2017 ANNUAL CANCER RESEARCH SYMPOSIUM

FRIDAY | JAN. 27 | 2016

Nicholson Conference Center
Stephenson Cancer Center
Oklahoma City, Oklahoma

HOSTED BY STEPHENSON CANCER CENTER
The Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Settlement Endowment Trust (TSET) for co-sponsoring the 2017 Stephenson Cancer Research Symposium.

In 2012 TSET awarded a five-year, $30.25 million grant to the Stephenson Cancer Center to establish the Oklahoma TSET Cancer Research Program.

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.

**FY 16 Highlights**

With support from the Oklahoma TSET Cancer Research Program the Stephenson Cancer Center accomplished the following in FY 16:

- Increased cancer center membership by 11% (226 to 252 members) at 11 academic institutions across Oklahoma
- Recruited six new cancer researchers to Oklahoma
- Secured $48.3 million in total grant funding related to cancer and tobacco prevention and control research
- Funded 9 seed and directed-research grants to cancer investigators in Oklahoma
- Enhanced five Shared Resource facilities: Biospecimen Acquisition Core and Bank, Biostatistics, Cancer Functional Genomics, Cancer Tissue Pathology, and Molecular Imaging
- Hosted over 39 research seminar speakers
- Hosted its 5th Annual statewide Cancer Research Symposium that brought together over 250 researchers from around the state
• Hosted ten undergraduate students from eight different universities for a summer cancer research experience
• Opened 105 new cancer clinical trials
• Enrolled 703 patients to interventional clinical trials
• Opened 25 new Phase I and Phase I/II clinical trials
• Enrolled 174 patients to Phase I clinical trials
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SCHEDULE & AGENDA
Cancer Research Symposium Schedule at a Glance

7:30 - 8:15 a.m.  Registration, Continental Breakfast and Poster Set Up
8:15 - 8:20 a.m.  Welcome and Opening Remarks
8:20 - 8:35 a.m.  Break
8:35 - 9:35 a.m.  Concurrent Session I
9:35 - 10:35 a.m.  Concurrent Session II
10:35 - 10:50 a.m.  Break
10:50 - 11:20 a.m.  State of the Cancer Center
11:20 - 1:00 p.m.  Lunch and Poster Viewing
1:00 - 2:00 p.m.  Concurrent Session III
2:00 - 3:00 p.m.  Concurrent Session IV
3:00 - 3:15 p.m.  Break
3:15 - 4:15 p.m.  Concurrent Session V
4:15 - 4:30 p.m.  Break
4:30 - 4:15 p.m.  Awards and Closing Remarks
4:45 - 6:15 p.m.  Reception
Cancer Research Symposium Concurrent Session Agenda
Preclinical Translational Research (PTR)
Cancer Prevention and Control (CPC)
Clinical and Correlative Research (CCR)

8:35-9:35 a.m.  CONCURRENT SESSION I

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<td>MASS SPECTROMETRY DETECTION OF CHEMOTHERAPY DRUGS IN SINGLE BLADDER CANCER CELLS IN PATIENTS</td>
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<td>Zhibo Yang, PhD</td>
<td>Department of Chemistry and Biochemistry</td>
<td>The University of Oklahoma</td>
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<td>3D BREAST XACT FOR EARLY BREAST LESION DETECTION: A SIMULATION STUDY</td>
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<td>Shanshan Tang, PhD</td>
<td>Center for Bioengineering and School of Electrical and Computer Engineering</td>
<td>The University of Oklahoma</td>
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<td>QUANTITATIVELY ASSESS BREAST DENSITY AS A CANCER RISK PREDICTION FACTOR IN YOUNG WOMEN USING NONINVASIVE ELECTRICAL IMPEDANCE SPECTRUMS</td>
<td>9:15-9:35</td>
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<td>Ali Zarafshani, PhD</td>
<td>School of Electrical and Computer Engineering</td>
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<td>Bobby Saunkeah, MS, Chickasaw Nation</td>
<td>Dannielle Branam, Choctaw Nation</td>
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9:35-10:35 a.m.  CONCURRENT SESSION II

**CPC TOBACCO USE & CESSATION IN UNDERSERVED POPULATION I**
Moderator: Jennifer Vidrine, PhD

9:35-10:35  Smoking Cessation and Relapse Prevention in the Oncology Setting
Vani Nash Simmons, PhD
Department of Health Outcomes & Behavior
Moffitt Cancer Center

10:50-11:20  **STATE OF THE CANCER CENTER**
Robert Mannel, MD
Director, Stephenson Cancer Center
The University of Oklahoma Health Sciences Center

**PTR TARGETED THERAPIES**
Auditorium

Moderators: Rajagopal Ramesh, PhD & Priyabrata Mukherjee, PhD

9:35-9:55  PRE-INJECTION WHEEL RUNNING PREServes MOBILITY IN A RODENT MODEL OF PACLITAXEL PERIPHERAL NEUROPATHY
Elizabeth Hile, PT, PhD, NCS, CLT
Department of Rehabilitation Sciences
The University of Oklahoma Health Sciences Center

9:55-10:15  EVALUATING THE MECHANISM AND THERAPEUTIC ACTIVITY OF PTC-028, A NOVEL INHIBITOR OF BMI-1 FUNCTION IN OVARIAN CANCER
Anindya Dey, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center

10:15-10:35  RADIOTHERAPY TRIGGERED RD3 TRANSCRIPTIONAL REPRESSION IN GOVERNING CSC STATUS AND METASTATIC STATE OF SURVIVING NEUROBLASTOMA CELLS
Dinesh Babu Somasundaram, PhD
Department of Radiation Oncology
The University of Oklahoma Health Sciences Center

**CPC TOBACCO USE & CESSATION IN UNDERSERVED POPULATION I**
Moderator: Jennifer Vidrine, PhD

9:35-10:35  Smoking Cessation and Relapse Prevention in the Oncology Setting
Vani Nash Simmons, PhD
Department of Health Outcomes & Behavior
Moffitt Cancer Center

10:50-11:20  **STATE OF THE CANCER CENTER**
Robert Mannel, MD
Director, Stephenson Cancer Center
The University of Oklahoma Health Sciences Center
### 1:00-2:00 p.m.  CONCURRENT SESSION III

**PTR & CCR**  
**DRUG DEVELOPMENT & CLINICAL RESEARCH**  
Auditorium  
Moderators: C.V. Rao, PhD & Min Li, PhD

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| 1:00-1:20 | THE CURRENT STATE OF OVARIAN CANCER SCREENING AMONG AVERAGE-RISK WOMEN           | Laura Holman, MD            | Department of Gynecology Oncology  
The University of Oklahoma Health Sciences Center |
| 1:20-1:40 | BRINGING AN OKLAHOMA-MADE CANCER DRUG FROM DISCOVERY TO CLINICAL TRIAL          | Doris Benbrook, PhD        | Department of Obstetrics and Gynecology  
The University of Oklahoma Health Sciences Center |
| 1:40-2:00 | IS BMI1 A GOOD TARGET IN CANCER?                                                 | Resham Bhattacharya, PhD   | Department of Obstetrics and Gynecology  
The University of Oklahoma Health Sciences Center |

### CPC

**TOBACCO USE & CESSATION IN UNDERSERVED POPULATIONS II**  
Room A  
Moderator: Damon Vidrine, DrPH

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| 1:00-1:20 | TOBACCO CESSATION FOR CERVICAL CANCER SURVIVORS                                   | Jennifer Vidrine, PhD      | Department of Family and Preventive Medicine  
The University of Oklahoma Health Sciences Center |
| 1:22-1:42 | THE TOBACCO TREATMENT RESEARCH PROGRAM (TTRP): INTEGRATING TREATMENT AND RESEARCH | Darla Kendzor, PhD         | Department of Family and Preventive Medicine  
The University of Oklahoma Health Sciences Center |
| 1:44-2:04 | CREATIVE SYSTEMS CHANGE: OKLAHOMA TOBACCO HELPLINE INTEGRATION WITH 211 CRISIS HOTLINE | Stephen Gillaspy, PhD      | Department of Pediatrics  
The University of Oklahoma Health Sciences Center |
2:06-2:26  VAPING STATUS AND TOBACCO EXPOSER BIOMARKERS AMONG COHORT OF AMERICAN INDIAN SMOKERS
Ashley Comiford, DrPH
Community Health Promotions
Cherokee Nation

2:00-3:00 p.m.  CONCURRENT SESSION IV

PTR  BASIC CANCER BIOLOGY  Auditorium
Moderators: Ralf Janknecht, PhD & Jie Wu, PhD

2:00-2:20  BIOLOGICAL INVESTIGATION AND DRUG TARGETING OF THE ORP4 PROTEIN: A NEW POTENTIAL PRECISION MEDICINE TARGET IN ACUTE LYMPHOBLASTIC LEUKEMIA AND OVARIAN CANCER
Anthony Burgett, PhD
Department of Chemistry and Biochemistry
The University of Oklahoma

2:20-2:40  PROTO-ONCOGENIC FUNCTION OF BMI1 IS ENHANCED BY CK2A MEDIATED PHOSPHORYLATION: ITS IMPLICATIONS IN OVARIAN CANCER
Soumyajit Banerjee Mustafi, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center

2:40-3:00  A NOVEL ROLE OF MYOCARDIN-RELATED TRANSCRIPTION FACTORS IN PROSTATE CANCER
Bojie Dai, PhD
Department of Cell Biology
The University of Oklahoma Health Sciences Center

CPC  CANCER CHEMOPREVENTION  Room A
Moderator: C.V. Rao, PhD

2:45-3:15  ROLE OF THE MICROBIOME IN COLORECTAL CANCER
Mark Huycke, MD
Department of Internal Medicine
University of Oklahoma Health Sciences Center

3:15-3:45  DEFECTIVE INTESTINAL MUCIN-TYPE O-GLYCOSYLATION CAUSES SPONTANEOUS COLITIS-ASSOCIATED CANCER IN MICE
Lijun Xia, MD, PhD
Department of Biochemistry and Molecular Biology
The University of Oklahoma Health Sciences Center
PRECISION CANCER PREVENTION: BLOOD –BASED BIOMARKER IDENTIFICATION FOR ENVIRONMENTAL/LIFE-STYLE CANCER RISK FACTORS
Hiroshi Yamada, PhD
Department of Medicine
The University of Oklahoma Health Sciences Center

**CCR**  
**UPDATES & NOVEL THERAPEUTIC IN HEMATOLOGIC MALIGNANCIES**  
Room F
Moderator: Laura Holman, MD

2:00-2:15  
NOVEL THERAPEUTIC AGENTS FOR LYMPHOID MALIGNANCIES  
Mohamad Cherry, MD  
Department of Medicine  
The University of Oklahoma Health Sciences Center

2:15-2:30  
IMMUNOTHERAPEUTICS IN HEMATOLOGIC MALIGNANCIES  
Jennifer Holter-Chakrabarty, MD  
Department of Medicine  
The University of Oklahoma Health Sciences Center

2:30-2:45  
COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY  
Nicolas Pleat, MD  
Department of Medicine  
The University of Oklahoma Health Sciences Center

2:45-3:00  
SYSTEMIC REVIEW OF CENTRAL NERVOUS SYSTEM EXTRA-NODAL MARGINAL ZONE B-CELL LYMPHOMA (CNS EMZBL)  
Adanma Ayanambakkam, MD  
Department of Internal Medicine  
The University of Oklahoma Health Sciences Center

**3:15-4:15 p.m. CONCURRENT SESSION V**

**PTR**  
**TUMOR MICROENVIRONMENT & METASTASIS**  
Auditorium
Moderator: Resham Bhattacharya, PhD & Zhizhuang (Joe) Zhao, PhD

3:15-3:35  
ELUCIDATING THE ROLE OF XRN2 IN TUMOR CELL MOTILITY  
Julio Morales, PhD  
Department of Neurosurgery  
The University of Oklahoma Health Sciences Center
3:35-3:55 TARGETING GCNT3 DISRUPTS MUCINS SYNTHESIS AND INHIBITS PANCREATIC CANCER PROGRESSION
Altaf Mohammed, MD
Department of Medicine
The University of Oklahoma Health Sciences Center

3:55-4:15 MUCIN-TYPE O-GLYCAN DEFICIENCY IN THE SMALL INTESTINE PROMOTES DEVELOPMENT OF SPONTANEOUS DUODENAL TUMOR IN MICE
Kirk Bergstrom, PhD
Cardiovascular Biology Research Program
Oklahoma Medical Research Foundation

CCR TARGETING HPV RELATED CANCERS IN OKLAHOMA: DEMOGRAPHICS AND INTERVENTIONS
Moderator: Laura Homan, MD

3:15-3:30 SCREENING AND PREVENTION OF HPV RELATED CANCERS
Megan Buechel, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center

3:30-3:45 SMOKING, ORAL HEALTH, AND ORAL HPV INFECTION
Thanh Bui, DrPH
Department of Family and Preventive Medicine
The University of Oklahoma Health Sciences Center

3:45-4:00 COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY
Victoria Perkins, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center

4:00-4:15 IMPROVING CANCER CARE FOR AMERICAN INDIANS IN THE IHS SYSTEM – NAVIGATION MAY NOT BE ENOUGH
Lauren Dockery, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center
CANCER PREVENTION AND CONTROL: GUEST SPEAKER BIOGRAPHY
Vani Nash Simmons, PhD
Associate Member
Department of Health Outcomes & Behavior
Moffitt Cancer Center

Vani Nath Simmons, Ph.D., is an Associate Member in the Department of Health Outcomes & Behavior at the Moffitt Cancer Center and an Associate Professor in the Departments of Psychology and Oncologic Sciences at the University of South Florida. Dr. Simmons received a doctorate in clinical psychology from the University of South Florida. She served her internship at James A. Haley Veterans Affairs Medical Center in Tampa and completed a post-doctoral fellowship in Behavioral Oncology at the Moffitt Cancer Center. Dr. Simmons’s research interests include smoking cessation and relapse prevention in special populations. She has two ongoing randomized controlled trials funded by the National Cancer Institute (NCI) examining the efficacy of a smoking relapse prevention intervention in cancer patients and a smoking cessation intervention for Spanish-speaking smokers. In addition to NCI, Dr. Simmons’s research has been funded by the March of Dimes and the Florida Biomedical Research Program.
CONCURRENT SESSIONS: INFORMATION & ABSTRACTS
Concurrent Session I – Preclinical Translational Research
8:35 a.m. – 9:35 a.m. Auditorium

CANCER IMAGING & DETECTION
Moderators: Bin Zheng, PhD & Hong Liu, PhD

8:35 a.m. – 8:55 a.m.
MASS SPECTROMETRY DETECTION OF CHEMOTHERAPY DRUGS IN SINGLE BLADDER CANCER CELLS IN PATIENTS
Zhibo Yang, PhD
Department of Chemistry and Biochemistry
The University of Oklahoma

8:55 a.m. – 9:15 a.m.
3D BREAST XACT FOR EARLY BREAST LESION DETECTION: A SIMULATION STUDY
Shanshan Tang, PhD
Center for Bioengineering and School of Electrical and Computer Engineering
The University of Oklahoma

9:15 a.m. – 9:35 a.m.
QUANTITATIVELY ASSESS BREAST DENSITY AS A CANCER RISK PREDICTION FACTOR IN YOUNG WOMEN USING NONINVASIVE ELECTRICAL IMPEDANCE SPECTRUMS
Ali Zarafshani, PhD
School of Electrical and Computer Engineering
The University of Oklahoma
MASS SPECTROMETRY DETECTION OF CHEMOTHERAPY DRUGS IN SINGLE BLADDER CANCER CELLS IN PATIENTS
Presented by: Zhibo Yang


*Department of Chemistry and Biochemistry, OU-Norman; ‡ Assistant Professor, Department of Urology and SCC Member, OUHSC; § Assistant Professors, Dept. of Chemistry and Biochemistry, OU-Norman and SCC Affiliate Members; ¶ Co-corresponding authors

The development of precision cancer medicine will require the capability to administer drug treatments in an individually tailored manner that will maximize the benefit to the patient. Currently in the clinical treatment of cancer, there is a lack of bioanalytical methodology capable of providing information of the effectiveness of chemotherapy treatment on a real time, day-to-day basis. Cancer as a disease state is increasingly understood as a process defined and propagated at the single cancer cell biology level. A major unmet bioanalytical need at the interface of precision medicine and single cell analysis will be the capability to monitor the dosing and effectiveness of patient-administered chemotherapeutic therapies on the single cancer cell level. Currently, there are no clinical bioanalytical methods capable of determining the concentration of chemotherapeutic agents inside of a patient’s individual cancer cells, and such a method would be a powerful tool in establishing ideal dosing regimens that deliver effective chemotherapeutic concentrations with minimal toxicities. We have developed a novel first-in-class mass spectrometry (MS) technology—the Single-probe—capable of performing single cell mass spectrometry (SCMS) of compounds inside of living single cancer cells under ambient cell culture conditions. In our published results, we have used this device to detect the presence of anti-cancer compounds inside of singe cancer cells cultured and dosed in vitro, with a sampling time of ~3 minutes per cell with no sample preparation required. The Single-probe is ideally suited for the rapid SCMS analysis of cancer cells, including patient isolated cancer cells. In our current NCI funded research project, we are developing the capability of quantitating the amount of standard-of-care chemotherapy drugs in bladder cancer cells, including in both laboratory cultured cell lines and bladder cancer cells isolated from patient urine samples. If successful, this research project will mark the first time drug levels have been measured from patient-isolated cancer cells, and this advancement could lead to the development of single cell mass spectrometry analytical methods guiding chemotherapy drug administration in the clinical treatment of many different kinds of cancer treatment.
Mammography is a valuable screening tool for early breast un-palpable lesion detection and has greatly decreased the breast cancer mortality for women. However, the 2D projection of mammography causes tissue superposition which increase the false-positive, especially for women with dense breast. Breast tomosynthesis is a “pseudo 3D” imaging technique, since the poor resolution along the depth direction due to the thick slice size of tomosynthesis. The dedicated 3D breast CT has barriers to clinical use for its radiation dose, and lack of ability for micro-calcification (µCa) detection. Other 3D imaging techniques including magnetic resonance imaging (MRI), breast photoacoustic imaging, and breast ultrasonography also suffer from reduction of spatial resolution, imaging contrast, and/or detection sensitivity.

X-ray induced acoustic computed tomography (XACT) was investigated to be used in various applications for it combines both advantages of high X-ray contrast and high ultrasonic resolution. Here we proposed a 3D breast XACT technique with low-dose and high sensitivity for early breast lesion detection. The schematics of the 3D breast XACT system was revealed. Simulation study was performed to verify the feasibility and to evaluate the lesion detection ability of this proposed imaging technique. First, the breast tissue, including the skin, glandular tissue, and adipose tissue, was segmented from a breast CT image sequence. Micro-calcification (µCa) cluster was manually embedded inside the breast model. X-ray fluence in the breast model was acquired by numerical calculation, and the initial pressure rise was mapped according to the thermal acoustic principle. Then, acoustic propagation was simulated by Matlab K-wave toolbox and the 3D XACT breast volume was reconstructed through filtered back-projection. Results indicates that the proposed technique has the ability to detect µCa (~100µm) with high spatial resolution and signal-to-noise ratio. Furthermore, the minimal dose required by the proposed 3D breast XACT technique was calculated. The results shows that the minimal dose is 10 times smaller than the dose of the dedicated breast CT, and less than half of the dose of a typical two-view mammography. The proposed 3D Breast XACT imaging technique has the potential to detect the breast lesion with high spatial resolution and very low dose for clinic early breast cancer screening.
Breast density has been recognized as an important risk factor of developing breast cancer. Currently, breast density is visually assessed by radiologists from mammograms based on BI-RADS guidelines. This subjective determination is often unreliable due to the large inter-reader variability. In this study, we investigated and developed a novel breast density assessment method that can easily and reliably quantify breast density. The proposed technique is based on using a non-imaging Electrical Impedance Spectroscopy (EIS) technique and measuring the electrical impedance perturbation of different breast locations to quantitatively assess the breast density and its regional distribution. For this purpose, we assembled a new EIS experimental device based on an enhanced five-electrode transfer impedance measurement technique to measure eight electrical impedance spectrums of the different clock position of the breast, classifying breast density of upper inner, lower inner, lower outer and upper outer locations. We have designed and made four different breast phantoms where mimicking four different breast BI-RADS categories. These phantoms formed with different conductive materials based on different level of fat and fibro-glandular conductive tissues which were non-uniformly mixed to illustrate in vivo conditions. These breast phantoms were then used in our experiments to test and validate our new EIS based quantify breast density measurement technique. The measurement results showed a monotonically increasing trend of the measured EIS signals as the phantom density increases from the simulated BI-RADS category 1 to 4. The detected EIS signals also sensitively varied enabling to detect the regional density change by placing the EIS probes at different clock positions of the phantom. This study demonstrated the feasibility of developing and applying this new EIS technology to non-invasively assess both global and regional breast density. If successful in future human studies, this new EIS technology can be used as a pre-screening breast cancer assessment tool to identify women with high risk of harboring early breast cancer due to the significant asymmetry of breast density between two bilateral breasts.
Concurrent Session I – Cancer Prevention & Control
8:35 a.m. – 9:35 a.m.                                        Room A

GENOMIC RESEARCH & CANCER IN AMERICAN INDIAN COMMUNITIES
Moderator: Mark Doescher, MD, MSPH

8:35 a.m. – 9:35 a.m. PANEL DISCUSSION
Bobby Saunkeah, MS, Chickasaw Nation
Dannielle Branam, Choctaw Nation
Michael Peercy, MPH, Chickasaw Nation
Patrick Gaffney, MD, Oklahoma Medical Research Foundation
Paul Spicer, PhD, The University of Oklahoma
Tribes in Oklahoma wish to capitalize on advances in medical care that could benefit their patients with cancer, but little is known about the role of genetics in the development or treatment of cancer in American Indian patients.

