ovarian cancer patients regardless of their tumor’s p53 status. The significant dose reduction index will allow lower doses of drugs to be used thus reducing the overall toxicity of these drugs.

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Desmoplastic small round cell tumor (DSRCT) is a newly described and aggressive, often fatal, tumor typically presenting as an abdominopelvic mass in the second or third decade of life. DSRCT is a small round blue cell tumor with similar characteristics as lymphoma, Ewing sarcoma, and Wilm’s tumor among others. For this reason, DSRCT can be easily misdiagnosed. We present a rare case of thoracic DSRCT in a 3 year old male. This is the first known report of DSRCT presenting as a mediastinal mass in this age group.

A 3 year old male was admitted to the pediatric intensive care unit (PICU) with a working diagnosis of pneumonia with complete opacification of the left lung on chest x-ray. Further evaluation in the PICU revealed considerable hepatosplenomegaly. CT chest showed an anterior mediastinal mass with large pericardial effusion, nodules suggestive of metastatic disease, prominent spleen, and left basilar atelectasis.

An echocardiogram indicated a large pericardial effusion and a mass measuring 48mm x 44mm. Cytology results of the pericardial fluid were non-diagnostic but did show malignant cells, therefore a thoracotomy with lung biopsy was performed.

The biopsy indicated widespread pleural, parenchymal, and intralymphatic involvement by a poorly differentiated malignancy. The overall appearance of this tumor included nested growth in a densely fibrotic background, evidence of both epithelial differentiation with strong keratin positivity, and expression of mesenchymal intermediate filaments desmin and vimentin with strong perinuclear staining. This appearance was most concerning for a desmoplastic small round cell tumor (DSCRT). A tumor block was sent, and the EWS-WT1 translocation, typical of DSRCT, was positive.

DSCRT is a rare, aggressive tumor. Diagnosis is difficult and often delayed, as patients usually present with vague symptoms. Metastatic disease is frequently present at diagnosis due to the aggressive nature of the tumor. This case indicates that DSCRT may have a more varied presentation than previously described. DSCRT can present in patients younger than formerly outlined and should remain in the differential diagnosis for undifferentiated small round cell tumors of the thorax.

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EXAMINING OTHER TOBACCO AND MARIJUANA USE AMONG EXPERIMENTERS AND CURRENT USERS OF JUUL

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OBJECTIVE: Tobacco, marijuana, and now newly popular electronic cigarettes such as JUUL, are the most widely used drugs among young adults. Few studies have examined the co-occurrence of use in this population with these substances. To address this gap, this study examined the association of marijuana use and the use of tobacco products among young adult current or Ever JUUL users.

METHODS: Survey respondents were 752 U.S. adults (Mage = 32.6 years) registered on Amazon Mechanical Turk (MTurk) who reported ever using JUUL. Survey items included measures assessing JUUL and other tobacco product use behaviors/history, frequency/quantity and harm perceptions of marijuana use, and self-reported nicotine and/or marijuana addiction. Differences were examined using chi-square, logistic regression, and independent samples t-tests by JUUL use status (current user vs. experimenter).

RESULTS: The sample was comprised of approximately 60% JUUL experimenters (n=448) and 40% current JUUL users (n=304). Current JUUL users were younger than JUUL experimenters (p<.001) and were more likely to use other tobacco products (p =.001). Current users also tried JUUL at a younger age (<.001) and reported higher levels of nicotine addiction (p < .001). Interestingly, experimenters were more likely to use marijuana in the past 30 days (p = .001) than current users, but reported vaping (p =.017) and smoking (p = .006) less marijuana per session. While current users and experimenters perceived similar levels of harm from smoking and vaping marijuana, current JUUL users rated marijuana edibles (p=.002) as more harmful than experimenters. No differences were observed for self-reported marijuana addiction between groups.