This session will provide an opportunity to learn about:

- Cancer disparities that affect American Indians in Oklahoma
- Controversies regarding genetic knowledge in American Indian communities
- Tribal perspectives on genetic research and health care
- Strategies to move forward in this growing area of cancer control
Concurrent Session II – Preclinical Translational Research

9:35 a.m. – 10:35 a.m. Auditorium

TARGETED THERAPIES

Moderator: Rajagopal Ramesh, PhD & Priyabrata Mukherjee, PhD

9:35 a.m. – 9:55 a.m.

PRE-INJECTION WHEEL RUNNING PRESERVES MOBILITY IN A RODENT MODEL OF PACLITAXEL PERIPHERAL NEUROPATHY
Elizabeth Hile, PT, PhD, NCS, CLT
Department of Rehabilitation Sciences
The University of Oklahoma Health Sciences Center

9:55 a.m. – 10:15 a.m.

EVALUATING THE MECHANISM AND THERAPEUTIC ACTIVITY OF PTC-028, A NOVEL INHIBITOR OF BMI-1 FUNCTION IN OVARIAN CANCER
Anindya Dey, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center

10:15 a.m. – 10:35 a.m.

RADIOTHERAPY TRIGGERED RD3 TRANSCRIPTIONAL REPRESSION IN GOVERNING CSC STATUS AND METASTATIC STATE OF SURVIVING NEUROBLASTOMA CELLS
Dinesh Babu Somasundaram, PhD
Department of Radiology Oncology
The University of Oklahoma Health Sciences Center
PRE-INJECTION WHEEL RUNNING PRESERVES MOBILITY IN A RODENT MODEL OF PACLITAXEL PERIPHERAL NEUROPATHY
Presented by: Elizabeth Hile

Elizabeth S Hile PhD, PT¹, Nataliya Kostereva PhD², Kacey Marra PhD²

¹O UHSC Dept of Rehabilitation Sciences and Stephenson Cancer Center Cancer Rehabilitation Science Program, Oklahoma.
²Dept. of Plastic Surgery, Adipose Stem Cell Center and McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pennsylvania.

Introduction: Peripheral neurotoxicity (PN), a common dose-limiting side-effect of paclitaxel (Ptx) chemotherapy, impacts quality of life with persistent balance and gait dysfunction. Exercise before chemo exposure (‘prehabilitation,’ ‘prehab’) may protect cardiac and cognitive function, but few have investigated mobility, or identified spatiotemporal gait parameters most sensitive to toxicity. This was a pre-clinical pilot to determine 1) if pre-Ptx wheel running protects mobility, 2) key gait parameters for phenotypic characterization of Ptx-PN, and 3) neurophysiologic mechanisms for prehab protection.

Materials/Methods: Female Lewis rats were randomized into 3 groups: sedentary before vehicle (SedSham) or Ptx (SedPtx) injection, and prehab as wheel running 60 min, 5 days/wk before Ptx (ExPtx). Housing and handling were equivalent. Behavior as blinded mobility observation, DigiGait parameters and von Frey was assessed at baseline, before and after injection, and before euthanasia. Peripheral nerves were harvested for immunohistochemistry and quantitative histomorphometry with GAP43 (neuroplasticity) and S100 (Schwann) antibodies.

Results: A blinded assessor correctly identified group assignment for 7 of 8 rats by post-injection mobility observation alone, identifying slowness and flattened paws as SedPtx phenotype. Post-hoc visual comparison of DigiGait images confirms paw changes, and sensitivity analysis of the prehab non-responder suggests association with ‘percent propulsion’ gait parameter. Preliminary analyses suggest low S100 in SedPtx sural and sciatic nerves compared to ExPtx and SedSham, and low GAP43 in SedPtx fibular.

Discussion: Mobility dysfunction after Ptx is generally attributed to somatosensory impact, with peripheral neuromotor less quantified. While small n and preliminary, these pre-clinical results echo our anecdotal clinical observations in support of a distal neuromotor focus.

Key words: Chemotherapy, Peripheral Neuropathy, Sensorimotor Gait Disorder, Neurotoxicity Syndromes, Cancer
EVALUATING THE MECHANISM AND THERAPEUTIC ACTIVITY OF PTC-028, A NOVEL INHIBITOR OF BMI-1 FUNCTION IN OVARIAN CANCER
Presented by: Anindya Dey

Anindya Dey1, Xunhao Xiong2, Aleia Crim1, Shailendra Kumar Dhar Dwivedi1, Soumyajit Banerjee Mustafi1, Priyabrata Mukherjee3, Liangxian Cao3, Nadiya Sydorenko3, Ramil Baiazitov3, Young-Choon Moon3, Melissa Dumble3, Thomas Davis3 and Resham Bhattacharya1, 4*

1Department of Obstetrics and Gynecology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma; 2Department of Pathology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma; 3PTC Therapeutics, South Plainfield, New Jersey; 4Department of Cell Biology, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma; *Corresponding Author

BMI-1, a polycomb group protein that confers self-renewal property to normal and cancer stem cells has emerged as an important therapeutic target in several malignancies. Realizing the pathological significance, PTC-209, a small molecule that inhibits translation of BMI-1 was first described in 2014. More recently, PTC-028 was developed with optimized pharmaceutical properties. It is orally bioavailable and decreases BMI-1 by post-translational modification. This is the first study evaluating the biological and therapeutic activity of PTC-028. We report that PTC-028 significantly inhibits clonal growth and viability of high-grade serous ovarian cancer (HGS-OvCa) cells by specifically decreasing the levels of BMI-1 through hyper-phosphorylation mediated depletion, while normal ovarian cells with minimal expression of BMI-1 remain unaffected. At a lower concentration than required for PTC-209, PTC-028 induces faster depletion of BMI-1, decreases levels of RIPK1 and XIAP and potentiates caspase-dependent apoptosis through generation of mitochondrial reactive oxygen species (ROS). Importantly, orally administered PTC-028 exhibits significant single agent antitumor activity similar to that of the standard cisplatin/paclitaxel, administered by the intra-peritoneal route in an orthotopic mouse model of OvCa. Thus, PTC-028 has the potential to be used as an effective therapeutic in patients with HGS-OvCa, where treatment options are limited.
RADIOTHERAPY TRIGGERED RD3 TRANSCRIPTIONAL REPRESSION IN GOVERNING CSC STATUS AND METASTATIC STATE OF SURVIVING NEUROBLASTOMA CELLS

Presented by: Dinesh Babu Somasundaram

Dinesh Babu Somasundaram, Karthikeyan Subramanian, Mohan Natarajan, Sheeja Aravindan, Terence S. Herman and Natarajan Aravindan

1Division of Radiation Biology, Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; Department of Pathology, University of Texas Health Sciences Center at San Antonio, San Antonio, TX, USA.

Recently, we defined the novel tumor evolution stabilization role of Retinal degeneration protein 3 (RD3), regulating the metastatic state of neuroblastoma (NB) cells in vitro and their metastatic potential in vivo. Our earlier studies in various tumor models recognized the role of therapy resistant residual cells in tumor recurrence, relapse and dissemination to distant sites after treatment. Herein, we examined the effect of radiation on the RD3 status of surviving NB cells and investigated the role of RD3 in driving their metastatic potential and CSC status. Human NB (SH-SY5Y, SK-N-AS) cells exposed to single dose (SDR, 10, 20, 50cGy, 1, 2, 4, 5 or 10Gy) or fractionated (FIR, 2Gy/Day for 5 days) irradiation were examined after 1h through 72h for transcription (QPCR) and translational (immunoblotting) alterations of RD3. Clinical doses of radiation (2Gy SDR and FIR) resulted in significant transcriptional repression of RD3 and corresponded to complete loss of this protein in surviving NB cells. Induced transcriptional repression after radiation remained consistent at least up to 72h. RD3 gene silencing studies demonstrated a tight association of RD3-loss to the heightened tumor cell migration and invasion. Re-expression of radiation regulated RD3 overturned the metastatic state of these cells. Further, RD3 silencing/re-expression studies identified RD3-associated regulation of radiation induced clonal expansion (BRdU incorporation). In addition, RD3 gene manipulation studies defined the role of RD3 in regulating tumorosphere formation under serum free conditions (limited dilution tumorosphere assay). Immunoblotting analysis of EMT (E-Cadherin/N-Cadherin) and pluripotency maintaining (Nanog, SOX2, OCT3/4) factors with/without RD3 silencing/re-expression approach validated the role of RD3 in regulating the CSC status of surviving NB cells after treatment. Together, these results demonstrate a complete and persistent transcriptional loss of RD3 in NB cells that survive clinical radiation and, further imply that radiation induced RD3-loss mediates clonal expansion, metastatic state and CSC status of therapy resistant NB cells.

Concurrent Session II – Cancer Prevention & Control
9:35 a.m. – 10:35 a.m. Room A

TOBACCO USE & CESSATION IN UNDERSERVED POPULATION I
Moderator: Jennifer Vidrine, PhD

9:35 a.m. – 10:35 a.m.

SMOKING CESSATION AND RELAPSE REVENTION IN THE ONCOLOGY SETTING
Vani Simmons, PhD
Department of Health Outcomes & Behavior
Moffitt Cancer Center
Concurrent Session III – Preclinical Translational Research & Clinical & Correlative Research

1:00 p.m. – 2:00 p.m.                  Auditorium

DRUG DEVELOPMENT & CLINICAL RESEARCH
Moderators: C.V. Rao, PhD & Min Li, PhD

1:00 p.m. – 1:20 p.m.
THE CURRENT STATE OF OVARIAN CANCER SCREENING AMONG AVERAGE-RISK WOMEN
Laura Holman, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center

1:20 p.m. – 1:40 p.m.
BRINGING AN OKLAHOMA-MADE CANCER DRUG FROM DISCOVERY TO CLINICAL TRIAL
Doris Benbrook, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center

1:40 p.m. – 2:00 p.m.
IS BMI1 A GOOD TARGET IN CANCER?
Resham Bhattacharya, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center
The majority of small molecule compounds that show promising anti-cancer activity in preclinical studies are never advanced into clinical trials, and the majority that make it into clinical trials are discontinued before they are commercialized. In order to reduce the risk of drug failure, preclinical studies need to be optimally designed and interpreted. The US Food and Drug Administration (FDA) mandates specific preclinical studies that must be included in Investigational New Drug (IND) applications to initiate clinical trials. These studies often cost billions of dollars to complete. Our multi-disciplinary academic research group has been able to complete the preclinical studies needed to file a FDA IND application for clinical trials with our Oklahoma-made Drug, OK-1 (also called SHetA2, or NSC 721689), by utilizing resources within the National Cancer Institute (NCI). The NCI RAID Program developed an assay to measure OK-1 drug levels in tissue specimens and performed metabolism studies. The NCI RAPID program demonstrated that OK-1 does not cause mutagenicity, carcinogenicity or toxicity and developed formulations to increase OK-1 bioavailability. The NCI PREVENT program is funding studies to develop pharmacodynamic biomarkers to monitor and study SHetA2 in clinical trials. PREVENT is also producing a current Good Manufacturing Practice (cGMP) batch of SHetA2 capsules and performing two-year stability studies on the capsules. Recently awarded NCI R01 grants are providing the funds to conduct Phase 0 clinical trials of OK-1 in healthy volunteers and cervical cancer patients. Efforts to develop ovarian cancer therapeutic strategies targeted at the OK-1 mechanism and progress SHetA2 into Phase 1 single agent and combination clinical trials are included in a program project grant application under review at the NCI.
BMI1, a member of the nuclear Polycomb Repressor Complex 1 mediates gene silencing by regulating chromatin structure and is indispensable for self-renewal of stem cells. In the cancer context, BMI1 has been implicated in several major malignancies where its expression correlates with chemotherapy resistance and overall poor prognosis. In the past decade, our understanding of adaptive responses to chemotherapy leading to the emergence of drug resistant stem-like cancer cells has considerably evolved. While targeting BMI1 in various systems reduces clonal growth, a measure of stem cell maintenance, the mechanisms remain elusive. Here I will discuss a previously unknown extra-nuclear localization of BMI1 in the mitochondria, and novel functional interactions both in the nucleus as well as in the mitochondria that have implications in maintenance of a stem-like phenotype. Using newly developed pre-clinical and clinical inhibitors, the mechanism and consequences of targeting BMI1 in cancer will also be discussed.
Concurrent Session III – Cancer Prevention & Control
1:00 p.m. – 2:30 p.m. Room A

TOBACCO USE & CESSATION IN UNDERSERVED POPULATION II
Moderator: Damon Vidrine, DrPH

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<tr>
<td>1:00 p.m. – 1:20 p.m.</td>
<td>TOBACCO CESSATION FOR CERVICAL CANCER SURVIVORS</td>
<td>Jennifer Vidrine, PhD</td>
<td>Department of Family and Preventive Medicine</td>
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<td>1:22 p.m. – 1:42 p.m.</td>
<td>THE TOBACCO TREATMENT RESEARCH PROGRAM (TTRP): INTEGRATING TREATMENT AND RESEARCH</td>
<td>Darla Kendzor, PhD</td>
<td>Department of Family and Preventive Medicine</td>
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<td>The University of Oklahoma Health Sciences Center</td>
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<td>1:44 p.m. – 2:04 p.m.</td>
<td>CREATIVE SYSTEMS CHANGE: OKLAHOMA TOBACCO HELPLINE INTEGRATION WITH 211 CRISIS HOTLINE</td>
<td>Stephen Gillaspy, PhD</td>
<td>Department of Pediatrics</td>
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<td>2:06 p.m. – 2:26 p.m.</td>
<td>VAPING STATUS AND TOBACCO EXPOSER BIOMARKERS AMONG COHORT OF AMERICAN INDIAN SMOKERS</td>
<td>Ashley Comiford, DrPH</td>
<td>Community Health Promotions</td>
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Smoking prevalence is high among cervical cancer survivors, with rates approaching 50%. Survivorship care planning should include the delivery of smoking cessation treatment designed to address the specific treatment needs of these women. This study investigated the treatment needs of cervical cancer survivors to inform the adaptation of a theoretically- and empirically-based Motivation and Problem-Solving (MAPS) approach to facilitating smoking cessation in this vulnerable population.

Individual in-depth interviews were conducted with 10 female smokers with cervical cancer (80% non-Latino white; 50% >high school education; 80% <$30,000 annual household income). Interviews were audio-recorded and transcribed, and analyzed using NVivo 10. Thematic analyses revealed that cervical cancer significantly impacted participants’ lives; it resulted in changes to their outlook on life and led to worry about other potential health problems. Participants did not believe that smoking and cervical cancer were associated, and attributed their diagnosis solely to human papillomavirus (HPV).

Participants reported smoking out of habit and to cope with negative affect, particularly stress. They were interested in quitting, as a means for saving money and improving health, but concerned about coping with withdrawal and negative affect. It was suggested that smoking cessation treatment for cervical cancer survivors should be individualized, but include: psychoeducation about the impact of smoking on health and various cancers including cervical cancer, pharmacotherapy, and benefits of quitting; planning for quitting; strategies for coping with withdrawal and negative affect; real-time support; social support; and relapse prevention. Participants suggested the following components to include in a wellness program: stress management; physical activity and healthy eating; coping with what it means to be a cervical cancer survivor; and managing side effects of cancer and treatment.

Results highlight the unique treatment needs of smokers with cervical cancer and will be used to adapt an existing evidence-based intervention to encourage smoking cessation in cervical cancer survivors.
THE TOBACCO TREATMENT RESEARCH PROGRAM (TTRP): INTEGRATING RESEARCH AND PRACTICE
Presented by: Darla Kendzor

Darla E. Kendzor, Ph.D.
The University of Oklahoma Health Sciences Center, Department of Family and Preventive Medicine, Stephenson Cancer Center, Oklahoma Tobacco Research Center

This presentation will describe the newly established Tobacco Treatment Research Program (TTRP), which is part of the Stephenson Cancer Center and is located at the Oklahoma Tobacco Research Center (OTRC). The TTRP opened its doors in October 2016 and offers treatment for tobacco dependence free-of-charge to the public. The TTRP also functions as an observational research study, where participants are followed for data collection through 27 weeks post-enrollment. The aims of the IRB-approved TTRP protocol are to 1) provide a free intensive tobacco treatment intervention to the public, 2) serve as a comparison group for tobacco cessation treatment trials, 3) provide preliminary data for future grant funding applications that intend to utilize TTRP services, 4) measure variables relevant to the process of quitting and make these data available to researchers and students with IRB-approved protocols, and 5) facilitate the recruitment of participants into OTRC research studies. The TTRP offers weekly counseling and support sessions, as well as nicotine replacement therapy and/or other pharmacological treatments at no cost to those who qualify. Consenting participants complete surveys on tablets computers, and provide carbon monoxide breath samples and other physiological and anthropometric measures (e.g., height, weight, blood pressure) while they participate in tobacco cessation treatment. Key follow-up points occur at 5, 13, and 27 weeks post-enrollment. To date, participants have been predominantly female (63.9%), and non-Hispanic White (55.6%), Black/African American (16.7%), or American Indian/Alaska Native (13.9%). The average age of TTRP participants is 51.1 years, and the majority have reported an annual household income of < $16,000 (52.7%). In addition, more than half of participants report receiving Medicaid benefits or having no insurance (52.8%). The future directions of the TTRP will be discussed, including imminent changes to the electronic medical record which will facilitate the referral process and increase participant volume. Overall, it is expected that the TTRP will contribute to reductions in smoking among Oklahomans, while furthering the progress of tobacco-related research.
Quitlines reach 1-2% of tobacco users annually. We know certain populations use tobacco at higher rates, including low SES, and those with co-morbidities (chronic and behavioral health conditions). Creative systems change and referral approaches are needed to reach more tobacco users. 211 Heartline is a 24-hr call center in Oklahoma connecting people in crisis (medical, financial, or other) to information and resources. With over 4700 community agencies and programs in their database, and trained counselors staffing phone lines, 211 Heartline serves those who need help the most. In 2015, the Oklahoma Tobacco Helpline (OTH) and 211 Heartline began a collaboration to pilot test screening and referrals from 211 to the Helpline for callers who a) were not in immediate crisis, b) were tobacco users, and c) consented to a referral to the Helpline. Referrals included direct warm transfers, e-referrals, and providing 211 callers with the Helpline toll-free number. Integration of OTH referrals through 211 launched September 8, 2016. In the first six weeks of operation, 2,444 callers to 211 were asked about tobacco use, and 584 (24%) reported using tobacco. Of the tobacco users, 310 (53%) planned to quit in the next 30 days, and 289 (93%) accepted a referral. Of the referrals, 26 (9%) were warm-transferred directly to the quitline, 74 (26%) were electronically referred, and 189 (65%) were given the toll-free number. Preliminary results show that Helpline integration with a statewide 211 crisis hotline is feasible and acceptable. Referral demographics and enrollment rates will also be presented.
VAPEs AND TOBACCO EXPOSER BIOMARKERS AMONG A COHORT OF AMERICAN INDIAN SMOKERS
Presented by: Ashley Comiford

Ashley L. Comiford, DrPH¹; Dorothy A. Rhoades, MD, MPH²; Kai Ding, PhD³; Justin D. Dvorak, PhD⁴; Theodore L. Wagener, PhD⁵; Mark P. Doescher, MD, MSPH⁶

¹Epidemiologist, Cherokee Nation; ²Clinical Associate Professor, Department of Medicine, University of Oklahoma Health Sciences Center, and Stephenson Cancer Center; ³Assistant Professor, Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center; ⁴Research Biostatistician, Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center; ⁵Assistant Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center and Oklahoma Tobacco Research Center; ⁶Professor, Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, and Stephenson Cancer Center

Rationale: Electronic cigarettes (e-cigs) are increasingly popular among adults who smoke, and are often used to reduce or quit cigarette smoking. American Indians (AI) have a high prevalence of cigarette use and are disproportionately affected by tobacco-related diseases, but their concurrent use of cigarettes and e-cigs is unknown. Further, the question of whether concurrent use reduces exposure to tobacco constituents remains unknown.

Methods: We collected baseline survey and smoking biomarker data in a cohort of 375 adult AI smokers recruited from a Cherokee Nation healthcare facility in Oklahoma. We used multivariate logistic and linear regression analyses to determine the association between vaping status (never, past, or current (past 30 days) use) and any smoking quit attempt, cigarette packs smoked per day (< 1 or ≥ 1), and salivary cotinine levels, adjusted for socio-demographics, general health, selected medical history, depression, and other tobacco use.

Results: Overall, 37% of the cohort never used e-cigs, 47% were past users, and 16% were current users. Compared to never users, current users (OR = 3.5 95%CI = 1.5-8.5) and past users (OR = 1.9 95%CI = 1.1-3.3) were more likely to report any lifetime quit attempt. There were no statistically significant associations between vaping status and cigarette packs smoked per day or salivary cotinine level.

Conclusions: Current and past e-cig users were more likely than never users to have any lifetime smoking quit attempt, but cigarette pack consumption and cotinine levels were similar across e-cig groups. This suggests that in this population of AI who smoke, use of e-cigs may be associated with intentions to quit but may have limited effect on reducing cigarette consumption.
Concurrent Session IV – Preclinical Translational Research

2:00 p.m. – 3:00 p.m. Auditorium

BASIC CANCER BIOLOGY
Moderators: Ralf Janknecht, PhD & Jie Wu, PhD

2:00 p.m. – 2:20 p.m.
BIOLOGICAL INVESTIGATION AND DRUG TARGETING OF THE ORP4 PROTEIN: A NEW POTENTIAL PRECISION MEDICINE TARGET IN ACUTE LYMPHOBLASTIC LEUKEMIA AND OVARIAN CANCER
Anthony Burgett, PhD
Department of Chemistry and Biochemistry
The University of Oklahoma

2:20 p.m. – 2:40 p.m.
PROTO-ONCOGENIC FUNCTION OF BMI1 IS ENHANCED BY CK2A MEDIATED PHOSPHORYLATION: ITS IMPLICATIONS IN OVARIAN CANCER
Soumyajit Banerjee Mustafi, PhD
Department of Obstetrics and Gynecology
The University of Oklahoma Health Sciences Center

2:40 p.m. – 3:00 p.m.
A NOVEL ROLE OF MYOCARDIN-RELATED TRANSCRIPTION FACTORS IN PROSTATE CANCER
Bojie Dai, PhD
Department of Cell Biology
The University of Oklahoma Health Sciences Center
BIOLOGICAL INVESTIGATION AND DRUG TARGETING OF THE ORP4 PROTEIN: A NEW POTENTIAL PRECISION MEDICINE TARGET IN ACUTE LYMPHOBLASTIC LEUKEMIA AND OVARIAN CANCER
Presented by: Anthony W.G. Burgett

Naga Rama Kothapalli, Anh Le, Juan I. Nunez, Anh Le, Brett L. Roberts and Anthony W.G. Burgett
Dept. of Chemistry and Biochemistry, University of Oklahoma

The new era of cancer precision medicine will be built upon the therapeutic targeting of cancer-specific cellular proteins identified as drivers in individual patient’s disease; this new paradigm requires the identification and validation of new druggable cancer-specific targets. The cellular protein ORP4 (oxysterol-binding protein (OSBP)-related protein 4) is a cytoplasmic, non-enzymatic protein with unclear biological function and limited expression in normal tissue. In 2016, ORP4 was reported to be selectively expressed in and essential for the viability of acute lymphoblastic leukemia (ALL) cells. In these ALL cells, ORP4 function was linked to cellular energetics and overall ATP production. ORP4 protein expression is also reported to be highly expressed in a few other types of cancers, including ovarian cancer. The connection of ORP4 as a cancer drug target confirms our discovery that a class of potent anti-proliferative natural product compounds inhibit cell proliferation through targeting ORP4 and potentially related oxysterol-binding protein (OSBP) family members. Our group has an interdisciplinary chemistry and biology program to investigate the cellular function of the OSBP/ORP proteins, especially in human disease, and to develop novel small molecule ligands to probe and potentially drug this class of proteins. We have developed methods to determine the ORP4 transcription and protein expression levels in cancer cells, in addition to developing ORP4 overexpression systems in mammalian cells. Our results strongly support ORP4 as being the critical member of the OSBP/ORP protein essential for cancer cell proliferation. We have studied the cellular regulation of ORP4 expression levels, and we have established this protein is regulated in cancer cells in a manner completely distinct from OSBP/ORP family members. We have also established a high-throughput ORP4 ligand binding assay to identify high affinity and specific ORP4 small molecule ligands, and we are undertaking a ORP4-drug development program based on the structure of the natural product compound OSW-1; the OSW-1-compound is a highly potent anti-proliferative agent ($GI_{50} = 0.8$ nM against the NCI-60 cell line panel), and we have demonstrated that the OSW-1 compound is a high affinity ORP4 ligand ($K_i \approx 40$ nM). Our research program will seek to further validate and understand ORP4 as a precision cancer target in ALL and ovarian cancers while introducing novel OSW-1-compound-derived analogs with superior pharmacological properties for drug development exploration.
The polycomb group protein, BMI1 plays important roles in chromatin modification, stem cell function, DNA damage repair and in mitochondrial bioenergetics. Such diverse cellular functions of BMI1 could be, in part, due to post-translational modifications, especially phosphorylation. Till date, AKT has been reported as a kinase that by site specific phosphorylation of BMI1 modulates its oncogenic functions.

Here we report that CK2α, a nuclear serine threonine kinase, phosphorylates BMI1 at Serine 110 as determined by in-vitro/ex-vivo kinase assay and mass spectrometry. In ovarian cancer cell lines, expression of CK2α correlated with the phospho-species, as well as basal BMI1 levels. Preventing phosphorylation of BMI1 at Serine 110 significantly decreased half-life and stability of the protein. Additionally, re-expression of the phosphorylatable but not non-phosphorylatable BMI1 rescued clonal growth in endogenous BMI1 silenced cancer cells leading us to speculate that CK2α-mediated phosphorylation stabilizes BMI1 and promotes its oncogenic function. Clinically, compared to normal fallopian tube epithelial tissues, the expression of both BMI1 and CK2α were significantly higher in tumor tissues obtained from high-grade serous ovarian cancer patients. Among tumor samples, the expression of BMI1 and CK2α positively correlated (Spearman coefficient =0.62, P=0.0021) with each other. Taken together, our findings establish an important regulatory role of CK2α on BMI1 phosphorylation and stability and implicate the CK2α/BMI1 axis in ovarian cancer.
A NOVEL ROLE OF MYOCARDIN-RELATED TRANSCRIPTION FACTORS IN PROSTATE CANCER
Presented by: Bojie Dai

Bojie Dai, James Griffith, William Berry, James J. Tomasek

Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

The transcriptional co-activators myocardin-related transcription factors (MRTFs) are key regulators for cytoskeletal protein expression. 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. We and others have previously found that MRTFs are key players for wound healing. However, the role of MRTFs in prostate cancer still remains largely unknown. Herein, we demonstrate by using human tissue microarrays that MRTFs are strongly immunostained in both the cytoplasm and nucleus of prostate tumor cells, and, to a much lesser extent, in the luminal epithelial cells in benign samples. Moreover, there is a positive correlation of MRTFs immunoreactivity with the Gleason grades of the tumor samples. The protein expression of MRTFs is also increased in prostate carcinoma tissue from the well-defined mouse model with heterozygous Pten deletion compared with wild-type controls. The downregulation of MRTFs by their pharmacological inhibitor abrogates cell proliferation and migration in prostate cancer cells, supporting a critical role for MRTFs in prostate cancer development. MRTFs associate with ERK and activate ERK. Treatment with combination of MRTFs inhibitor and ERK inhibitor synergistically abrogates prostate cancer cell proliferation and migration compared with treatment of either drug alone. Our data reveal a previously unidentified role of MRTFs in prostate cancer development and support the potential combined therapeutic targeting of MRTFs and ERK in human prostate cancer.
Concurrent Session IV – Cancer Prevention & Control
2:45 p.m. – 4:15 p.m.                                 Room A

CANCER CHEMOPREVENTION
Moderator: C.V. Rao, PhD

ROLE OF THE MICROBIOME IN COLORECTAL CANCER
Mark Huycke, MD
Department of Internal Medicine
University of Oklahoma Health Sciences Center

DEFECTIVE INTESTINAL MUCIN-TYPE O GLYCOSYLATION CAUSES SPONTANEOUS COLITIS-ASSOCIATED CANCER IN MICE
Lijun Xia, MD, PhD
Department of Biochemistry and Molecular Biology
The University of Oklahoma Health Sciences Center

PRECISION CANCER PREVENTION: BLOOD-BASED BIOMARKER IDENTIFICATION FOR ENVIRONMENTAL/LIFE-STYLE CANCER RISK FACTORS
Hiroshi Yamada, PhD
Department of Medicine
The University of Oklahoma Health Sciences Center
Colorectal cancer (CRC) is a leading cause of cancer death and archetype for cancer as a genetic disease. However, mechanisms for genetic change and their interactions with environmental risk factors have been difficult to unravel. New hypotheses, models, and methods are being used to investigate a complex web of risk factors that includes the intestinal microbiome. Recent research has clarified how the microbiome can generate genomic change in CRC. Several phenotypes among a small group of selected commensals have helped us better understand how mutations and chromosomal instability (CIN) are induced in CRC (e.g., toxin production, metabolite formation, radical generation, and immune modulation leading to a bystander effect). This seminar discusses recent hypotheses, models, and mechanisms by which the intestinal microbiome contributes to the initiation and progression of sporadic and colitis-associated forms of CRC. Overall, it appears the microbiome can initiate and/or promote CRC at all stages of tumorigenesis by acting as an inducer of DNA damage and CIN, regulating cell growth and death, generating epigenetic changes, and modulating host immune responses. Understanding how the microbiome interacts with other risk factors to define colorectal carcinogenesis will lead to more accurate risk prediction. A deeper understanding of CRC etiology will help identify new targets for prevention and treatment and accelerate the decline in mortality for this common cancer.
DEFECTIVE INTESTINAL MUCIN-TYPE O-GLYCOSYLATION CAUSES SPONTANEOUS COLITIS-ASSOCIATED CANCER IN MICE
Presented by: Lijun Xia

Kirk Bergstrom, Jianxin Fu, and Lijun Xia

Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA.

Core 1- and 3-derived O-glycans are major components of the colonic mucus layer. Defective O-glycosylation is such as Tn antigen expression frequently observed in ulcerative colitis and colorectal cancer with unknown etiological role. We investigated whether and how impaired O-glycosylation predisposes to colitis-associated colon cancer. A new mouse line lacking both core 1- and 3-derived intestinal O-glycans (DKO) was generated and then analyzed together with our previously generated mice lacking intestinal core 1 O-glycans (IEC C1galt1–/–) and mice lacking core 3 O-glycans (C3GnT–/–) over time by comparing intestinal mucus integrity, Tn antigen exposure, colitis and cancer susceptibility, and inflammatory mediators/pathways via macroscopic, biochemical, and molecular approaches (imaging, western blot, qPCR, etc.). DKO mice expressed higher Tn antigen and exhibited worsened spontaneous chronic colitis than IEC C1galt1–/– mice. Both IEC C1galt1–/– and DKO mice developed spontaneous colon tumors at older ages, however the disease in DKO mice occurred earlier and with greater severity by comparison. Colitis and cancer were dependent on inflammation rather than aberrant Tn exposure because microbial depletion in DKO mice reduced colitis and neoplasia but not Tn expression. Moreover, microbiota-mediated activation of epithelial caspase 1–dependent inflammasomes was required for spontaneous colitis-associated cancer in DKO mice. Impaired expression of O-glycans causes colonic mucus barrier breach and subsequent microbiota-mediated activation of epithelial caspase 1–dependent inflammasomes, which contributes to the pathogenesis of colitis-associated colon cancer in our models. These findings reveal an important role for mucin-type O-glycans in intestinal mucus barrier function.
Many cancers are preventable. However, identifying high-risk individuals is difficult. Decades of cancer chemoprevention studies have identified chemicals and natural compounds that significantly inhibit and prevent the development of various cancers. If properly applied to high-risk individuals, these measures can prevent cancer development. Applying this knowledge to humans in the public setting is challenging because it is hard to identify individuals with high cancer risk. Finding biomarkers that correctly indicate the high risk for cancer development will significantly advance the application of preventive medicine to the public.

Blood samples are an ideal material for biomarker identification. Blood collection is minimally invasive and will merge well with public programs. Much like cholesterol measurements for cardiovascular health or blood sugar/HbA1c measurements for diabetes, if blood biomarkers can be used to identify high cancer-risk individuals, and counseling or chemoprevention measures can be initiated, the mortality rate from cancer will drop significantly.

Environmental and Lifestyle factors relevant to the state of Oklahoma. The state of Oklahoma shows higher-than-average cancer incidence. The high incidence may be attributed to a combination of various environmental factors (e.g., Arsenic exposure from drinking water) and lifestyle factors (e.g., smoking, high-fat diet).

In this presentation, we will discuss our rodent-based translational studies with RNAseq-transcriptome analysis, which have yielded a wealth of information as to how genomic instability may affect carcinogenesis in the colon and lung, and the roadmap for the studies to be translated to human populations in public settings in the near future.
Concurrent Session IV – Clinical & Correlative Research
2:00 p.m. – 3:00 p.m.                        Room F

UPDATES & NOVEL THERAPEUTICS IN HEMATOLOGIC MALIGNANCIES
Moderator: Laura Holman, MD

2:00 p.m. – 2:15 p.m.
NOVEL THERAPEUTIC AGENTS FOR LYMPHOID MALIGNANCIES
Mohamad Cherry, MD
Department of Medicine
The University of Oklahoma Health Sciences Center

2:15 p.m. – 2:30 p.m.
IMMUNOTHERAPEUTICS IN HEMATOLOGIC MALIGNANCIES
Jennifer Holter-Chakrabarty, MD
Department of Medicine
The University of Oklahoma Health Sciences Center

2:30 p.m. – 2:45 p.m.
COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY
Nicolas Pleat, MD
Department of Medicine
The University of Oklahoma Health Sciences Center

2:45 p.m. – 3:00 p.m.
SYSTEMIC REVIEW OF CENTRAL NERVOUS SYSTEM EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA (CNS EMZBL)
Adanma Ayanambakkam, MD
Department of Internal Medicine
The University of Oklahoma Health Sciences Center
Lymphoid malignancies include acute and chronic lymphoid leukemias, Hodgkin’s and Non-Hodgkin’s lymphomas as well as less well-defined malignancies affecting the lymphoid lineage. Since the FDA approval of the anti-CD20 monoclonal antibody rituximab in the treatment of lymphoid malignancies 2 decades ago, the use of targeted therapy for this class of cancers has shown an exponential growth in the discoveries of numerous monoclonal and biclonal agents, tyrosine kinase inhibitors, epigenetic modifiers, agents that target the tumor microenvironment, notably the immunomodulatory agent lenalidomide and most recently we have witnessed the revolution of immunotherapy with the checkpoint inhibitors and chimeric antigen receptor (CAR)-T-cell therapy.

In this review, we will highlight on the most recent advances on the use of the Bruton Tyrosine kinase (BTK) inhibitors, PI3K inhibitors, BCL2 inhibitors, and novel monoclonal and biclonal antibodies that have been recently approved by the FDA as well as their optimal use clinically.

In a matter of fact, the landscape of drugs for the treatment of lymphoid leukemia and lymphoma has become crowded in light of the plethora of new agents, necessitating the efficient prioritization of drugs for expedited development. This has resulted in the emergence of new challenges that could potentially encounter the practicing oncologist: these include determining the optimal duration of therapy, and the need to balance costs, benefits, and the risk of late-onset toxicities.
Introduction: IVL is a rare entity characterized by proliferation of clonal lymphoma cells in vessel lumina of organs & is a subset of large cell NHL with Western & Asian types. Asian type can have hemophagocytic syndrome & bone marrow disease while Western has neurological & cutaneous symptoms. Commonalities are constitutional symptoms, elevated sLDH/anemia, aggressive/disseminated pattern, & fatal outcome. Given its rarity, poor prognosis, & non-specific symptoms, establishing a diagnosis is a challenge. Therefore, we reviewed published case reports to analyze related outcomes to heighten an understanding of this disease.

Materials/Methods: Systematic review of Medline/Embase databases via OVID engine was conducted under keywords “intravascular lymphoma”, “angiotropic lymphoma” & “malignant angioendotheliomatosis”. Search was limited to publications from Jan 1994 - Dec 2015 & included all English language pathologically confirmed human cases of Western IVL. Asian type & insufficient reports were excluded. End points were demographics, outcomes, & overall survival. Chi-squared test was used for categorical covariates & student T-test compared subgroup means for continuous covariates. Statistical analysis was via SAS 9.3 software.

Results: Total of 155 pts were identified with B-Cell (77%, n=119) & T-Cell (9%, n=14) types being most common. Males were 53% (n=82) & median presentation age was 65. All had stage IV & 14% (n=21) involved bone marrow. Symptoms were fever (52%), neurologic (51%), fatigue (46%), night sweats (23%), weight loss (23%), edema (22%), GI (14%), RESP (14%), GU (7%), MSK (5%) & CV (1%). Diagnosis was made after autopsy in 32% (n=49) & others by biopsy (skin 23%, brain 10%, bone marrow/lymph node 9%, other 26%). Median survival at diagnosis of all types was 5 months with a mean of B & T-Cell variants being 10.8 & 10.4 respectively (P=0.9472). Total of 57% (n=88) got chemotherapy (19% CHOP, 16% R-CHOP, & 21% other) with a mean survival of 16 months (95% CI, 12-20; P<0.0001). Rituximab was used in 19% (n=30) & 10% (n=15) got IV MTX. Mean survival of pts given Rituximab was 19.4 months (95% CI, 13.1-25.8) vs 8.3 (95% CI, 5.7-10.9; P=0.0008) if not. B-cell type treated by R-CHOP vs CHOP had a mean survival of 21.2 & 10.2 months respectively (P<0.0247) & for MTX vs no MTX had a mean of 37.4 & 14.3 months respectively (P=0.115). For all chemotherapy pts, MTX median survival was 25 months (95% CI, 11.3-38.7) vs a mean of 14.3 months (95% CI, 10.4-10.8; P=0.0232) if not.

Discussion: No statistical difference was found in overall survival amongst B & T-Cell types. Pts of B-Cell type treated with chemotherapy had a clinically prolonged survival with MTX & Rituximab but was not statistically significant. For pts treated with chemotherapy, MTX prolonged survival & was statistically significant. In conclusion, our analysis of Western IVL published cases identifies an inherently poor prognosis without chemotherapy & combining a MTX & Rituximab backbone suggests providing a clinical benefit.
CNS EMZBL, an indolent, radiosensitive lymphoma with good treatment outcomes and prognosis, is an important differential to consider in patients with extra-axial dural based masses. Individual therapy with preference to localized treatment options, should be tailored after consideration of extent of disease, surgical resectability and adverse effects of chemotherapy.

We hereby present systemic literature review of 57 cases of CNS EMZBL (including one case report diagnosed at OUMC) with describing the clinical presentation, treatment options and prognosis. A 33-year-old female was initially diagnosed as meningioma based on imaging, and was diagnosed with CNS EMZBL based on histopathological examination. CNS EMZBL is the most common primary CNS low grade lymphoma. Despite no mucosal tissue being present in the CNS, numerous cases of CNS EMZBL presenting as extra-axial dural based masses have been reported.

**Methods:** Systemic literature review of articles from 1997 to 2016, identified 29 unduplicated peer reviewed articles of marginal zone B cell lymphoma involving the central nervous system. A total of 56 reported cases of CNS EMZBL were identified and included in the review. Data about baseline population characteristics, type of intervention, outcome and study design were collected.

**Results:** Median age of 51 (range 18 - 77) with a significantly increased incidence in females (75%). Dural based extra-axial lesions with a presumptive diagnosis of meningioma were the most common (60%). Four cases, presented initially as a subdural hematoma and subsequently diagnosed with meningioma. Localized therapies such as radiotherapy (n=16), radiotherapy with surgery (n=15) and surgery (n=10) were the most common treatment regimens. Various chemotherapy agents ranging from systemic to intrathecal chemotherapy were used.

**Outcomes:** Out of the 57 reported cases 17.5% (n=10) of patients were not followed up after treatment and 82.5% (n=47) had a median follow up of 22 months. Out of the patients who were followed up, complete remission was achieved in 74.46 % (n=35) and 23.40% (n=11) were alive with disease. 6.38% of patients (n=3) had evidence of disease relapse with one patient with evidence of relapse in a different site. Out of the 3 patients with evidence of recurrence, one was alive with disease at 47 months, another achieved complete remission with treatment and another died due to complications of chemotherapy. There were no reported cases of mortality attributed to CNS EMZBL.