CONCLUSIONS: In this sample, Current JUUL users reported using JUUL more frequently, had higher nicotine addiction scores, tried JUUL at a young age, and reported using greater quantity of marijuana. Prevention and intervention programs may need to target poly-use of electronic cigarettes, marijuana, and tobacco rather than focusing on a single risk behavior during these critical years.
Multicellular spheroids (hereinafter referred to as spheroids) are 3D biological models to fill the gap between 2D cultured cells and the real tissues. The metabolomic profiles inside spheroids provide crucial information reflecting the molecular phenotypes and microenvironment of cells. Herein, we used the Single-probe mass spectrometry imaging (MSI) technique to study the trends of metabolites distribution in spheroids treated using anticancer drug Irinotecan under a series of different time- and concentration-dependent conditions. The MSI data were analyzed using advanced data analysis methods to efficiently extract metabolomic information. Multivariate Curve Resolution Alternating Least Square (MCR-ALS) was used to decompose each MS image into two major components (i.e., inner and outer regions) containing different metabolomic features. To improve the efficiency of data analysis, both supervised (e.g., Random Forest) and unsupervised (e.g., Cluster Large Application (CLARA)) machine learning methods were used to cluster MS images according to their metabolomic features. Our results indicate that anticancer drug significantly affected the abundances of a variety of metabolites in different regions of spheroids. This integrated experiment and data analysis approach can facilitate the studies of metabolites in 3D tumor models and potentially in many other different types of tissues, and may benefit the drug discover, therapeutic resistance, and other biological research fields.
The mitotic spindle is a complex array of microtubules whose function is to move chromosomes to alignment at the spindle equator at metaphase and then segregate sister chromatids during anaphase. Previous analysis of spindle microtubule kinetics utilizing fluorescence dissipation after photoactivation experiments described two main populations, a slow turn-over population and a fast turn-over population. Conventionally, these two populations have been equated to kinetochore microtubules and non-kinetochore microtubules respectively. This demarcation is likely to be an oversimplification. Microtubule turnover varies among different mitotic spindle microtubules, dictated by their spatial distribution within the spindle and by their interactions with each other and with other organelles such as kinetochores, chromosome arms, and the cell cortex. How turnover among the various spindle microtubules is differentially regulated and the significance of differential turnover for chromosome segregation remains a mystery. We tested the basic model of kinetochore versus non-kinetochore microtubules by eliminating kinetochores through the depletion of the NDC80 complex in U2OS cells. In the absence of kinetochores, microtubule dynamics remained best described by fast and slow turnover populations. However, loss of kinetochores resulted in an increase in the percent of the fast-turnover microtubule population and a decrease in the slow-turnover microtubule population when compared to controls. Additionally, a decrease in the $t_{1/2}$ of the slow-turnover population was observed when compared to controls, consistent with the reduction in the slow-turnover microtubule population. Importantly, the data obtained following double exponential curve fitting following Hec1 depletion suggests that other sub-populations, in addition to kinetochore microtubules, contribute to the slow-turnover population. Dissection of the dynamics of microtubule sub-classes will provide a greater understanding of mitotic spindle kinetics and its role in facilitating chromosome attachment, movement, and segregation during mitosis.

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CHLOROQUINE-ENCAPSULATED LIPOSOMES REDUCE GOLD NANOPARTICLE UPTAKE INTO MACROPHAGES

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The mononuclear phagocyte system (MPS) includes cells of liver and spleen and is a major barrier to nanoparticle-mediated drug delivery in the body. Our recent meta-analysis of preclinical studies revealed that only 1% (median value) of the injected nanoparticle dose reaches solid tumors [1]. The majority of systemically administered nanoparticles is cleared from the blood via phagocytosis by MPS cells [2]. We hypothesize that therapeutic strategies can transiently block the MPS by inhibiting macrophage phagocytosis. Our long-term goal is to increase nanoparticle accumulation in solid tumors by transient temporal drug-mediated MPS blockage.

Here, we report our preliminary results on macrophage inhibition via chloroquine-encapsulated liposomes to reduce gold nanoparticle cell uptake. Chloroquine is an antimalaria drug and has recently been explored for transient temporal inhibition of liver macrophages, i.e., Kupffer cells [3]. These cells clear nanoparticle drug carriers efficiently from the blood and represent a major biological barrier for nanomedicine applications [1].