**Conclusion:** Marginal Zone B-Cell Lymphoma (MZBL) a non-Hodgkin lymphoma arising from the post-germinal center marginal zone B cells is sub-classified into EMZBL, nodal marginal zone B cell lymphoma & splenic MZBL. CNS EMZBL is the most common primary CNS low grade lymphoma. Numerous cases of CNS EMZBL present as extra-axial dural based masses mimicking meningioma and should be considered in the differential diagnosis. Treatment mainly include surgery with or without radiation, although systemic chemotherapy has been used with excellent outcome. Radiologists, neurosurgeon and pathologist should consider this entity in their differential diagnosis of meningiomas as the treatment may be different.
Concurrent Session V – Preclinical Translational Research

3:15 p.m. – 4:15 p.m. Auditorium

TUMOR MICROENVIRONMENT & METASTASIS
Moderator: Resham Bhattacharya, PhD & Zhizhuang (Joe) Zhao

3:15 p.m. – 3:35 p.m.
ELUCIDATING THE ROLE OF XRN2 IN TUMOR CELL MOTILITY
Julio Morales, PhD
Department of Neurosurgery
The University of Oklahoma Health Sciences Center

3:35 p.m. – 3:55 p.m.
TARGETING GCNT3 DISRUPTS MUCINS SYNTHESIS AND INHIBITS PANCREATIC CANCER PROGRESSION
Altaf Mohammed, MD
Department of Medicine
The University of Oklahoma Health Sciences Center

3:55 p.m. – 4:15 p.m.
MUCIN-TYPE O-GLYCAN DEFICIENCY IN THE SMALL INTESTINE PROMOTES DEVELOPMENT OF SPONTANEOUS DUODENAL TUMOR IN MICE
Kirk Bergstrom, PhD
Cardiovascular Biology Research Program
Oklahoma Medical Research Foundation
Tuyen T. Dang and Julio C. Morales

XRN2 is a 5’-3’ exo-nuclease traditionally associated with transcription elongation and termination. Recently, we uncovered a role for XRN2 in the DNA damage response. Loss of XRN2 lead to increased double strand breaks, RNA:DNA hybrids, radiation sensitivity, chromosomal aberrations and replication stress. We also found that loss of XRN2 impairs the cells ability to perform non-homologous end joining. Additionally, loss of XRN2 sensitizes cells to PARP1 and DNA repair inhibition. Surprisingly, we also found that XRN2 plays a role in tumor cell motility. Loss of XRN2 decreases tumor cell motility. Thus, we hypothesize that XRN2 plays a role in the chemo resistance of invasive tumor cells.
TARGETING GCNT3 DISRUPTS MUCINS SYNTHESIS AND INHIBITS PANCREATIC CANCER PROGRESSION
Presented by: Altaf Mohammed

Altaf Mohammed1, Naveena B. Janakiram1, Venkateshwar Madka1, Gaurav Kumar1, Scott Edgar2, Gopal Pathuri3, Taylor Bryant3, Hannah Kutche3, Yuting Zhang3, Laura Biddick1, Hariprasad Gali3, Yan Daniel Zhao4, Stan Lightfoot1, and Chinthalapally V. Rao1

1Center for Cancer Prevention and Drug Development, Department of Medicine, Hem-Onc Section, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 2Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 3College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 4Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Pancreatic cancer (PC) is a lethal disease, and its management is an ongoing challenge. PC is the fourth leading cause of deaths due to cancer in the United States. It is a highly aggressive cancer that is usually diagnosed at an advanced stage, and has the worst prognosis of any malignancy, with a five year survival of <7% due to high chemoresistance. This chemoresistance is due in part to altered expressions of mucins, which form a mesh that makes target sites inaccessible to drugs. Clinical and preclinical studies have shown aberrant expression of mucins during PC development. The mucins may prevent drugs from accessing their sites of action. Although several mucins that lead to chemoresistance have been targeted, to date, no mucin synthesizing genes have been identified as targets. Using human pancreatic cancer patient survival data (90 cases of tumor and matched normal adjacent tissue), next-generation sequencing (NGS) of genetically engineered Kras mouse pancreatic tumors (N=6/group), human PC cells, we identified novel core mucin synthesizing gene target GCNT3 (core 2 beta 1,6 N-acetylgalcosaminyltransferase). NGS revealed that GCNT3 upregulation (103-fold; p<0.0001) was correlated with increased mucins Muc4 (50-fold; p<0.04), Muc5ac (87-fold; p<0.01), Muc6 (67-fold; p<0.008), Muc1 (5-fold; p<0.009), Muc16 (5-fold; p<0.0003) and Muc20 (17-fold; p<0.007). Aberrant GCNT3 expression was associated with increased mucin production and aggressive tumorigenesis and reduced patient survival. Patients with low expression of GCNT3 had a longer survival time than patients with high expression of GCNT3 (median survival: 17.5 vs. 10.5 months, p=0.036). Further, using in-silico approaches of small molecular docking simulations, we identified talniflumate as a novel inhibitor that specifically binds to GCNT3. Our blind docking simulations reveal that talniflumate binds to GCNT3 with a docking affinity of -8.3 kcal/mol and deeper in the pocket of GCNT3. The docking predictions suggest three notable hydrogen bonds between talniflumate and GCNT3: Arg192 (3.0 Angstroms), Try288 (3.5 Angstroms), and Ala287 (2.9 Angstroms). Pancreata from 6-week-old Kras mice treated with talniflumate for 1 week showed a significant decrease in GCNT3 and mucin expression in PanIN lesions. mRNA expression of GCNT3 was also observed to be lower in pancreatic tissues from talniflumate-treated mice. CRISPR knock-out of GCNT3 in PC cells reduced proliferation and spheroid formation. Further, talniflumate alone and in combination with low-dose gefitinib reduced GCNT3 leading to disruption of mucins in vivo and in vitro. Hence, mucin disruption might enhance targeted therapy. These findings suggest a prominent role for Kras activation and aberrant mucin synthesis leading to PC pathogenesis, and warrant consideration of GCNT3 and EGFR inhibitors as a combination treatment for PC.

(Grant Support: COMAA, Kerley-Cade Endowed Fund).
DEFECTIVE INTESTINAL MUCIN-TYPE O-GLYCOSYLATION CAUSES SPONTANEOUS COLITIS-ASSOCIATED CANCER IN MICE
Presented by: Kirk Bergstrom

Kirk Bergstrom, Jianxin Fu, and Lijun Xia
Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA.

Core 1- and 3-derived O-glycans are major components of the colonic mucus layer. Defective O-glycosylation is such as Tn antigen expression often observed in ulcerative colitis and colorectal cancer with unknown etiological role. We investigated whether and how impaired O-glycosylation predisposes to colitis-associated colon cancer. A new mouse line lacking both core 1- and 3-derived intestinal O-glycans (DKO) was generated and then analyzed together with our previously generated mice lacking intestinal core 1 O-glycans (IEC C1galt1–/–) and mice lacking core 3 O-glycans (C3GnT–/) over time by comparing intestinal mucus integrity, Tn antigen exposure, colitis and cancer susceptibility, and inflammatory mediators/pathways via macroscopic, biochemical, and molecular approaches (imaging, western blot, qPCR, etc.). DKO mice expressed higher Tn antigen and exhibited worsened spontaneous chronic colitis than IEC C1galt1–/– mice. Both IEC C1galt1–/– and DKO mice developed spontaneous colon tumors at older ages, however the disease in DKO mice occurred earlier and with greater severity by comparison. Colitis and cancer were dependent on inflammation rather than aberrant Tn exposure because microbial depletion in DKO mice reduced colitis and neoplasia but not Tn expression. Moreover, microbiota-mediated activation of epithelial caspase 1–dependent inflammasomes was required for spontaneous colitis-associated cancer in DKO mice. Impaired expression of O-glycans causes colonic mucus barrier breach and subsequent microbiota-mediated activation of epithelial caspase 1–dependent inflammasomes, which contributes to the pathogenesis of colitis-associated colon cancer in our models. These findings reveal an important role for mucin-type O-glycans in intestinal mucus barrier function.
Concurrent Session V – Clinical & Correlative Research
3:15 p.m. – 4:15 p.m.                         Room F

TARGETING HPV RELATED CANCERS IN OKLAHOMA: DEMOGRAPHICS & INTERVENTIONS
Moderator: Laura Holman, MD

3:15 p.m. – 3:30 p.m.
SCREENING AND PREVENTION OF HPV RELATED CANCERS
Megan Buechel, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center

3:30 p.m. – 3:45 p.m.
SMOKING, ORAL HEALTH, AND ORAL HPV INFECTION
Thinh Bui, DrPH
Department of Family and Preventive Medicine
The University of Oklahoma Health Sciences Center

3:45 p.m. – 4:00 p.m.
COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY
Victoria Perkins, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center

4:00 p.m. – 4:15 p.m.
IMPROVING CANCER CARE FOR AMERICAN INDIANS IN THE IHS SYSTEM – NAVIGATION MAY NOT BE ENOUGH
Lauren Dockery, MD
Department of Gynecology Oncology
The University of Oklahoma Health Sciences Center
Oral human papillomavirus (HPV) infection is the cause of 40–80% of oropharyngeal cancers. Our works examined the independent and interactive effects of smoking, oral health, and oral hygiene on oral HPV infection. Our analyses used data from the nationally representative 2009–2012 US National Health and Nutrition Examination Survey (NHANES). In Study 1, our analysis comprised 3,439 participants aged 30–69 years for whom data on oral HPV and oral health were available. Results showed that higher unadjusted prevalence of oral HPV infection was associated with four measures of oral health, including self-rated oral health as poor-to-fair, indicated the possibility of gum disease, reported use of mouthwash to treat dental problems in the past week, and higher number of teeth lost. In a multivariable logistic regression model, oral HPV infection remained statistically associated with self-rated overall oral health and smoking, after controlling for age, sex, and number of oral sex partners. In Study 2 which aimed to investigate risk factors for oral HPV infection with multiple genotypes, our analysis comprised 9,257 participants for whom data on oral HPV (37 genotypes) and associated risk factors were available. Multiple-type oral HPV infection was defined as being infected with 2 or more genotypes. Results showed that being male, being a current cigarette smoker, and having a new sex partner in the past year were associated with an increased risk of multiple-type oral HPV infection over single-type HPV infection. In conclusion, poor oral health and smoking are independent risk factors of oral HPV infection. Smoking also elevates the risk of multiple-type oral HPV infection; this effect is stronger and more consistent than that of oral health and oral sex behaviors.
COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY
Presented by: Victoria Perkins

Victoria Perkins, MD1, Koji Matsuo, MD2, Sayedamin Mostofizadeh, MD2, Travis Sims, MD3, Jayanthi Lea, MD3, Dominique Barnes, MD4, Sixia Chen, PhD5, Matthew Carlson, MD4, Lynda Roman, MD2, Bradley Monk, MD4, Kathleen Moore, MD1, Laura L. Holman, MD1

1Section of Gynecologic Oncology, Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, 2Division of Gynecologic Oncology, The University of Southern California, Los Angeles, CA, 3Division of Gynecologic Oncology, The University of Texas Southwestern Medical Center, Dallas, TX, 4Division of Gynecologic Oncology, University of Arizona Cancer Center, Phoenix, AZ, 5Department of Biostatistics and Epidemiology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK,

Objectives: Chemotherapy is the standard choice to treat stage IVB cervical cancer (CC). However, given the significant pelvic disease burden and its potential relation to complications and death in these women, whole pelvic radiation (WPR) in addition to chemotherapy for primary treatment may have utility. The aim of this study was to compare the overall survival (OS) and complication rates between combination WPR and chemotherapy versus chemotherapy alone in the management of stage IVB CC.

Methods: A multi-institutional, IRB-approved, retrospective review of patients (pts) with stage IVB CC, diagnosed between 2005 and 2015, was performed. Four academic, high-volume cervical cancer sites were included in this study. Descriptive statistics of the demographic, oncologic, and treatment characteristics were performed. OS was estimated using the Kaplan Meier method.

Results: A total of 127 pts met inclusion criteria. Median age was 54 yrs, 36% were Caucasian, 35% Hispanic, and 16% were African-American. The majority (73%) had squamous cell carcinoma and 95% were grade 2 or 3. Twenty percent elected for hospice care at diagnosis (OS 2.2 mo). Of pts who underwent treatment, 35% received WPR with chemotherapy and 65% received chemotherapy alone. The OS was significantly longer in the WPR with chemotherapy group (22 mo vs 10 mo, p < 0.01, HR:0.30; Figure 1). The rates of ureteral obstruction, vaginal bleeding, pelvic infection, pelvic pain, and fistula were not significantly different between the 2 groups (all p>0.05).

Conclusion: A significant number of women with stage IVB CC experience morbidity directly related to their pelvic disease. This study found that treating the pelvic disease with WPR in addition to chemo gives a 12-month survival benefit to these pts. Interestingly, there was a trend towards less frequent use of WPR with the introduction of bevacizumab into standard of care. Further study is warranted to determine which subgroups may benefit the most from this novel treatment strategy.
IMPROVING CANCER CARE FOR AMERICAN INDIANS IN THE IHS SYSTEM – NAVIGATION MAY NOT BE ENOUGH

Presented by: Lauren Dockery

Lauren E Dockery, MD1, Anita Motwani2, Kai Ding, PhD3, Kathleen N Moore, MD1, Laura L Holman, MD1

1 Stephenson Cancer Center, Division of Gynecologic Oncology at the University of Oklahoma Health Sciences Center, Oklahoma City, OK. 2 University of Oklahoma College of Medicine Oklahoma City, OK. 3 Department of Biostatistics at the University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Objectives: American Indian (AI) patients (pts) have decreased access to health care with worse 5-year survival compared to white pts. The use of Indian Health Service (IHS) as primary payer adds complexity to receipt of timely care. Pt navigation programs aim to ameliorate the complexities of cancer care, particularly among underserved pts. This study aimed to characterize the impact of an AI navigation program in gynecologic oncology pts at a tertiary care center.

Methods: A retrospective review of all AI gynecologic cancer pts receiving navigation services since 2005 as well as a cohort of AI pts not receiving navigation was performed. Summary statistics were used to describe demographic, clinical characteristics, treatment and survivorship across groups. Pts with cervical cancer were used for comparison of outcomes.

Results: Of the 221 pts included, 141 received navigation and 80 did not. In navigated pts, median age was 57 yrs (15-84 yrs), and 27, 44, 22, 5 and 2% carried a diagnosis of ovarian, uterine, cervical, vulvar/vaginal or synchronous primary cancer, respectively. Median time to initiation of treatment was 33 days (95% CI: 28-39). In pre-navigation pts, median age was less (45.5 yrs, range 14-80 yrs p<0.0001) and 18, 14, 64, 4 and 1% had ovarian, uterine, cervical, vulvar/vaginal or synchronous primary cancer respectively. Pre-navigation median time to initiation of treatment was 27 days (95% CI: 19-29) and was less than navigated pts (p=0.0019). Among insurance holders, 80.1% of navigated pts had IHS compared to 67.7% of pre-navigation pts (p=0.05). Median time to initiation of treatment was 33 days in those with IHS. There was no difference in the mean number of surveillance visits attended (2.86 pre-navigation vs 1.71 navigated p=0.079).

Conclusions: AI pts with gynecologic cancers using navigation services had longer time to treatment as compared with non-navigated pts. However, this difference is not clinically significant and may be explained by more pts in the navigated group with IHS as primary payer given the intricacies of working within the IHS system. Further study is needed to better characterize the delays associated with the interface of IHS and tertiary care centers to tailor the navigation program to AI pts’ needs.
### Cancer Research Symposium Poster Session

**11:20 p.m. – 1:00 p.m.**

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MECHANISM OF ANTI-TUMOR ACTIVITIES OF Z-TMS AGAINST HEPATOCELLULAR CARCINOMA AND ERLOTINIB-RESISTANT LUNG ADENOCARCINOMA
Presented by: Naushad Ali

Charles B. Nguyen, Parthasarathy Chandrakesan, Randal May, Altaf Mohammed, Danny N. Dhanasekaran, Michael S. Bronze, and Courtney W. Houchen, Naushad Ali

1Department of Medicine, Section of Digestive Diseases and Nutrition, 2College of Medicine, 3Department of Cell Biology, 4Peggy and Charles Stephenson Cancer Center, and 5Department of Veterans Affairs Medical Center, Oklahoma City, 6Center for Cancer Prevention and Drug Development, University of Oklahoma Health Sciences Center, Oklahoma City OK73104.

Introduction: Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide with a 5-year survival rate of <15%. Chronic viral hepatitis, NASH, and cirrhosis are major risk factors for the HCC development. Thus, HCC represents a major public health issue worldwide. Currently, sorafenib is the only FDA-approved drug used for HCC treatment. Unfortunately, it increases patient’s survival by only 3 months. Tumor stem cells (TSCs) are likely responsible for resistance to chemotherapy, relapse, and metastasis. We have demonstrated that a TSC marker, doublecortin-like kinase (DCLK1), is induced during hepatic injury, cirrhosis and HCC, and its overexpression in HCC patient’s liver significantly reduces survival. Therefore, development of effective therapy against HCC is an unmet medical need. These observations prompted us to find means for targeting DCLK1-positive cells and to investigate the impacts of interference with DCLK1 on liver tumor growth.

Methods: The antitumor effects of a resveratrol analogue, Z-3,5,4’-Trimethoxystilbene (Z-TMS), were determined in cell culture and diethylnitrosamine (DEN)/carbon tetrachloride (CCl4)-induced HCC mouse model. Following Z-TMS treatment, gene expression profile, proliferation, survival and cell cycle of DCLK1-positive cancer cells were determined by flow cytometry, immunohistochemical staining, confocal microscopy, real-time PCR and Western blot.

Results: DCLK1 is extensively expressed in cirrhosis and HCC but not in normal human livers. HCC patients (n= 369) overexpressing DCLK1 in liver showed approximately 3 times reduction in 5-year survival rate. Z-TMS (1 μM) inhibited hepatoma cell spheroids/aggregates in a magnetic levitation-based culture model. It also resulted in bundling of DCLK1 with microtubules and cell cycle arrest at G2/M phase in hepatoma cells via downregulation of CDK1, induction of p21cip1/waf1 expression, and inhibition of Akt (Ser473) phosphorylation. DEN/CCl4 extensively induced expression of DCLK1 in the livers of C57BL/6 mice following hepatic injury. Z-TMS exhibited hepatoprotective effects against DEN/CCl4-induced injury in these mice by reducing DCLK1 expression and improving histological outcomes. In addition, Z-TMS inhibited proliferation of erlotinib-resistant lung adenocarcinoma cells (H1975) bearing the T790M EGFR mutation most likely by promoting autophagy and nuclear fragmentation.

Conclusions: Z-TMS exhibits potent anti-tumor activities without exhibiting cytotoxicity to human hepatocytes in vitro or in mice livers. It appears to target drug-resistant carcinomas and DCLK1-expressing cancer stem cells that promotes neoplasia in liver including pancreas, intestine, and colon.
CASE REPORT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH HYPERLEUKOCYTOSIS
(1114 k/mm³) WITHOUT LEUKOSTASIS
Presented by: Adanma Ayanambakkam

Introduction: We present a case report of a 53 year old gentleman with chronic lymphadenopathy and elevated white blood cell count of 1114 k/mm³ without leukostasis, who was eventually diagnosed with chronic lymphocytic leukemia.

Case Report: A 56 year old Caucasian gentleman presented with intermittent painless lymphadenopathy, night sweats, epistaxis, dizziness and difficulty breathing. A complete blood count revealed leukocytosis (1,114 k/mm³ - 100% lymphocytes) anemia and thrombocytopenia. Peripheral blood smear revealed atypical cells consistent with a lymphoid malignancy, without granules or auer rods. Admission labs were consistent with tumor lysis syndrome and he was started on rasburicase and leukapheresis. Bone marrow biopsy and excision biopsy of the right supraclavicular lymph node was consistent with chronic lymphocytic leukemia (CLL). Fluorescent Insitu Hybridization (FISH) was significant for deletion of the ATM gene (94%) and 13q deletion (88%) with normal cytogenetics. After cytoreduction with leukopheresis he was randomized to the Ibritunib arm in the randomized phase III study comparing Ibrutinib based therapy and standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) regimen.

Discussion: Leukemic proliferation resulting in an elevated white blood cell (WBC) count above 100 k/mm³, is arbitrarily defined as hyperleukocytosis. Leukostasis (symptomatic hyperleukocytosis) is “the morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin”. Leukostasis is an extremely rare complication in chronic lymphocytic leukemia (CLL), despite hyperleukocytosis occurring in a significant proportion of patients. Asymptomatic hyperleukocytosis in CLL has been associated with various complication such as spurious hyperkalemia, hypophosphataemia and spurious hypoxemia. Reduction in total white blood cell count with induction chemotherapy remains the mainstay treatment for hyperleukocytosis and leukostasis, with proven survival benefit. The role of leukopheresis in hyperleukocytotic patients remains controversial with no guidelines for initiation or cessation of treatment. Literature review rivals that leucoreductions have not been associated with significant mortality benefit. Further studies comparing the efficacy of cytoreductive chemotherapy and leukopheresis are needed. The prognostic significance of hyperleukocytosis in CLL remains uncertain despite being an obvious reflection of tumor burden. Several studies examining the prognostic value of WBC counts in CLL have yielded controversial results.
A METHOD FOR SAFELY RESECTING ANTERIOR BUTTERFLY GLIOMAS: THE SURGICAL ANATOMY OF THE DEFAULT MODE NETWORK AND THE RELEVANCE OF ITS PRESERVATION

Presented by: Cordell Baker

Joshua D. Burks, BS; Phillip A. Bonney, BS; Andrew K. Conner, MD; Chad A. Glenn MD; Robert G. Briggs, BS; James D. Battiste, MD PhD; Daniel L. O’Donoghue, PhD; Dee H. Wu, PhD; and Michael E. Sughrue, MD

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Gliomas invading the anterior corpus callosum are commonly deemed unresectable due to an unacceptable risk/benefit ratio including the risk of abulia. In this study, we investigate the anatomy of the cingulum and its connectivity within the default mode network. We describe a technique involving awake subcortical mapping with higher attention tasks to preserve the cingulum and reduce the incidence of postoperative abulia for patients with so-called butterfly gliomas. We performed a review of clinical data on all patients undergoing glioma surgery performed by the senior author during a four-year period at our institution. Forty patients were identified who underwent surgery for butterfly gliomas. Each patient was designated as having undergone surgery either with or without the use of awake subcortical mapping and preservation of the cingulum. Data recorded on these patients includes the incidence of abulia/akinetic mutism. In the context of our findings, we conducted a detailed anatomic study of the cingulum and its role within the default mode network using postmortem fiber tract dissections of 10 cerebral hemispheres and in vivo diffusion tractography of 10 healthy subjects. We treated 40 patients with butterfly gliomas, 25 (62%) with standard surgical methods and 15 (38%) with awake subcortical mapping and preservation of the cingulum. Only 1/15 (7%) patient experienced postoperative abulia following surgery with the latter technique. We achieved greater than 90% resection in 13/15 (87%) of these patients. We present evidence that anterior butterfly gliomas can be safely removed using a novel attention-based awake brain surgery technique that focuses on preserving the anatomic connectivity of the cingulum and relevant aspects of the cingulate gyrus.
BMI1 INHIBITION FOR THE TREATMENT OF ENDOMETRIAL CANCER
Presented by: Megan Buechel

Buechel, M., Crim, A., Dey, A., Dwivedi, SK., Banarjee Mustafi, S., Bhattacharya, R.
Stephenson Cancer Center, University of Oklahoma Health and Science University

Objectives: Endometrial cancer is the most common gynecologic malignancy with rising incidences in
developed countries. While surgery provides significant survival benefit to early stage patients, those
with recurrent or metastatic disease have dismal prognosis. There is emerging knowledge of molecular
alterations such as PI3K pathway and KRAS mutations; however, there are no approved targeted
therapies for endometrial cancer. Hence there is a critical need to identify novel therapeutic targets.
BMI1, a member of the polycomb repressor complex-1 regulates chromatin structure and is
indispensable for self-renewal of both normal and cancer stem cells. BMI1 is frequently upregulated and
its expression correlates with poor prognosis in several types of cancer making it a promising target for
therapeutics. We seek to determine the clinical significance of BMI1 in endometrial cancer with an effort
to develop it as a potential therapeutic target.

Methods: Using endometrial cancer cell lines that represent Type I and Type II disease and patient tissue
microarray we are investigating association of BMI1 with clinicopathologic variables. Standardized cell
based assays of viability, invasion, clonal growth and quantitative RT-PCR are being utilized. PTC-028 is a
small molecule from PTC Therapeutics (South Plainfield, NJ), that reduces levels of BMI1 and is being
utilized to determine mechanism and impact in functional cellular assays. PTC-028 is an analog of the
clinical candidate PTC596 currently in Phase 1 trials (ClinicalTrials.gov identifier: NCT02404480).

Results: BMI1 levels are elevated in endometrial cancer cell lines and depletion of BMI1 using PTC-028 i)
inhibits cell viability, ii) decreases invasion, iii) reduces clonal growth and iv) induces caspase-dependent
apoptosis both in Type I (endometrioid) and Type II (non-endometrioid) endometrial cancer cell lines.
HEC50, a Type II serous cell line, showed the greatest sensitivity to BMI1 inhibition compared to other
endometrial cancer cell lines.

Conclusions: Our in vitro work supports the use of anti-BMI1 strategies in endometrial cancer. We
expect to extend the PTC-028 studies to in vivo xenograft models of endometrial cancer where
combination with standard cisplatin/taxane treatment will be tested to determine enhanced efficacy.
Breast cancer is maintained by a tiny fraction of breast cancer stem cells (BCSCs), the cells with the capacity to self-renew and differentiate into the heterogeneous cancer cell lineages that comprise the tumor. BCSCs are resistant to conventional therapies and contribute to the recurrence of breast cancer. Conventional drugs cannot target BCSCs specifically and kill them efficiently, so a BCSC-specific is needed to improve the conventional cancer therapies. Phage display technique can identify cell-specific peptides through several rounds of affinity selection. I present my work there about the identification of breast cancer stem cell-binding peptides by phage display technique.
DETERMINING THE ROLE OF XRN2 IN GLIOMA DISEASE PROGRESSION
Presented by: Tuyen T. Dang

Tuyen T. Dang, PhD., Julio C. Morales, PhD.
University of Oklahoma Health Science Center, Neurosurgery Department, Stephenson Cancer Center

Glioblastoma is a highly aggressive brain cancer with a 4 to 7% 5-year survival rate. The standard course of treatment is radiation and chemotherapy, typically Temozolomide. However, even with the combinational treatment, approximately 16,050 deaths will occur in 2016 due to brain or nervous system cancers. A possible reason for the poor survival rate is the presence of radiation/chemotherapy resistant invasive cancer cells in the tumor.

XRN2 is up-regulated in solid tumors such as gliomas and breast cancer. XRN2 is a 5′-3′ exonuclease and have been shown to resolve R loops, short RNA: DNA hybrid, in transcription termination. Increasing amount of evidence support a 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.

Motile cells have shown to be resilient to radiation and chemotherapy. Preliminary data show a correlation between XRN2 expression and cell motility. Breast cancer cells with a higher intrinsic motility seem to also have a higher expression of XRN2 compared to slower cells. This correlation of XRN2 expression and aggressiveness of cancer cells may explain the poor survival rates of glioblastoma patients.

Based on these observations, we hypothesized that XRN2 contributes to glioma disease progression by acting as a radiation protectant and driver of neoplastic cell motility and/or invasion. To elucidate how XRN2 protects motile cells from DSBs during IR, I will isolate motile cells from non-motile cells and probe the DDR landscape in non-treated and radiation treated scenarios. To resolve how XRN2 may contribute to disease progression, I will assess if XRN2 is required for cell motility in glioma cells since motility is required for invasion. I will also elucidate if XRN2 is required for the initial invasion/migration of glioma cells away from the primary mass. Since XRN2 may regulate numerous genes that may regulate disease progression, I will determine which genes require XRN2 expression and are required for motility. Findings from these studies would impact on radiation treatment of cancer patients by identifying who would best benefit from conventional radiation and possibly new drug targets to work in concert with radiation to increase efficacy.
DISTINCT COMPLEXES FORMED BY PBAF CHROMATIN-REMODELING COMPONENTS ACT AT DIFFERENT CRITICAL STEPS IN THE DNA DAMAGE respuesta

Presented by: Rodrigo Orlandini de Castro

Rodrigo Orlandini de Castro¹, Luciana Previato¹, Victor Goitea¹, Anna Felberg¹, Michel F. Guiraldelli¹, Adrian Filiberti¹, and Roberto J. Pezza¹,²

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PBAF chromatin-remodeling complex have been implicated in transcriptional regulation, development, DNA repair and failures in the proper function of these enzymes contribute to tumorigenesis. Although the PBAF plays essential roles in DNA repair, the mechanism by which it contributes to this cellular function is poorly understood. Here, we reveal that Baf200 (Arid2) and Baf180 (Pbrm1), subunits of the PBAF chromatin-remodeling complex, can participate in complexes that are structurally and functionally distinct from PBAF. Further, we show that Baf200 plays a dual function in the repair of double-strand breaks (DSBs). Immediately after DSB induction, Baf200 and Baf180 establish a Brg1-dependent interaction with chromatin influencing DNA damage signaling. Later during the DNA damage response, Baf200 and Baf180 form a Brg1-independent association with chromatin, which acts in concert with Rad51 to promote recombination repair of DSBs. We propose that subunits of PBAF form complexes with distinct composition that perform specialized DNA repair functions. This may explain the broad importance of certain PBAF components in cancer as tumor suppressors.
EVALUATING THE MECHANISM AND THERAPEUTIC ACTIVITY OF PTC-028, A NOVEL INHIBITOR OF BMI-1 FUNCTION IN OVARIAN CANCER

Presented by: Anindya Dey

Anindya Dey1, Xunhao Xiong2, Aleia Crim1, Shailendra Kumar Dhar Dwivedi1, Soumyajit Banerjee Mustafi1, Priyabrat Mukherjee3, Liangxian Cao3, Nadiya Sydorenko3, Ramil Baiazitov3, Young-Choon Moon3, Melissa Dumble3, Thomas Davis3 and Resham Bhattacharya1, 4*

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BMI-1, a polycomb group protein that confers self-renewal property to normal and cancer stem cells has emerged as an important therapeutic target in several malignancies. Realizing the pathological significance, PTC-209, a small molecule that inhibits translation of BMI-1 was first described in 2014. More recently, PTC-028 was developed with optimized pharmaceutical properties. It is orally bioavailable and decreases BMI-1 by post-translational modification. This is the first study evaluating the biological and therapeutic activity of PTC-028. We report that PTC-028 significantly inhibits clonal growth and viability of high-grade serous ovarian cancer (HGS-OvCa) cells by specifically decreasing the levels of BMI-1 through hyper-phosphorylation mediated depletion, while normal ovarian cells with minimal expression of BMI-1 remain unaffected. At a lower concentration than required for PTC-209, PTC-028 induces faster depletion of BMI-1, decreases levels of RIPK1 and XIAP and potentiates caspase-dependent apoptosis through generation of mitochondrial reactive oxygen species (ROS). Importantly, orally administered PTC-028 exhibits significant single agent antitumor activity similar to that of the standard cisplatin/paclitaxel, administered by the intra-peritoneal route in an orthotopic mouse model of OvCa. Thus, PTC-028 has the potential to be used as an effective therapeutic in patients with HGS-OvCa, where treatment options are limited.
IMPROVING CANCER CARE FOR AMERICAN INDIANS IN THE IHS SYSTEM – NAVIGATION MAY NOT BE ENOUGH

Presented by: Lauren Dockery

Lauren E Dockery, MD, Anita Motwani, Kai Ding, PhD, Kathleen N Moore, MD, Laura L Holman, MD

Objectives: American Indian (AI) patients (pts) have decreased access to health care with worse 5-year survival compared to white pts. The use of Indian Health Service (IHS) as primary payer adds complexity to receipt of timely care. Pt navigation programs aim to ameliorate the complexities of cancer care, particularly among underserved pts. This study aimed to characterize the impact of an AI navigation program in gynecologic oncology pts at a tertiary care center.

Methods: A retrospective review of all AI gynecologic cancer pts receiving navigation services since 2005 as well as a cohort of AI pts not receiving navigation was performed. Summary statistics were used to describe demographic, clinical characteristics, treatment and survivorship across groups. Pts with cervical cancer were used for comparison of outcomes.

Results: Of the 221 pts included, 141 received navigation and 80 did not. In navigated pts, median age was 57 yrs (15-84 yrs), and 27, 44, 22, 5 and 2% carried a diagnosis of ovarian, uterine, cervical, vulvar/vaginal or synchronous primary cancer, respectively. Median time to initiation of treatment was 33 days (95% CI: 28-39). In pre-navigation pts, median age was less (45.5 yrs, range 14-80 yrs p<0.0001) and 18, 14, 64, 4 and 1% had ovarian, uterine, cervical, vulvar/vaginal or synchronous primary cancer respectively. Pre-navigation median time to initiation of treatment was 27 days (95% CI: 19-29) and was less than navigated pts (p=0.0019). Among insurance holders, 80.1% of navigated pts had IHS compared to 67.7% of pre-navigation pts (p=0.05). Median time to initiation of treatment was 33 days in those with IHS. There was no difference in the mean number of surveillance visits attended (2.86 pre-navigation vs 1.71 navigated p=0.079).

Conclusions: AI pts with gynecologic cancers using navigation services had longer time to treatment as compared with non-navigated pts. However, this difference is not clinically significant and may be explained by more pts in the navigated group with IHS as primary payer given the intricacies of working within the IHS system. Further study is needed to better characterize the delays associated with the interface of IHS and tertiary care centers to tailor the navigation program to AI pts’ needs.
Cancer metastasis is the leading cause of cancer-related death, and one of the greatest difficulties in treating cancer patients. Laser Immunotherapy (LIT) is a novel cancer treatment modality that is designed to treat metastatic cancers by inducing a systemic, antitumor immunity. LIT uses a combination of glycated chitosan, an immunoadjuvant, and near-infrared laser irradiation to stimulate the host immune response. Achieving the optimal temperature distribution in the target tumor tissue using the photothermal effect of the near-infrared laser light is critical to destroy the tumor cells and release tumor antigens as a precursor of the systemic immunological effect. In this study, we investigated the heat shock protein expression of cancer cells in response to temperature stress *in vitro* using western blot analysis and found that maximal HSP expression was at ~45 to 50°C. We studied the temperature distribution in a tumor under laser irradiation *ex vivo* using a uniquely designed thermal device and *in vivo* using magnetic resonance thermometry. We found that a steady temperature in the range of 45 to 70°C for maximum immunological response could be achieved by using interstitial laser treatment with a laser power of 2 to 3 watts, depending on tumor size, for a 10 minute. Our results can be used to further advance laser immunotherapy to an effective option for patients with late-stage, metastatic cancers.
PROOF-OF-CONCEPT FOR A LOW-COST, MOBILE-DRIVEN AEROSOL CONCENTRATION ESTIMATOR

Presented by: Evan Floyd

Evan Floyd, Tyler Watson, David Johnson

Objective: Most real-time aerosol instruments utilize light scattering to estimate aerosol concentration, but are moderately expensive and therefore not widely available outside the environmental health fields. The purpose of this study was to develop a proof-of-concept aerosol measurement device using components similar to those incorporated in modern smart phones, i.e. a digital camera and low voltage power port.

Methods: An aluminum tube was equipped with: loose fitting end caps to block light from entering, a small electric fan to draw e-Cig aerosol through the tube, a laser to provided polarized light, and a webcam to capture scattered light from the laser beam. The system was designed such that outside air was drawn into the tube and across the laser beam before encountering the fan. The fan and laser were powered by a laptop USB port. Scattered laser light was detected by the webcam. This device was evaluated against a wide range of e-cigarette aerosol concentration in an exposure chamber. Pictures were analyzed by counting all pixels with light value above zero and plotted against results from a Grimm Aerosol Spectrometer (Grimm).

Results: The prototype system underestimated e-Cig aerosol concentration by 10%, had a modest $R^2 = 0.88$, relatively high LOQ = 1.3 mg/m$^3$, and relatively high variability, SD = +/-13%, but was able to reliably detect e-Cig aerosol concentrations well below the OSHA exposure limit of 5 mg/m$^3$ for respirable particulate.

Conclusions: Limitations of this proof-of-concept device were: incomplete isolation of outside light, large laser-to-camera distance, low camera resolution, single picture and manual pixel analysis. This prototype successfully demonstrates the capability to measure sub-occupational levels of e-Cig aerosol with components analogous to those found in smart phones. With further development a small mobile-driven device could be built that accurately measure occupational and ambient aerosol concentrations.

Funding Sources: This project was funded in part by the Oklahoma Tobacco Research Center (OTRC) Summer Scholars Program.
ELECTRONIC CIGARETTES INDUCE SIGNIFICANT DNA DAMAGE AND REDUCE CELLULAR ANTIOXIDANT LEVELS

Presented by: Vengatesh Ganapathy

Vengatesh Ganapathy1, Jimmy Manyanga1,2, Lacy Brame1,3 David Rubenstein4, Theodore Wagener5,6,7, Ilangovan Ramachandran1, and Lurdes Queimado1,2,5,7

Departments of 1Otorhinolaryngology, 2Cell Biology, 3Biostatistics and Epidemiology, and 5Pediatrics; 6The Oklahoma Tobacco Research Center and 7The Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma. 4Department of Biomedical Engineering, Stony Brook University, New York.

Background: Cigarette smoking is the leading preventable cause of mortality in the world and the main risk factor for lung and head and neck cancer. E-cigarettes (ECs) are battery-operated devices that deliver nicotine via inhaled aerosols. Although ECs are marketed as a less harmful alternative to tobacco cigarettes and a smoking cessation aid, the health risks posed by exposure to EC aerosols are unknown. Nonetheless, the use of ECs has increased exponentially since 2003, with EC users reporting inhaling on average 200 puffs a day. EC aerosols have been reported to contain variable levels of genotoxins, including carcinogenic substances and reactive oxygen species (ROS). Some toxins in EC aerosols have been reported to reach the levels of similar to those in tobacco smoke. However, the genotoxicity of EC aerosols has not been characterized.

Aims: (1) To determine the cytotoxicity and genotoxicity of short and long-term exposure to EC aerosols on human epithelial normal and cancer cell lines. (2) To evaluate whether exposure of EC aerosols modifies the cellular total antioxidant capacity (TAC).

Methods: EC extracts were prepared from NJOY (12 or 18 mg/ml of nicotine) and Oakley eGo-T (0, 12 or 18 mg/ml of nicotine). Standard tobacco extracts were used for comparison. To assess the effects of short-term exposure, human epithelial normal (NuLi-1) and cancer (UD-SCC1) cell lines were exposed for 1 hour to various EC extract concentrations. To assess the effects of long-term exposure, cells lines were exposed every other day for 2 weeks to EC extracts. Cytotoxicity, DNA damage and TAC were evaluated at 1 h and 2 weeks. Cell viability was determined by MTT assay. DNA damage was quantified using the primer anchored DNA damage detection assay (PADDA). TAC was determined by the Antioxidant Assay Kit (Cayman). Data were analyzed by Student’s t-test.

Results: At the range of EC extract concentrations used in this study and expected to occur in EC users (1 to 100 puffs/5 L of blood), no cytotoxicity was observed for either normal or cancer cells. However, significant levels of DNA damage were observed in cancer cells exposed to 10 or more puffs/5 L of EC extracts and in normal cells exposed to 100 puffs/5 L. Long-term exposure to EC extracts resulted in a significant decrease in TAC, a measure of free radical scavengers.

Conclusion: Even short-term exposure to low levels of EC aerosols can cause significant DNA damage. Our study emphasizes the need to further investigate the carcinogenic potential of EC aerosols and highlights the importance of regulating EC use.

Grant support: This work was supported by the Oklahoma Tobacco Research Center (LQ). Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.
Abstract

The objective of this study was to demonstrate the detectability of simulated objects within a dense breast phantom using high energy x-rays for phase sensitive breast imaging in comparison with conventional imaging. A 5 cm thick contrast-detail (CD) phantom representing a compressed breast consisting of 70% glandular and 30% adipose tissue ratio by weight was used. The phantom has a 6 x 6 matrix of holes with milled depths ranging from 1 to 0.1 mm and diameters ranging from 4.25 to 0.25 mm representing the simulated tumors. All the CD phantom images were acquired using a micro-focus x-ray source with a 50 µm focal spot and a flat panel detector a 50 µm pixel pitch. Phase sensitive images were acquired at 120 kVp, 4.5 mAs with source to object distance (SOD) of 68 cm and a magnification factor (M) of 2.5. Conventional images were acquired at 40 kVp, 12.5 mAs and 120 kVp, 4.5 mAs with a source to imaging distance (SID) of 68 cm. The observer study and contrast-to-noise ratio (CNR) indicates an improvement by the phase sensitive images as compared to the conventional images. The edge enhancement provided by the phase sensitive images warrants in identifying boundaries of malignant tissues and in providing optimal results in phase retrieval process. The potential demonstrated by this study for imaging a dense breast with a high energy phase sensitive x-ray imaging to improve tumor detection in warrants further investigation of this technique.
TOXICITIES ASSOCIATED WITH LONG-TERM BEVACIZUMAB USE IN PATIENTS WITH RECURRENT OVARIAN CANCER

Presented by: Molly Greenwade

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Objectives: Bevacizumab is commonly used in the treatment of ovarian cancer (OC). Acute side effects of bevacizumab have been well characterized, but there is limited information on the toxicities associated with its prolonged use. We aimed to characterize toxicities associated with long-term bevacizumab use in women with recurrent OC and compare these with short-term side effects.

Methods: We conducted a multi-institutional, retrospective review of pts with OC who were treated with bevacizumab for at least 18 cycles between 2006 and 2016. Demographic, clinical, and pathological data were analyzed with descriptive statistics. Toxicities were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicities during cycles 1-17 were compared with toxicities during cycles ≥18 using exact McNemar tests. The Kaplan-Meier method was used to determine overall survival (OS).

Results: Study criteria were met by 37 pts. Mean pt age was 58.5 yrs (range 32-80). The majority of pts (69.4%) had stage IIIC OC, while the most common histology was serous (61.1%). The mean number of total bevacizumab cycles was 33.2 (range 18-95). Only 12 pts (32.4%) received bevacizumab during primary treatment and 6 pts (16.2%) received it for more than 1 line of therapy. The median OS was 109.1 months. Anorexia was more common during cycles 1-17 than cycles ≥ 18 (37.8% vs 13.5%, p=0.01). Toxicities listed as “other nervous system disorders” were also more common during cycles 1-17 (73% vs 27%, p=0.002). There was no difference in any other toxicities between the two time points, including fistula, headache, increased creatinine, proteinuria, epistaxis, hypertension, and thromboembolic events (all p>0.05). One patient was diagnosed with grade 3 CHF during > 18 cycles, but the etiology of this event was unclear.