First, we encapsulated chloroquine into 100-nm liposomes. After physicochemical characterization of chloroquine-encapsulated liposomes, we studied the tolerable drug dosing range using cytotoxicity tests for two murine cell lines (RAW 267.4 and J744A.1). These cell lines were used as model macrophages. Next, we preconditioned macrophages in tissue culture with chloroquine-encapsulated liposomes and then administered fluorescently labeled 50-nm gold nanoparticles. We then quantified the inhibitory effect of chloroquine-liposomes on gold nanoparticle cell uptake using flow cytometry. Our tissue culture results revealed that liposome-encapsulated chloroquine is a potent strategy to significantly reduce gold nanoparticle phagocytosis of tested macrophage cell lines.

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References:

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HARM PERCEPTIONS OF TOBACCO/NICOTINE PRODUCTS AND CHILD EXPOSURE: DIFFERENCES BETWEEN NON-USERS, CIGARETTE-EXCLUSIVE, AND ELECTRONIC CIGARETTE-EXCLUSIVE USERS

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Objective: Over the past decade, the rate of cigarette use has declined while use of alternative products like electronic cigarettes (e-cigarettes) has increased. The perception that e-cigarettes are less harmful than regular cigarettes may impact caregivers’ choices to use e-cigarettes at home and in their car with children. Further, in previous examinations of biomarkers of exposure (NNAL/cotinine; Wagener et al., 2017), significant differences were observed for child exposure across groups. Therefore, the purpose of this study is to contextualize those findings to examine how caregiver perception of harm may influence child exposure (both objective and subjective) and child pulmonary functioning in a sample of e-cigarette-exclusive, cigarette-exclusive, and non-tobacco/nicotine users (non-users).

Methods: Cigarette-exclusive (n = 19), e-cigarette-exclusive (n = 12), and non-users (n = 20) and their children (n = 51, M_age = 10.47) completed self-report items assessing harm perceptions of 15 tobacco/nicotine products, frequency of use, completed pulmonary functioning, and provided biospecimens for biomarkers of exposure (NNAL/cotinine). Harm perceptions were examined using analysis of variable (ANOVA) and weekly use, child in-home and in-car exposure were examined using T-test.

Results: Compared to non-users, both e-cigarette and cigarette users rated tank refillable e-cigarettes (p < .001) and modifiable e-cigarettes (refillable/customizable; p < .001) as less harmful. Compared to non-users, e-cigarettes users also rated dissolvable tobacco (p = .04); hookah (p = .04); marijuana (p = .02) as less harmful. No significant differences were observed for pipe tobacco, cigars, snuff/dip, snus, and cigarettes between user groups. E-cigarette-exclusive users reported more frequent use in their home (p = .006), car (p = .01), and around their children (p = .01) when compared with cigarette users. However, children living with e-cigarette users evidenced lower levels of exposure of both cotinine (p = .03, M_Difference = 1.21; a biomarker of nicotine), and NNAL (p = .003, M_Difference = 1.66; a biomarker of NNK, a potent lung carcinogen), when compared to cigarette-exclusive users. No differences were observed for child pulmonary functioning among e-cigarette-exclusive, cigarette-exclusive, and non-users.
Discussion: Results indicated that caregivers who use e-cigarettes perceive them as less harmful, use them at home and in the car, and report higher frequency of use, even when their children are present. Despite this, exposures did not result in higher biological exposure. Future interventions should target harm perceptions of caregivers' e-cigarette and cigarette use.

Figure 1. Caregiver perception of harm for various tobacco products and marijuana.

Note. Percentages endorsed by caregivers reflect the percent within each respective user category. Ratings range from 0 = not at all harmful to 100 = extremely harmful. ** Significant at $p < .001$. * Significant at $p < .05$. 

PERCEIVED HARM RELATED TO A SPECIFIC TOBACCO PRODUCT AND MARIJUANA
Silencing of ZIP4 inhibits pancreatic cancer invasion and metastasis through regulating epithelial-mesenchymal transition

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Background: We have previously shown that a zinc transporter ZIP4 was upregulated in human pancreatic cancer and promotes cell proliferation and migration. EMT is considered to be important in pancreatic cancer metastasis. However, how does ZIP4 regulate pancreatic cancer invasiveness and EMT still remains elusive. Our goal is to study the underlying mechanism of ZIP4-regulated EMT and metastasis in pancreatic cancer.