Conclusions: In this multi-institutional study, there were no toxicities associated with prolonged bevacizumab treatment. A limitation of this analysis is the small cohort of patients who receive ≥18 cycles of bevacizumab. Larger studies are needed to further characterize toxicities that may be associated with the long-term use of this therapy.
Background: microRNAs (miRNAs) are small, noncoding RNA molecules that regulate gene expression at the post-transcriptional level. Depending on the target, microRNAs may function as tumor suppressors or oncogenes. microRNAs can be transferred to surrounding cells or into the circulation via secretion by exosomes. Exosomes are small nanometer-sized extracellular vesicles that mediate intercellular communication. The dysregulation of miRNAs has been observed in many types of cancer, including breast cancer. However, there is no consensus on the specific role of certain miRNAs (such as miR-23b and miR-27b) as oncogenes or tumor suppressors, likely due to the limitations of available technologies or experimental approach.

Objective: Recent advancements in genetic engineering offer a powerful new approach to completely delete miR-23b and miR-27b from the genome. Our objective was to examine the effects of miR-23b and miR-27b knockout on breast cancer cell phenotypes.

Methods: The CRISPR/Cas9 endonuclease technology was utilized to knockout (KO) miR-23b and miR-27b from the MCF7 breast cancer cell genome. The phenotype of the KO cells and their exosomes was characterized by several assays including: cell proliferation, colony formation, wound healing/migration, and endothelial tube formation.

Results: Genomic DNA sequencing and qRT-PCR confirmed miR-23b and miR-27b KO in MCF7 cells. The KO cells grew significantly slower than control cells (miR-23b p<0.05; miR-27b p<0.05), and produces significantly fewer (miR-23b p<0.001; miR-27b p=.151) and smaller colonies (miR-23b p<0.0001; miR-27b p<0.0001) than control cells. These observations were further confirmed by soft agar colony formation assay. A wound healing/migration assay showed that the miR-27b KO cells migrated differently than the control (p<0.05). When endothelial cells were treated with exosomes derived from miR-23b or miR-27b knockout cells, capillary tube formation was slightly reduced as compared to those treated with exosomes from control cells, suggesting that exosome miR-23b and miR-27b promote tumor angiogenesis.

Conclusions: These results demonstrate that knockout of miR-23b and miR-27b causes phenotypical changes and alters exosome-signaling in breast cancer cells, favoring the concept that these miRNAs possess oncogenic properties during breast cancer progression. Further studies using additional breast cancer cell lines and a xenograft mouse model are warranted to solidify this conclusion.
THE EFFECTIVENESS OF A TAILORED, REAL TIME SMARTPHONE INTERVENTION FOR REDUCING SMOKING LAPSE RISK
Presented by: Emily T. Hébert

Emily T. Hébert, DrPH,1 Darla E. Kendzor, Ph.D.,1,2 Ping Ma, Ph.D.,3 and Michael S. Businelle, Ph.D.1,2

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Background: Almost 30% of all cancer deaths among U.S. adults are attributable to cigarette smoking. While most smokers want to quit, most smoking cessation attempts are unsuccessful. Ecological momentary assessment (EMA), in which smartphones are used to record behaviors and experiences in their natural settings in real-time, can facilitate a better understanding of the moment to moment socioenvironmental cues associated with smoking lapse. Using smartphone technology, it is possible to predict smoking lapse risk in real-time, and to deliver just-in-time smoking cessation interventions at moments of highest risk for relapse. The purpose of this study was to determine if messages that were specifically tailored to reduce urges to smoke, stress, and cigarette availability were more effective at reducing these symptoms compared with messages that were not tailored to these symptoms.

Methods: Participants recruited from a safety-net smoking cessation clinic were loaned smartphones for 3 weeks and asked to complete EMAs 5 times per day. At the end of each EMA, participants received automated and individually tailored messages based upon current level of risk for imminent smoking lapse and self-reported symptoms. Generalized linear mixed models with restricted maximum likelihood estimation were used to determine if messages that were tailored specifically to stress, urge, and cigarette availability reduced these symptoms more than messages that were not tailored to these symptoms.

Results: A total of 59 participants completed 3,608 EMAs during the 2-week post-cessation period. Tailored messages were significantly more likely to decrease targeted symptoms (i.e., urge, stress, cigarette availability) compared with messages that were not tailored to these specific symptoms. Additional analyses that limited the sample to only EMAs where urge to smoke was high or cigarettes were readily available indicated that tailored messages reduced these symptoms more than messages that were not tailored (all p’s<.001). However, the effect of tailored messages on stress was no longer significant when only moments of high stress were included in the model (p=0.052).

Discussion: Tailored messages delivered in real-time were more effective in reducing smoking lapse triggers such as urge, stress, and easy availability of cigarettes than messages that were not tailored to these specific triggers. Smartphones can be used to deliver cost effective, accessible interventions that may improve the effectiveness of smoking cessation programs.
MOMENTARY MEASURES OF URGE, STRESS, CIGARETTE AVAILABILITY, CESSATION MOTIVATION, ALCOHOL USE, AND INTERACTING WITH SOMEONE SMOKING PREDICT DAILY POST-CESSATION SMOKING STATUS
Presented by: Emily T. Hébert

Emily T. Hébert, DrPH,1 Darla E. Kendzor, Ph.D.,1,2 Ping Ma, Ph.D.,3 and Michael S. Businelle, Ph.D.1,2

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Background: A novel smoking lapse risk estimator was previously developed by our laboratory. This estimator weighs and combines 6 variables that are repeatedly collected via smartphone in real-time real-life environments (i.e., current smoking urge, stress, recent alcohol consumption, interaction with someone smoking, cigarette availability, and cessation motivation) to predict imminent smoking lapse. The purpose of this study was to determine if these individual risk factors were predictive of daily smoking status among socioeconomically disadvantaged adults receiving an adjunctive, smartphone-based smoking cessation treatment.

Methods: Participants recruited from a safety-net smoking cessation clinic received a tailored, smartphone-based smoking cessation intervention (Smart-T). The Smart-T app prompted one daily diary assessment and four random assessments each day. A generalized linear mixed model with a binary logistic response function of daily smoking status was used to simultaneously evaluate the relationships between smoking urge, stress, recent alcohol consumption, interaction with someone smoking, cigarette availability, and cessation motivation with within-day smoking.

Results: Participants (N=57) were on average 52.0 years old, female (54.2%), African-American (52.5%), earned less than $16,000 per year (69.0%), and smoked 20.3 cigarettes per day at baseline. A total of 4,084 smartphone based EMAs were used in the current analyses. The odds of smoking relapse were significantly higher (p<.01) with higher smoking urge, stress, cigarette availability, when interacting with someone smoking, when alcohol had been consumed in the previous hour, and when motivation to quit was low.

Discussion: Psychosocial and socio-environmental factors were strongly predictive of smoking lapse. Future smoking cessation interventions may benefit from tailoring just-in-time treatments to help smokers avoid and/or cope with these individual lapse risk factors.
ARTHRALGIA ASSOCIATE WITH LOWER BALANCE CONFIDENCE AMONG BREAST CANCER SURVIVORS ON AROMATASE INHIBITORS: ACCELERATED AGING?

Presented by: Elizabeth Hile

Elizabeth Hile PhD PT1; Susan Whitney PhD PT.2; Justin Dvorak MS3; Kai Ding PhD3; Stephanie Studenski MD MPH.4

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Introduction: An estimated 50% of breast cancer survivors (BCS) on aromatase inhibitors (AI) have arthralgias (AIA). Because chronic or multisite pain is associated with worse balance in aging, and BCS fall more than age-matched peers, we explored the relationship between balance and AIA, hypothesizing that pain would be associated with worse balance among BCS on AI.

Methods: Observational, cross-sectional study (V1) with optional reliability (V2). Participants were 37 BCS (stage0-III, age 40+), on AI for 3 mo to 3 yrs. All completed active cancer treatment with curative resection, were free of frank lymphedema and neuropathy, and denied imbalance or persistent pain pre-AI. BCS were classified as having AIA (n=23), defined as onset of persistent joint pain only after AI, or no-AIA (n=14). Scores on Activities specific Balance Confidence (ABC), Timed Up &Go (TUG), gait speed (GS), and timed balance tasks were compared at V1 across 2 groups (AIA, no-AIA) by Wilcoxon rank-sum. After dividing the AIA group based on prior chemotherapy (chemo), no-AIA group was compared to both AIA-chemo (n=11) and AIA-no chemo (n=12); by overall Kruskal-Wallis test before Wilcoxon rank-sum tests with Bonferroni adjustment. For effect of pain on outcomes, mixed models were used, adjusted for age, toe vibration (vib), and session. Given that chemo effects on balance could extend beyond peripheral somatosensory neuropathy, Wilcoxon rank-sum and mixed model analyses were repeated after excluding BCS with prior chemo.

Results: The AIA group was younger (60.6±10.3 v. 68.2±9.3yrs, p=0.016), yet had worse ABC scores (83.2±11.6 v 96.2±3.3%, p<0.001). Overall, the three groups differed in ABC (p<0.001), with both AIA-chemo (p=0.013) and AIA-no chemo (p<0.001) reporting lower confidence than no-AIA. In adjusted mixed models, mean reduction in ABC score with AIA (vs. no-AIA) was 15.2% (p<0.0001). More in the AIA group had prior chemo (48% v. 17% no-AIA, p<0.001, Fisher’s exact test), but excluding for chemo did not change results. Significant mean reduction (11.5±4.4s, p=0.013) with AIA was also found for eyes closed tandem in adjusted mixed models. Differences in other balance tasks, GS, and TUG did not reach statistical significance after adjusting for age & vibration, but may have clinical meaning.

Conclusions: BCS with AIA had worse balance confidence than an older painfree AI group, after controlling for vibration and prior chemo. Given the younger age of the AIA group, even a lack of mean differences (vs. no-AIA) may support accelerated aging theories for BCS with AIA. Worse balance confidence is linked to falls and may interfere with social participation, return to work and roles, and activity including exercise, potentially impacting recurrence and survival. Our results suggest that BCS with AIA may benefit from interventions to improve balance confidence. Limitations: small sample, cross-sectional design.

FUNDING: NIA P30AG024827 Pittsburgh Pepper Center (PI: Studenski) pilot funds awarded to E. Hile
Activation of cellular responses, such as the homing of cells during fetal development and the immune response, by small signaling proteins called chemokines, through their binding to membrane-bound chemokine receptor proteins, is a fundamental biological process. Yet, chemokine-receptor pairs participate in a number of abnormal conditions, such as the development and progression of inflammation, and the growth and spread of malignant cells. Often in these disease states, receptor over-expression is observed, and progression of the abnormality can be mediated by small molecule receptor antagonists. Significant recent efforts in the cancer research community have focused on the CXCR4 chemokine receptor/CXCL12 chemokine axis, which is intimately involved in the tumor growth and metastasis of dozens of cancers.

We have chosen to design, synthesize, and screen the biological activity of CXCR4 antagonists based on topologically constrained tetraazamacrocycle transition metal complexes. The synthesis and characterization of these complexes, along with screening data on their CXCR4 binding properties and antagonism will be presented. From these studies, lead compound SJA5, the di-copper complex of a cross-bridged bis-tetraazamacrocycle has been selected for further development.

As a copper complex, SJA5 can seamlessly incorporate $^{64}$Cu Positron Emission Tomography (PET) imaging capability by simply using positron emitter $^{64}$Cu in place of “cold” copper during synthesis. Initial imaging studies in healthy mice show no loss of $^{64}$Cu from its chelator, a biodistribution consistent with CXCR4 binding, and facile renal excretion of intact $^{64}$CuSJA5. PET imaging studies on tumors in mice show no PET enhancement of low-CXCR4-expressing tumors, high intensity PET enhancement of high-CXCR4-expressing tumors, and strong binding of $^{64}$CuSJA5 at the high-CXCR4-expressing tumors. An initial study on the effect of lead CXCR4 antagonist, SJA5, on MDA-MB-231 tumor growth in a mouse model gave preliminary findings including delayed tumor growth and extended survival.
IMPACT OF DURATION OF NEUTROPENIA AND LYMPHOPENIA ON AML PATIENTS UNDERGOING INDUCTION CHEMOTHERAPY  
Presented by: Madiha Iqbal

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Background: Various demographic, clinical and cytogenetic factors have been shown to affect the outcome of patients with acute myeloid leukemia (AML). Some of these risk factors are well-described with performance status and patient age being principal predictors of early death while cytogenetic and molecular factors allow stratification into prognostic categories. However, several critical factors have not been adequately assessed. Typically AML patients treated with standard induction chemotherapy will have cytopenias requiring intervention. Often the neutropenia is prolonged and results in neutropenic fevers and a high risk of infections. We hereby describe a single institution retrospective analysis at the University of Oklahoma Health Sciences Center (OUHSC) in which we evaluate the effect of duration of days with at risk absolute neutrophil (ANC) and absolute lymphocyte counts (ALC) and the occurrence of neutropenic fever on survival and response rates of AML patients.

Methods: This is a retrospective chart review of AML adult patients who were diagnosed and treated at OUHSC between 2000 and 2014 and were undergoing initial induction chemotherapy. Outcomes of interest were overall survival (OS), event free survival (EFS: in case of relapse or death) and complete response (CR). Variables of interest were neutropenic fever, and duration of decreased ANC and ALC counts (ANC<500, ANC<100, ALC<500, ALC<100). Institution policy did not allow granulocytes colony stimulating factors use because of the interference with bone marrow aspirate results. Nonetheless it was rarely used in few cases of septic shock, so this variable was not included in this analysis. Descriptive and bivariate analyses were conducted to evaluate the variables of interest and the outcomes. Models were used to assess the relationship between the variables of neutropenic fever, duration of decreased counts (ANC<500, ANC<100, ALC<500, ALC<100) and the outcome of interest after adjusting for age, race, gender, risk group and white blood count (WBC). Multivariable Cox proportional hazard models were used for OS and EFS and multivariable logistic regression models were used for CR. SAS 9.4 was used for all analyses. An alpha of 0.05 was used.

Results: A total of 153 patients were analyzed. Mean age was 50 years, 35.7 % female, 64.3% male. Based on cytogenetic 16.9% were in favorable category, 28.6% in intermediate, 25.3% in unfavorable risk group, and 29.2% unknown. Mean number of weeks with ANC<500 was 3.58 (25 days), ANC<100 was 2.81 (20 days), ALC<500 was 4.47 (31 days), ANC<100 was 3.24 (23 days). Incidence of neutropenic fever was 86.9%. Total number of positive cultures was 55.2%, of which 78.3% were bacterial, 25.3% fungal and 7.7% viral. After adjustment for age, race, gender, WBC and risk group, both neutropenic fever and duration during which ANC<100 were associated with worse OS (p value <0.05) while duration of ANC<500 was not significant (p value < 0.0576). When we considered EFS, the duration where ANC<500, ANC <100, and neutropenic fever occurrence were significant (p value <0.05). The hazard ratio of death is 3.15 for those with neutropenic fever compared to those without. With regard to CR, duration of ANC < 100 was significant (p value 0.0272). The duration of ALC<500 or <100 was not
significant for OS nor EFS. Examining duration of neutropenia, for every week with ANC <500, there was a 9% higher hazard ratio of death after adjusting for other covariates.

**Cox Proportional Hazard Models Predicting Survival – Adjusted (Age, Race, Gender, WBC and Risk Group) - Weekly**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS</th>
<th></th>
<th></th>
<th>EFS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>126</td>
<td>3.15 (1.29 – 7.67)</td>
<td>0.0116</td>
<td>2.88 (1.24 – 6.72)</td>
<td>0.0143</td>
</tr>
<tr>
<td>Yes vs No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC &lt; 500 NOD – wk</td>
<td>137</td>
<td>1.09 (1.00-1.19)</td>
<td>0.0576</td>
<td>1.10 (1.01-1.20)</td>
<td>0.0315</td>
</tr>
<tr>
<td>ANC &lt; 100 NOD – wk</td>
<td>135</td>
<td>1.13 (1.02-1.24)</td>
<td>0.0143</td>
<td>1.13 (1.03-1.24)</td>
<td>0.0093</td>
</tr>
<tr>
<td>ALC &lt; 500 NOD – wk</td>
<td>137</td>
<td>1.05 (0.99-1.12)</td>
<td>0.1075</td>
<td>1.06 (1.00-1.13)</td>
<td>0.0661</td>
</tr>
<tr>
<td>ALC &lt; 100 NOD – wk</td>
<td>136</td>
<td>1.04 (0.98-1.10)</td>
<td>0.2276</td>
<td>1.04 (0.98-1.10)</td>
<td>0.2232</td>
</tr>
</tbody>
</table>

NOD – wk = Number of days neutropenia/lymphopenia calculated weekly.

**Conclusion**: In this single-institution, retrospective study, we identified that the duration of neutropenia along with the presence of neutropenic fever during induction therapy adversely affected OS and EFS. Shorter duration of neutropenia significantly correlated with CR. Duration of days with ALC count <500 was not predictive of OS nor EFS. Larger studies are needed to examine the prognostic significance of neutropenia duration and its relationship to OS and CR. Neutropenia duration during induction chemotherapy may be an important risk factor in making decisions regarding future treatments including allogeneic transplant tolerability and aggressiveness of consolidation chemotherapy. It is important to look at this variable in more intensive induction regimens (using higher dose of cytarabine or adding a nucleoside analogue), as prolonged neutropenia may be a marker of poor general health rather than the induction regimen.
CHEMOPREVENTIVE EFFECTS OF LFA-9, A NOVEL DUAL MPGES-1/5-LOX INHIBITOR IN COLORECTAL CANCER

Presented by: Naveen B. Janakiram

Naveena B. Janakiram1, Altaf Mohammed1, Gopal Pathuri1, Venkateshwar Madka, Rebekah Ritchie, Taylor Bryant1, Yuting Zhang1, Qian Li1, Stan Lightfoot1, Hariprasad Gali2, Vernon E. Steele3, Chen S. Suen3, and Chinthalapally V. Rao1

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Colorectal cancer (CRC) protective effects of NSAIDs and COX-2 inhibitors are well established; however, they are associated with gastrointestinal (GI) bleeding and cardiovascular risk. Mechanistic studies suggest that sparing COX-1/2, prostaglandin (PG)2 synthase and selectively targeting microsomal PG synthase-1 (mPGES-1) and 5-lipoxygenase (5-LOX) would inhibit PGE2 and Leukotrienes (LTs), respectively. To design and develop selective inhibitors of mPGES-1/5-LOX, we used in silico small molecular docking simulation approaches, and identified LFA-9 as a novel selective dual mPGES-1/5-LOX inhibitor among >20 analogs. Azoxymethane (AOM)-induced rat colonic tumors were utilized to assess inhibitory effects of LFA-9 on mPGES-1 and 5-LOX ex-vivo. At 7.5 μM, LFA-9 inhibited the mPGES-1 and 5-LOX activities by ~57% and ~68%, respectively. Maximum tolerable dose (100–1,600 ppm) of LFA-9 in AIN-76A diet on male C57Bl/6 mice were tested and observed that <1,600 ppm dietary LFA-9 to be safe and free from liver, GI and hematological toxicities. In AOM/DSS-induced colonic inflammation in rat, LFA-9 at ≥200 ppm abolished the inflammation and suppressed mPGES-1 and 5-LOX activities in a dose-response manner.

Potential CRC preventive efficacy of LFA-9 was assessed in AOM-rat carcinogenesis with colonic Aberrant Crypt Foci, (ACF) as surrogate marker in male F344 rats and intestinal tumor inhibition in APCMin/+ mice. In rats, colonic ACF were induced by AOM/DSS treatment and two week after the AOM/DSS treatment, LFA-9 (200, 400, and 600 ppm) was fed by diet and ACF were evaluated after six-weeks. LFA-9 showed dose-response (P<0.0001) inhibitory effect on ACFs formation. At 600 ppm, LFA-9 significantly inhibited colonic total ACF and multi-crypts by >60% (P<0.0001). In APCMin/+ mice study, six-week-old male and female mice (10/group) were fed diet containing 0, 350, and 700 ppm LFA-9 for 14 weeks. Male and female APCMin/+ mice fed control diet developed 58±3.8 (Mean±SEM) and 59±5.9 polyps, respectively. LFA-9 administration at 350 and 700 ppm in APCMin/+ mice significantly (p<0.0001) reduced total intestinal tumor multiplicity and size dose-dependently (31.6±5.9 and 24.3±3.7, male mice; and 26.2±5.6 and 15.5±1.8, female mice, respectively). At the high dose both male and female mice showed > 80% suppression of polyps with >2mm size. Mice fed 350ppm LFA9 showed colon tumor inhibition of 60% (male) and 90% (female). It is noteworthy that both male and female mice fed 700ppm LFA-9 showed 91% inhibition of colon tumors. LFA-9 showed significant suppression of markers of proliferation and inflammation. Overall, above results suggest LFA-9 as a novel dual mPGES-1/5-LOX inhibitor, a safer agent than other NSAIDs and has a potential for prevention of CRC in high-risk patients.

(Grant Support: NCI N01-CN 25001-26).
LIQUID BIOPSY GENOTYPING FOR BIOMARKERS OF PLATINUM SENSITIVE OVARIAN CANCER PATIENTS
Presented by: Muralidharan Jayaraman

Muralidharan Jayaraman, Rangasudhagar Radhakrishnan, Kathleen M. Moore, Danny N. Dhanasekaran, and Camille C. Gunderson.

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Analysis of cell-free circulating tumor DNA (ctDNA) may serve as a liquid biopsy to enable quantification and genotyping in order to molecularly characterize tumors. Sequencing ctDNA has been shown to have several distinct utilities including monitoring of tumor alterations relative to oncogenesis and tumor progression, defining the mechanisms of response and chemoresistance, and interrogation of selective exomes to quantify DNA content. Although ovarian cancer is exquisitely sensitive to chemotherapy, the vast majority of advanced stage patients will experience disease recurrence. The driving factor in determining prognosis is the platinum free interval, defined as the interval from completion of platinum-based chemotherapy to time of disease recurrence. The study objective was to develop a prognostic ctDNA panel that can distinguish platinum resistant ("poor prognosis") versus very platinum sensitive ("good prognosis") ovarian cancer patients. Patients with stage IIIC or IV, high grade serous ovarian cancer who underwent primary debulking surgery and received adjuvant chemotherapy were identified. Two prognostic groups were created from these patients for comparison: those with platinum-free interval (PFI) of less than 6 months and those with PFI ≥ 24 months. Serum from these patients were subjected to ctDNA isolation and characterization. Our results comparing the ctDNA profile of "good prognosis" versus "poor prognosis" patients indicated that the poor prognosis patients showed an increase in the ctDNA signatures for several tumor-promoting genes such as CTGF, MUM1, PLD4, P2RX1, and ERCC5. In addition, the ctDNA profile of these patients showed a decrease in the signatures of known tumor suppressor genes such as CTNNA2, GLUD2, MCART6, GABBR1 and UBE2L3, thereby validating our approach and analysis. Following further validation of these biomarkers in the ovarian cancer tissues derived from the respective patients, the prognostic value of the identified panel of genes will be tested in a larger cohort of samples and in the clinic.
Chiedza Kanyumbu, Irene Chen, Kyle Cahill, Molly Denny, Jugmen Sherpa, Karissa Hughes, Akila Venkataramany, and Blaine Mooers

Department of Biochemistry and Molecular Biology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Jumonji domain-containing protein 4 (JMJD4) belongs to the Jumonji C (JmjC) family of oxygenases. Several members of the JmjC family play important roles in gene regulation and, consequently, diseases including several cancers. JMJD4 hydroxylates a specific lysine side chain of eukaryotic release factor 1 (eRF1). eRF1 is a key mediator of the accurate termination of eukaryotic translation. The improper termination of translation is linked to colorectal, breast and ovarian cancers. Improper termination of translation is also linked to the inherited diseases cystic fibrosis and muscular dystrophy. The structure of JMJD4 would be useful for designing drugs that target JMJD4. However, the structure is currently unknown. Our long-term goal is to use the structural data for structure-based drug design.

Our immediate objective is to study JMJD4 in solution by small angle X-ray scattering (SAXS) and in crystals by X-ray diffraction. We have made several MBP-JMJD4 fusions with different N- and C-terminal truncation sites. Homology modeling using available JmjC protein crystal structures guided the design of these constructs. We are able to make large amounts of soluble recombinant proteins without protein aggregation. These proteins are suitable for solution studies and are in crystallization trials.

We plan to use the crystal structure to develop a 3-D model of how JMJD4 interacts with eRF1. We will use SAXS studies to determine the shape of the JMJD4 protein in solution. The shape in solution will be compared to the shape of the crystal structure. This comparison will reveal the relevance of the crystal structure to the structure in solution.
Tobacco quitlines provide a cornerstone of the national and state approach to tobacco control and cessation, with over $118 million being spent each year (2015 NAQC annual survey). NAQC has provided guidelines and standards for quitline operations, data collection and reporting, and evaluation. Yet little is available in the way of guidance for quitline administrators regarding quality improvement/quality assurance (QI/QA). In 2016, the Oklahoma Tobacco Helpline launched a systematic and ongoing effort to monitor the quality of quitline services being provided to tobacco users. Both secret shopping and review of recorded calls with actual tobacco users were used. Review protocols focused on contractual obligations, concerns of key partners, and findings from one earlier secret shopper evaluation (in 2009). Findings revealed both major and minor gaps in quality, including data transfer issues for e-referrals, the need for additional training of quitline staff who would be dosing callers for NRT, opportunities for better promotion of all types of services offered, and gaps in data collection. The QA/QI process will continue quarterly. A protocol has been developed for review of issues with the quitline service provider, and developing solutions collaboratively. Conclusion: A secret shopper/recorded call QA/QI process is feasible, and results in program improvements that increase and maintain the quality of services provided to tobacco users.
Smoking prevalence is high among cervical cancer survivors, with rates approaching 50%. Survivorship care planning should include the delivery of smoking cessation treatment designed to address the specific treatment needs of these women. This study investigated the treatment needs of cervical cancer survivors to inform the adaptation of a theoretically- and empirically-based Motivation and Problem-Solving (MAPS) approach to facilitating smoking cessation in this vulnerable population. Individual in-depth interviews were conducted with 10 female smokers with cervical cancer (80% non-Latino white; 50% >high school education; 80% <$30,000 annual household income). Interviews were audio-recorded and transcribed, and analyzed using NVivo 10. Thematic analyses revealed that cervical cancer significantly impacted participants’ lives; it resulted in changes to their outlook on life and led to worry about other potential health problems. Participants did not believe that smoking and cervical cancer were associated, and attributed their diagnosis solely to human papillomavirus (HPV). Participants reported smoking out of habit and to cope with negative affect, particularly stress. They were interested in quitting, as a means for saving money and improving health, but concerned about coping with withdrawal and negative affect. It was suggested that smoking cessation treatment for cervical cancer survivors should be individualized, but include: psychoeducation about the impact of smoking on health and various cancers including cervical cancer, pharmacotherapy, and benefits of quitting; planning for quitting; strategies for coping with withdrawal and negative affect; real-time support; social support; and relapse prevention. Participants suggested the following components to include in a wellness program: stress management; physical activity and healthy eating; coping with what it means to be a cervical cancer survivor; and managing side effects of cancer and treatment. Results highlight the unique treatment needs of smokers with cervical cancer and will be used to adapt an existing evidence-based intervention to encourage smoking cessation in cervical cancer survivors.
SIMULTANEOUS TARGETING OF ODC AND 5-LOX/COX BLOCK THE TOBACCO CARCINOGEN-INDUCED LUNG ADENOMA PROGRESSION TO ADENOCARCINOMA IN A/J MICE

Presented by: Gaurav Kumar

Gaurav Kumar¹, Jagan Mohan R. Patolla¹, Venkateshwar Madka¹, Altaf Mohammed¹, Qian Li¹, Yuting Zhang¹, Laura Biddick¹, Anil Singh¹, Allison Gillaspy², Stanley Lightfoot¹, Levy Kopelovich³, Vernon E. Steele³, Chinthalapally V. Rao¹

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Increased polyamine synthesis and inflammation have long been associated with intraepithelial neoplasia and their progression to malignant tumor growth, including lung cancer. Targeting multiple pathways simultaneously with low-dose combinations may be an effective approach to modulate different pathways and their downstream signaling, which may result in an increased efficacy and reduced side effects than a single-agent high dose strategy. The aim of the present study was to investigate the effects of DFMO (ODC inhibitor) and licofelone, a dual 5-LOX-COX inhibitor, individually and in combination, on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone NNK-induced lung adenoma and progression to adenocarcinoma in female A/J mice. At 6 weeks of age, mice (25/group) were fed AIN-76A–modified diet, and one week later, lung tumors were induced with a single intraperitoneal (i.p.) injection of 10 µmol NNK/mouse. Three weeks after the NNK treatment, groups of mice were fed with either control or experimental diets containing DFMO (1500 or 3000 ppm) or Licofelone (200 or 400 ppm) or combination of low doses of DFMO and Licofelone. Mice were killed after 17 or 34 weeks of drug exposure and tumors were evaluated via histopathology and lung tumors were assayed for modification of various biomarkers of proliferation and apoptosis. Results suggest that both DFMO and licofelone showed dose-dependent inhibition of NNK-induced lung adenoma progression to adenocarcinoma. At high dose DFMO and Licofelone showed 46% and 55% of adenocarcinoma inhibition. Importantly, low dose combination of DFMO and licofelone showed more pronounced effects at both 17 or 34 weeks in inhibiting the total adenocarcinomas (adenoma and adenocarcinoma progression) by >65% and somewhat in a synergistic manner as compared to individual low doses of DFMO and licofelone. Combination-treated lung tumors exhibited modulation of ODC pathway key components (Arg1, Oat, Oaz, SRM, SMS, and SAT) along with decreased proliferation (PCNA, cyclin D1 and Cyclin A) and increased expression of p53, p21 and p27 compared to tumors from mice fed with control diet. These data suggest that targeting ODC plus 5-LOX/COX decreases the progression of adenoma to adenocarcinoma. Furthermore, adenoma progression delay by combination of DFMO and Licofelone is associated with decreased tumor invasive markers such as MMTPs and EMT markers. In conclusion, targeting two or more pathways is an effective chemopreventive approach for high-risk lung cancer individual’s particularly former tobacco smokers with lung hyperplasia and adenomas.

(Supported by Kerley-Cade Chair Endowment and NCI-N01-CN-53300)
COMPARISON OF A PREFERRED VERSUS NON-PREFERRED WATERPIPE TOBACCO FLAVOR: SUBJECTIVE EXPERIENCE, SMOKING BEHAVIOR, AND TOXICANT EXPOSURE

Presented by: Eleanor L. Leavens

Eleanor L. Leavens, MS1,2 Leslie M. Driskill, MS1,5 Neil Molina, BS1,5 Thomas Eissenberg, PhD3 Alan Shihadeh, PhD4 Emma I. Brett, MS2 Evan Floyd, PhD1 Theodore L. Wagener, PhD1,5

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Introduction: One possible reason for the rapid proliferation of waterpipe (WP) smoking is the pervasive use of flavored WP tobacco. To begin to understand the impact of WP tobacco flavors, the current study examined the impact of a preferred WP tobacco flavor compared to a non-preferred tobacco flavored control on user’s smoking behavior, toxicant exposure, and subjective smoking experience.

Method: Thirty-six current WP smokers completed two, 45-minute ad libitum smoking sessions (preferred flavor vs. non-preferred tobacco flavor control) in a randomized crossover design. Participants completed survey questionnaires assessing subjective smoking experience, exhaled carbon monoxide (eCO) testing, and provided blood samples for monitoring plasma nicotine. WP smoking topography was measured continuously throughout the smoking session.

Results: While participants reported an enhanced subjective smoking experience including greater interest in continued use, greater pleasure derived from smoking, increased liking and enjoyment, and willingness to continue use after smoking their preferred WP tobacco flavor (ps < .05), no significant differences were observed in nicotine and CO boost between flavor preparations. While not significant, topography measures of flow rate, interpuff interval (IPI), and total number of puffs were trending towards significance (ps < .10), with decreased IPI and greater total number of puffs during the preferred flavor session.

Discussion: The current study is the first to examine flavors in WP smoking by measuring preferred versus control preparations to understand the impact on subjective experience, smoking behavior, and toxicant exposure. The pattern of results suggests that even this relatively minor manipulation resulted in significant changes in subjective experience. These results have implications for regulation of flavors in WP smoking.
Fluorescence in situ hybridization (FISH) is a powerful tool of clinical cancer researches due to its ability to visualize and detect chromosomal abnormalities. However, manually analyzing FISH samples is tedious and time-consuming, and the results can lack comparability due to inter-observer and inter-laboratory variability. Automated methods can conveniently overcome these difficulties and potentially expand the sample size indefinitely.

A fluorescence microscope is required to image fluorescent probes, the fluorophores that are chemically conjugated with the targeted proteins. Since most FISH experiments employ probes of multiple colors, multi-spectral acquisition capability is usually required. Whereas plentiful sophisticated technologies have been developed over the years, i.e. laser-based point and line scanning methods, the simple and relatively low-cost conventional wide-field microscopes are still prevailingly used as the diagnostic and research tool.

Naturally, acquisition efficiency will be critical for automated microscopy. In order to maximize acquisition efficiency, we developed an automated microscope that utilize a different approach than filter wheels to simultaneously acquire up to four color spectra. Because of elimination of redundant acquisitions and filter switching, our system can scan microscope slides faster. Unlike other high-throughput multispectral methods, the resolution and quality of the images are not sacrificed. As a result, we are hoping this method to be of good merits for the era of automated clinical pathology to come.

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Oncogenic fusions of RET protein tyrosine kinase (PTK) have been found in non-small cell lung cancer. Several PTK inhibitors (TKIs) are being studied in clinical trials of non-small cell lung cancer for RET kinase targeted therapy. However, previous clinical experience suggests that drug-resistant mutations in the targeted kinase domain are likely to develop during therapy. Therefore, mutation-effective secondary drugs need to be in place in order to prolong the therapeutic responses. Using random mutagenesis followed by drug-resistant selection with cabozantinib, vandetanib, or lenvatinib, we identified 56 mutations of KIF5B-RET affecting 9 different RET amino acid residues in 87 cell lines. We then cross-profiled the sensitivity of these mutants with these three RET TKIs and nintedanib, which we have identified as a potent RET inhibitor. Our results showed that the cabozantinib-resistant RET^{E732K} mutation became hypersensitive to vandetanib and remained sensitive to lenvatinib and nintedanib. The cabozantinib-resistant RET^{V871I} and the lenvatinib-resistant RET^{A807V} remained sensitive to vandetanib and nintedanib. The lenvatinib-resistant RET^{V738A} remained sensitive to vandetanib. All mutations in this study were resistant to cabozantinib. Thus, we have discovered a panel of drug-resistant RET mutations and found secondary drugs to inhibit a subset of these RET mutants.
CHARACTERIZE HUR (ELAV1) AS A POTENTIAL PREDICTIVE AND PROGNOSTIC MARKER IN GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMA

Presented by: Wenyi Lou

John Ward, BS, Wenyi Luo, MD, PhD, and Erin Rubin, MD (corresponding author: erin-rubin@ouhsc.edu)
Department of Pathology, University of Oklahoma Health Sciences Center

HuR (ELAV1) is a master protein involved in regulation of mRNA stability. Upon activation, HuR translocates from the nuclei (the location at resting state) to the cytoplasm, binds to the AU rich elements located at the 3 terminal untranslated regions of many mRNAs and prevents them from degradation. The net effect is an elongated mRNA half life and increased expression of corresponding proteins. The mRNAs targeted by HuR include many genes involved in tumorigenesis such as VEGF and COX-2.

The prognostic and predictive values of HuR have been explored in several gastrointestinal malignancies including gastric adenocarcinoma, pancreatic ductal adenocarcinoma, hepatocellular carcinoma, and colorectal adenocarcinoma. In all these malignancies, HuR cytoplasmic translocation was associated with a higher tumor stage and poorer survival. HuR expression also predicts responses to chemotherapy reagents in pancreatic ductal adenocarcinoma and colorectal adenocarcinoma. HuR expression has been studied in esophageal squamous cell carcinoma, but not in GEJ adenocarcinoma arising in Barrett’s esophagus, which are highly prevalent in the United States.

We propose to study the role of HuR expression in GEJ biopsies obtained from patients with Barrett’s esophagus without dysplasia or adenocarcinoma (study group 1) to those with GEJ adenocarcinoma (study group 2). We expect HuR expression patterns in biopsies with Barrett’s esophagus (study group 1) to be weak and localized to the nuclei of the columnar epithelial cells. We will compare these results of biopsies from patients of Barrett’s esophagus without associated GEJ adenocarcinoma to biopsies from patients with adenocarcinoma of the GEJ arising in a background of Barrett’s esophagus (study group 2). In the biopsies with adenocarcinoma, we expect HuR expression to be significantly increased and localized into the cytoplasm of the columnar epithelial cells. We expect these results, namely a change in the intensity of staining and location change from nuclei to cytoplasm, to be associated with higher tumor stages, worse patient survival, and poor responses to chemotherapy.

Successful completion of the proposed studies will provide a novel diagnostic marker and insight into the pathogenesis of esophageal adenocarcinoma. Future studies after completion of the proposal will be conducted to compare HuR expressions in Barrett’s with or without dysplasia to aid in differentiating high grade dysplasia from low grade dysplasia. Understanding HuR expression may also provide a novel therapeutic opportunity such as by inhibiting HuR with an inhibitor.
Nitric Oxide-Releasing Naproxen Prevents Muscle Invasive Bladder Cancer
Presented by: Venkateshwar Madka

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Bladder cancer is the second most common and a leading cause of death among genitourinary cancers worldwide. Particularly, untreated muscle invasive bladder cancer has high mortality (>85% patients) leading to death within 2 years of diagnosis. Preventing this deadly form is highly imperative since the currently available options to patients with invasive disease remained essentially unchanged and no effective drugs have been approved in past two decades. Several non-steroidal anti-inflammatory agents (NSAIDs) have shown promising chemopreventive activity in many cancers. The common adverse events with NSAIDs, especially gastrointestinal (GI) morbidities, including complications in both upper and lower GI tract drives the need for development of safer agents. To overcome this various nitric oxide (NO)-linked NSAIDs have been synthesized. Here we investigated the NO-releasing Naproxen (NO-Naproxen) with proven anti-inflammatory and GI protecting effects for its efficacy in preventing bladder cancer. Transgenic mouse model (UPII-SV40T; n=30/group) that develop muscle invasive urothelial tumors were generated, genotyped and fed modified AIN-76A diet containing NO-naproxen (0, 300 and 600 ppm) starting at 6 weeks of age. At 40 weeks age, control (0 ppm) and experimental diet (300 and 600 ppm) fed mice were euthanized and urinary bladders were analyzed. Control diet fed male and female transgenic mice developed high grade, invasive transitional cell carcinoma (TCC) of bladder resulting in significant increase in bladder weights (140.2±9.8 mg; p<0.0001 and 34.2±0.8 mg; p<0.0001 respectively) compared with wild type mice (27.3±0.8 mg and 14.8±0.53 mg). These tumors had a significant disregulation of proliferation, cell cycle markers and antioxidant enzymes similar to human tumors. NO-Naproxen administered mice had normal body weight gain; and gross tissue analysis and showed no signs of overt toxicities. Treatment of transgenic mice with NO-Naproxen led to significant suppression of bladder weight in both genders (up to 58% in males, p<0.0001; up to 21% in females, p<0.005) compared to control group. While there was no dose-dependent increase in tumor inhibition, mice on NO-Naproxen diet had developed significantly less muscle invasive tumors suggesting inhibitory effect of treatment on disease progression. Urothelial tumor progression to invasive TCC was inhibited in both male (up to 54%; p<0.005) and female mice (up to 85%; p<0.0001) of the experimental diet groups. Molecular analysis of urothelial tumors via real-time PCR, IHC and/or western blotting showed inhibitory effect of NO-Naproxen on proliferation and inflammatory markers (PCNA, Cyclins, COX2, and IL1b) and showed modulation of antioxidant enzymes (CAT, GPx, GST, NQO1, and SOD3). Our results suggest that NO-Naproxen may be a promising agent for preventing urothelial TCC and warrants further investigation. (Supported in part by NCI-CN53300)
EPIGENETIC SILENCING OF CATALASE INDUCES ACCUMULATION OF REACTIVE OXYGEN SPECIES IN CHRONIC LYMPHOCYTIC LEUKEMIA B CELLS LEADING TO ACTIVATION OF AXL: AN ESCAPE STRATEGY?

Presented by: Guru P. Maiti

1Guru P. Maiti, 2Sutapa Sinha, 2Justin Boysen, 2Neil E. Kay and 1,3Asish K. Ghosh

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Reactive oxygen species (ROS) plays a critical role in regulating prosurvival receptor tyrosine kinase (RTK) signaling pathways in human cancers. Studies have identified mitochondrial metabolism as a key source for abundant ROS in chronic lymphocytic leukemia (CLL) B-cells. CLL B-cells express constitutively active Axl RTK acting as a docking site of multiple kinases/lipase. Most recently, we found that Axl regulates the fibroblast growth factor receptor (FGFR) signaling pathway and that, inhibition of Axl induces robust apoptosis in CLL B-cells. However the mechanism of Axl activation in CLL B-cells remains largely unknown. An earlier study indicates increase of ROS may activate Axl signaling in smooth muscle cells. Given this, we hypothesize that accumulation of ROS in CLL B-cells leading to activation of Axl which promotes enhanced survival of the leukemic B-cells.

Here we report that enforced induction of ROS significantly increases tyrosine phosphorylation levels on multiple cellular proteins in CLL B-cells. Further analysis finds that increased ROS activates Axl and its downstream signal mediators; AKT and Erk1/2 MAPK. Interestingly, phosphorylation level on FGFR was also enhanced which we recently defined as a downstream target of Axl, but not on cMET or IGFR1, in response to increased ROS. Indeed, flow cytometric analysis finds lower levels of O2− but accumulation of H2O2 in CLL B-cells. Of relevance, the histone deacetylase SIRT3 which activates mitochondrial SOD2 via deacetylation, we found, was overexpressed in CLL B-cells indicating more efficient conversion of O2− into H2O2 in the leukemic B-cells. Consistent with the findings, expression of catalase which converts H2O2 into O2 and H2O, was reduced significantly in CLL B-cells as compared to normal B-cells both at mRNA and protein levels.