Methods: Migration and invasion assay were performed in human pancreatic cancer cell lines with ZIP4 blocked. Correlations between ZIP4 and EMT markers ZO-1, claudin-1, ZEB1, Slug, MMP7, MMP9 were studied in human pancreatic cancer specimen, xenograft tumor tissue and pancreatic cancer cell lines with IHC, Western blot and RT-qPCR.

Results: In both orthotopic xenografts and human pancreatic cancer tissues, the expression of ZIP4 was positively correlated with the mesenchymal markers ZEB1, Slug, MMP7 and MMP9, while reversely associated with epithelial markers ZO-1 and Claudin-1. Consistently, in vitro and in vivo approach showed that knocking down ZIP4 inhibited ZEB1, Slug, MMP7, MMP9 expression but increased level of ZO-1 and Claudin-1 in pancreatic cancer cell lines which led to less invasive capacity. Further analysis demonstrated that ZIP4-mediated repression of ZO-1 and Claudin-1 leads to upregulation of their targets FAK and Paxillin.

Conclusion: Our findings indicate that knocking down ZIP4 inhibits pancreatic cancer invasion, migration and metastasis through repression of EMT. This study suggests a novel signaling pathway initiated by ZIP4, and may provide new insights on targeted therapy for this devastating disease.
DNA MUTATION ANALYSIS IN ENDOMETRIAL CANCERS WITH AND WITHOUT POL E MUTATIONS

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Background:
Endometrial adenocarcinomas with POL E mutations have been recently described and show ultra mutated patterns with markedly increased numbers of DNA mutations due to errors in transcription. These are reported to have a relatively favorable prognosis in the context of high histologic grade. We have analysed a database of endometrial cancers from OUHSC for POL E mutations in an effort to better understand these lesions.

Methods:
DNA was extracted from thick sections of formalin fixed paraffin embedded tissues from archival tissue blocks from the files of OU Medical Center Surgical Pathology Laboratory. Cases with POL E mutations were identified using Sanger Sequencing. DNA from 91 cases including both POL E mutated and wild type were further studied for somatic DNA mutations with amplicon deep sequencing using a Tru Seq 48 gene cancer panel (Illumina). 11 cases did not yield sufficient product after amplification and were deleted from further study. Five cases were analyzed in duplicate with comparable results. Pilot data from 79 patient samples are reported here.

Results:
15 cases with POL E mutations had significantly more single nucleotide variants (SNV) across all amplicons (mean=29.1± 9.1) compared with those in 64 POL E wild type cases (mean=18.3 ± 6.4)(p<.0001 ). This SNV pattern was also seen in exons (mean 17.7 vs 10.0), in coding regions (mean 16.2 vs 8.9) including non-synonymous SNV ( mean 7.1 vs3.1) and synonymous SNV ( mean 7.7 vs 5.2).

The most frequently mutated genes in these endometrial cancer cases were PIK3CA (n=28 [35.4%]), PTEN (n=20 [25.3%]), and TP53 (n=19 [24.1%]). POL E mutated cases had more SNV in these significantly mutated genes compared with POL E wild type.

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>POL E Mutated (%)</th>
<th>POL E Wild Type (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>8/13 (61.5)</td>
<td>20/66 (30.3)</td>
<td>.054</td>
</tr>
<tr>
<td>PTEN</td>
<td>9/13 (69.2)</td>
<td>11/66 (16.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TP53</td>
<td>7/13 (53.8)</td>
<td>12/66 (18.2)</td>
<td>.011</td>
</tr>
</tbody>
</table>
Conclusions:

These results support the hypothesis that POL E mutated cases show a significantly greater number of SNV compared with those harboring POL E wild type. In addition, this difference is also seen in key genes that are significantly mutated in cancers. (Funding: Presbyterian Health Foundation Seed Grant Program RSRCH141391)

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