To delineate the mechanism of reduced expression of catalase we studied promoter methylation of the gene. We have detected that distal region of CAT gene promoter remains methylated in both normal B- and CLL B-cells while proximal region has displayed low to high level methylation of the CpG sites in CLL B-cells but not in normal B-cells. Taken together, these findings suggest that although SOD2 remains highly active, increased accumulation of H2O2 may occur in CLL B-cells due to epigenetic silencing of the catalase gene.

Thus, increased accumulation of H2O2 primarily due to epigenetic silencing of the catalase gene may account for constitutively active Axl signaling pathway and prolonged survival of the leukemic B-cells.
SECON DHAND SMOKE: EFFECTS ON DRUG RESISTANCE AND STEM CELL PROLIFERATION IN ORAL EPITHELIAL CELLS.

Presented by: Jimmy Manyanga

Jimmy Manyanga\textsuperscript{1,2}, Célia Bouharati\textsuperscript{1}, Vengatesh Ganapathy \textsuperscript{1} and Lurdes Queimado \textsuperscript{1,3,5}, Departments of \textsuperscript{1}Otorhinolaryngology, \textsuperscript{2}Cell Biology and \textsuperscript{3}Pediatrics; \textsuperscript{4}The Oklahoma Tobacco Research Center and \textsuperscript{5}The Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma

\textbf{Background:} Cigarette smoking remains the leading cause of preventable disease and death. Cigarette smoking is the main risk factor for oral cancer, and continued smoking after diagnosis increases drug resistance and reduces overall survival rate by 50%. The mechanisms underlying these dramatic effects are poorly understood. A cigarette produces two kinds of smoke: mainstream (MS) smoke, the main smoke directly drawn and inhaled by an active smoker, and sidestream (SS) smoke, the smoke released into the air from the smoldering cigarette tip. SS smoke constitutes more than 90% of secondhand smoke. MS and SS smoke differ in their chemical composition. With 60% of children and almost half of non-smokers estimated to be exposed to secondhand smoke, there remains a pressing need to study the short and long term effects of secondhand smoke exposure. Cancer stem cells (CSCs) are a small subset of cells which have been shown to drive tumor initiation, progression, metastasis, and therapeutic resistance. The effects of secondhand smoke on CSCs or drug resistance are unknown.

\textbf{Aims:} To examine the effects of SS smoke exposure on cisplatin resistance and the stemness in oral epithelial cells.

\textbf{Methods:} Epithelial cell lines in different stages of oncogenesis were exposed to 10 puffs or 100 puffs/5L of MS and SS smoke extracts for 48 h (acute exposure) or 2 weeks (chronic exposure). MS smoke was used as a positive control. For cisplatin resistance, cancer cells were subsequently exposed to cisplatin (0.1-100 µM) and extracts for 48 hours post acute or chronic exposure. Cell viability was assessed by the MTT assay. The number of stem-like cells was evaluated using ALDEFLOUR assay and spheroid formation assay. Gene and protein expression were assessed by quantitative PCR and western blotting respectively.

\textbf{Results:} Relative to untreated control, exposure to SS smoke caused a significant increase in resistance to cisplatin treatment marked by increased cell viability, increased levels of multidrug protein genes, and increased expression of the repair enzyme ERCC1, a major player in the removal of cisplatin adducts. Exposure to SS smoke also caused a significant increase in the number of cancer and non-cancer stem-like cells (ALDH+), as well as an increase in sphere formation. Exposure to SS smoke caused a significant increase in the expression of key stem cell- and Wnt/β-catenin genes including OCT4, TCF4, WNT1, WNT3A and BMI1. The overexpression of BMI1 and WNT1 were confirmed at the protein level, suggesting a potential role of for these proteins in the phenotypes observed.

\textbf{Conclusion:} These data provide new insights into the mechanisms by which secondhand smoke might contribute to tumor initiation, progression, and therapy resistance. Most importantly, our data suggests for the first time that exposure to secondhand smoke might be detrimental to non-smokers and may worsen cancer prognosis.

\textbf{Funding:} This work was supported by the OCAST, OTRC, and PHF. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.
SYNERGISTIC PHOTOTHERMAL ABLATION AND IMMUNOSTIMULATION TREATMENT OF MELANOMA METASTASIS
Presented by: Patrick McKernan

Patrick McKernan¹, Dr. Barry Lavine², Ragagopal Ramesh³, Roger Harrison¹

¹Biomedical Engineering Center, University of Oklahoma, ²Department of Chemistry, Oklahoma State University, ³Department of Pathology, University of Oklahoma Health Science Center

Introduction: Despite its infrequent appearance in dermatology, cutaneous malignant melanoma (CCM) represents the most frequent source of skin cancer related deaths. When CCM metastasizes, patient survival rates fall as low as 5%. By employing a recombinant protein-nanotube conjugate, we selectively target the tumor vasculature for photothermal ablation [1, 2]. Harnessing the phosphatidylserine ligand, annexin V (AV), we direct a single-walled nanotube-AV conjugate (SWNT-AV) to the tumor vasculature. The SWNTs then serve as a near infrared radiation (NIR) target resulting in tumor eradication. Antigen rich cell debris generated via ablation synergistically interact with immunostimulatory agents promoting a heightened immune response leading to decreased metastatic tumor burden and increased survival.

Materials and Methods: All mice are of the B6 Albino strain. The SWNT-AV conjugate is generated by conjugating AV to a SWNT backbone via a DSPE-PEG-malameide linker. In pharmacokinetics studies, mice receive a SWNT dose of 0.8 mg/kg via intravenous injection at 12 weeks of age, tissue samples are collected after 3 hours. Tissue samples are then analyzed for the presence of SWNTs. In tumor studies 1x10⁶ B16F10-luciferase murine metastatic melanoma cells are injected subcutaneously (s.c.) into the animals’ flank to create primary tumors. Pulmonary tumors are generated via intravenous injection of 1x10⁶ B16F10-luciferase cells and monitored via bioluminescent live animal imaging. Primary tumors are treated with NIR irradiation 1 hour after SWNT-AV injection at an energy and power level of 175 J/cm² and 1 W/cm², respectively (time of 175 s; Diodevet-50 NIR laser at 980 nm). Tumor regression is evaluated by bioluminescent imaging and by H&E staining.

Results and Discussion: Primary tumors generated via flank inoculations reached a volume of approximately 60 mm² within 1 week and were then eradicated via thermal ablation. Doses of SWNT-AV less than 0.8 mg/kg failed to fully eradicate primary tumors. Tumors treated with a dose of 0.8 mg/kg remained eradicated for the 12 day duration of the study, and differed significantly in size (p<0.02) from all other groups.

Conclusions: Having established the necessary treatment profile for our model, we are currently undertaking an assay of the synergism between photothermal therapy and a combination of immunostimulants including anti-PD1, anti-OX40, anti-CD73, and cyclophosphamide to ascertain possible mechanisms of harnessing photothermal antigen production to eradicate distant metastases following primary tumor ablation.
The most promising treatment method for metastatic cancer would destruct the primary tumor, and eradicate any metastasis, as well as build a long-term immunity to the disease. One possible solution to this problem is laser immunotherapy (LIT). LIT combines the application of a photothermal laser with an immunoadjuvant such as Glycated Chitosan (GC). Studies using GC have been very successful in combination with single-walled carbon nanotubes (SWNTs), as well as irradiation of near-infrared laser. However, it would be useful to determine if GC and/or SWNT alone can inhibit the migration of metastatic cancer cells. Nested collagen lattices were used to determine the effects of GC and SWNT on cell migration out of the nested lattice into a cell-free collagen matrix. This model was used to induce an in vivo like environment where cells migrate through a 3D matrix. EMT6 and 4T1 cells were treated in the presence or absence of GC and/or SWNT. Preliminary results from these experiments show that the migration properties of cells cultured in collagen matrices are inhibited by SWNT-GC. Future studies should be performed to irradiate by laser the collagen matrices to complete the LIT treatment. Previous data suggest that the LIT treatment would inhibit migration and cause apoptosis. Results that mirror the previous data would indicate a possibility for more comfortable means of treatment. These results could also further explain why LIT in combination with an immunoadjuvant such as GC has gained popularity in cancer research.
Assessment of the potential consequences of chemotherapy to cancer patients is a crucial requirement for developing precision medicine in cancer treatment. According to previous research, the total psoas area (TPA) measured on preoperative cross-section CT image might be a good image marker to predict long-term outcome of pancreatic and ovarian cancer patients after surgery and chemotherapy. However, accurate and automated segmentation of TPA from the CT image is difficult due to the fuzzy boundary or connection of TPA to other muscle areas. In this study, we have developed a new interactive computer-aided detection (ICAD) scheme aiming to more accurately segment TPA from the abdominal CT images and assess the feasibility of using this new quantitative image marker to predict the benefit of ovarian cancer patients who receiving Bevacizumab-based chemotherapy. ICAD scheme was applied to identify a CT image slice of interest, which locates at the level of L3 (vertebral spines). The cross-sections of the right and left TPA are segmented using a set of adaptively adjusted boundary conditions. TPA is then quantitatively measured. In addition, recent studies investigate that muscle radiation attenuation which reflects fat deposition in the tissue might be a good image feature for predicting the survival rate of cancer patients. The scheme and TPA measurement task was applied to a large national clinical trial database involving 1247 ovarian cancer patients. By comparing with manual segmentation results, we found that ICAD scheme could yield higher accuracy and consistency for this task. Using a new ICAD scheme can provide clinical researchers a useful tool to more efficiently and accurately extract TPA as well as the muscle radiation attenuation as new image makers, and then investigate the discriminatory power of it to predict progression-free survival and/or overall survival of the cancer patients before and after taking chemotherapy.

ICAD scheme was processed to illustrate the every stages: first, the operator should specify the region of interest. Then, two seed points should be selected manually in the left and right TPA sections as shown in Figure 1-a, which can be any points inside the TPA sections. The scheme then automatically segment TPA sections as shown in Figure 1-b. Following that there are some correction tools in the ICAD to modify the automatic segmented region, in this example we used the limit button to correct the automatic segmentation as it can be seen in Figure 1-c. afterwards, in figure 1-d we applied color map on the skeleton muscle to demonstrate the muscle attenuation.
Figure 1: demonstration of ICAD scheme process (a) two seed points for region growing is selected. (b) Region growing algorithm is applied. (c) Limiting the selected area after drawing boundary around the unwanted region. (d) Attenuation for the right segmented muscle is shown.
IL-24 INHIBITS GLI-1 AND INDUCES DNA DAMAGE IN LUNG CANCER CELLS
Presented by: Janani Panneerselvam

Janani Panneerselvam, 1,4 Meghna Mehta, 2,4 Alshine Chen, 3,4 Yan D. Zhao, 3,4 Anupama Munshi, 2,4 and Rajagopal Ramesh 1,4,5

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Introduction: Major cause of lung cancer-treatment death is due to drug resistance and metastasis. Advances made in targeted therapies have not improved the overall five-year survival and continues to be dismal (< 16%). Therefore, continued efforts for improved therapies are warranted. Gli-1 a transcriptional factor and downstream target of the canonical Sonic Hedgehog signaling (sHH) and non-canonical signaling pathways is overexpressed in lung cancer and is associated with tumor progression resulting in poor prognosis. Further, Gli-1 plays a role in drug resistance by modulating the DNA damage response pathways. Thus, Gli-1 is a molecular target in lung cancer treatment. Here we investigated whether interleukin (IL)-24 can reduce the expression of Gli-1 and its associated ATM mediated DNA damage response pathway in human lung cancer cells.

Methods: Human H1299 lung tumor cell line was stably transfected with a tetracycline-inducible plasmid vector carrying the IL-24. Upon addition of doxycycline (Dox; 1µg/ml), cells were induced to express IL-24 protein. The expression levels of Gli-1 and its downstream molecular targets as a consequence of IL-24 expression were analyzed in H1299 cells. The inhibitory effect of IL-24 on HH signaling was determined by RT-qPCR, western blot, luciferase reporter assay, immunofluorescence assay and COMET assay.

Results: IL-24 treatment reduced the mRNA and protein expression of Gli-1 and its downstream targets (Zeb1 and Zeb 2). Gli-1 reporter assay demonstrated IL-24 regulated Gli-1 at the transcriptional level. Further, Gli-1 inhibition significantly inhibited the ATM mediated DNA damage response pathway and produced increased DNA damage as evidenced by γ-H2AX foci and COMET assay. Finally, attenuation of Gli-1 expression by IL-24 increased caspase-3 and PARP activity resulting in apoptosis.

Conclusions: Together our study provides (i) evidence that IL-24 treatment can induce DNA damage in lung cancer cells by regulating Gli-1 expression and (ii) offers an opportunity to test combinatorial therapies of IL-24 with GANT61, a Gli1 inhibitor for lung cancer.
COMBINING WHOLE PELVIC RADIATION WITH CHEMOTHERAPY IN STAGE IVB CERVICAL CANCER: A NOVEL TREATMENT STRATEGY
Presented by: Victoria Perkins

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Objectives: Chemotherapy is the standard choice to treat stage IVB cervical cancer (CC). However, given the significant pelvic disease burden and its potential relation to complications and death in these women, whole pelvic radiation (WPR) in addition to chemotherapy for primary treatment may have utility. The aim of this study was to compare the overall survival (OS) and complication rates between combination WPR and chemotherapy versus chemotherapy alone in the management of stage IVB CC.

Methods: A multi-institutional, IRB-approved, retrospective review of patients (pts) with stage IVB CC, diagnosed between 2005 and 2015, was performed. Four academic, high-volume cervical cancer sites were included in this study. Descriptive statistics of the demographic, oncologic, and treatment characteristics were performed. OS was estimated using the Kaplan Meier method.

Results: A total of 127 pts met inclusion criteria. Median age was 54 yrs, 36% were Caucasian, 35% Hispanic, and 16% were African-American. The majority (73%) had squamous cell carcinoma and 95% were grade 2 or 3. Twenty percent elected for hospice care at diagnosis (OS 2.2 mo). Of pts who underwent treatment, 35% received WPR with chemotherapy and 65% received chemotherapy alone. The OS was significantly longer in the WPR with chemotherapy group (22 mo vs 10 mo, p < 0.01, HR:0.30; Figure 1). The rates of ureteral obstruction, vaginal bleeding, pelvic infection, pelvic pain, and fistula were not significantly different between the 2 groups (all p>0.05).

Conclusion: A significant number of women with stage IVB CC experience morbidity directly related to their pelvic disease. This study found that treating the pelvic disease with WPR in addition to chemo gives a 12-month survival benefit to these pts. Interestingly, there was a trend towards less frequent use of WPR with the introduction of bevacizumab into standard of care. Further study is warranted to determine which subgroups may benefit the most from this novel treatment strategy.
Figure 1: OS among stage IVB cervical cancer patients stratified by treatment with WPR and chemotherapy vs. chemotherapy alone (22 mo vs 10 mo, p < 0.01, HR:0.30)
A PRELIMINARY STUDY OF PREDICTING CHEMOTHERAPY RESPONSE AT EARLY STAGE USING QUANTITATIVE RADIOMICS APPROACH
Presented by: Yuchen Qiu

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Ovarian cancer is the second leading cancer with highest mortality rate in gynecologic oncology. For the treatment planning of the ovarian cancer patients, it is critically important to predict the tumor response to the chemotherapy at early stage. However, one of the major clinical limitations in treating ovarian cancer patients is that radiologists and oncologists are not satisfied with the predicting accuracy of current method, response evaluation criteria in solid tumors (RECIST). In this study, we developed a new computer aided diagnosis (CAD) scheme based on quantitative radiomics, which is able to accurately evaluate and predict the tumor response to chemotherapy treatment. This new scheme consists of three modules. First, a hybrid tumor segmentation module was applied to segment the metastatic tumors depicted on the CT images. Next, a total of 149 features were estimated on these segmented tumors, which can be grouped as 1) tumor volume based features; 2) tumor boundary based features; 3) tumor texture based features; and 4) wavelet features. After that, we selected the best performing features as a radiomics feature signature. The new scheme was tested on a retrospectively collected dataset consisting of 91 advanced stage, recurrent ovarian cancer patients. The preliminary results demonstrates that our new signature is able to achieve an area under the receiver operating characteristic curve (AUC) of 0.8103 ± 0.0447. This initial study demonstrates the potential of applying quantitative radiomics method to accomplish high accuracy early stage prediction of the chemotherapy response for ovarian cancer patients in the future clinical practice.

Keywords: Computer aided detection (CAD), ovarian cancer, quantitative radiomics, chemotherapy response evaluation at early stage, Response Evaluation Criteria in Solid Tumors (RECIST).
Currently there is no existing modality that is capable of imaging leukemia cells in a high-resolution label-free way in vivo. We are developing a nanoscale photoacoustic tomography for label free 3D imaging of red blood cells within zebrafish, which are often used as animal models for leukemias. In nPAT, a highly focused pulsed laser results in the creation of an ultrasonic wave through the photoacoustic effect. This ultrasonic wave can be detected with a laser as opposed to a transducer, in a pump-probe set-up. The reflectance change induced by the ultrasound wave can be probed by a laser beam separate from the beam that generated the signal, allowing for signal detection with theoretically unlimited bandwidth and improved resolution in the axial direction as compared to existing photoacoustic imaging modalities. We have derived in our recent work the sensitivity, resolution, and penetration depth of nPAT. We have also run simulations in order to demonstrate the validity of these equations. Lastly, we have set up an nPAT system and obtained an experimental signal, demonstrating proof-of-concept of this novel imaging modality.
DOES DISEASE PROGRESSION POTENTIATE THE EFFECTS OF POLYTOBACCO USE? A CHARACTORIZATION OF INTENTION TO QUIT AMONG NEWLY DIAGNOSED HIV SEROPOSITIVE SMOKERS
Presented by: Micah Savin

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Objectives: Little research has examined the mechanisms by which HIV disease progression may impact intention to quit among people living with HIV/AIDS (PLWHA). HIV disease progression’s impact upon intention to quit may differ between monocigarette and polytobacco users. The aim of this secondary analysis was to describe, over time, the relationship between HIV disease progression and intention to quit among these two groups of tobacco users.

Methods: Participants completed a baseline assessment at the initiation of their HIV care and four follow-up assessments at three month intervals (3, 6, 9, &12-months). Assessments included biochemically verified (carbon monoxide) smoking status and audio computer assisted self-interviews. Independent variables included time from HIV diagnosis, disease progression, and tobacco product use. Covariates included demographics, behavioral, and psychosocial factors. Linear mixed modeling (LMM) was used to evaluate the association of the independent variables and covariates with the primary outcome, intention to quit.

Results: Participants (n=383) were 73.1% male, 67.3% black/African American, and had a mean (SD) age of 38.7 (10.6) years. Most participants reported acquiring HIV through sexual contact, 42.6% heterosexual and 37.1% homosexual. Data were stratified by disease progression and tobacco product use (mono vs. poly) into four subsets. Bivariate analyses revealed significantly greater symptom burden among polytobacco users (p = .0013). Results from LMM indicated that intention to quit was predicted by a three-way interaction between time from HIV diagnosis, disease progression, and tobacco product use (beta = -.0939, p = .0347). Overall, progressive HIV was associated with greater intention to quit. However, this relationship differed over time in the two tobacco use groups.

Conclusion: Findings suggest time from HIV diagnosis, disease progression, and tobacco product use (mono vs. poly) to be determinants of intention to quit among PLWHA. Future studies should consider tailoring the timing of cessation interventions based on an individual’s tobacco use and disease progression characteristics.

Funding: National Cancer Institute R01 CA132636-04: The influence of HIV disease events/stages on smoking attitudes and behaviors.
Cancer is the most lethal disease of U.S. pediatric patients. Current multi-agent chemotherapy regimens achieve survival in many patients, but the drugs used carry considerable short- and long-term toxicity. To improve efficacy and minimize harm in pediatric oncology patients, we must develop strategies to "personalize" oncology regimens based on the unique genetic makeup and empirically-determined drug sensitivities of each patient's cancer. Zebrafish (Danio rerio) provide a cost-effective alternative for patient-specific drug testing, compared to mammalian xenograft cancer models. Transplants of D. rerio tumor cells into wild-type (WT) zebrafish (allo-transplants) or human cancers into WT zebrafish embryos (xeno-transplants) have been used to assay oncogenicity, metastasis, and drug efficacy. However, both strategies are limited by transient immunosuppression in WT hosts, which prevents stable engraftment of xeno-transplants.

To alleviate this problem, we aim to establish xeno-transplants in rag2 E450fs-mutant D. rerio. Humans with Recombination Activating Gene 2 (RAG2) mutations and rag2-mutant fish both fail to assemble their immunoglobulin and T-cell receptor genes, which arrests their B- and T-cell development. Thus, rag2-mutant zebrafish have impaired adaptive immunity and may be suitable for xeno-grafting. We used a human T-cell acute lymphoblastic leukemia cell line (ALLSIL) as a xenograft donor. Zebrafish live at 25-29°C, while human cells grow at 37°C; to mitigate this temperature difference, we are housing rag2-mutant fish and culturing ALLSIL cells at 33°C. After acclimatizing at 33°C, ALLSIL cells were labeled with the fluorophore CM-DiI and intra-peritoneally injected into rag2-mutant fish. After injection, recipients were screened by serial fluorescent microscopy. Animals with increased fluorescence post-transplant were euthanized, single cell suspension prepared, stained with anti-human CD45, and analyzed flow cytometrically. Some recipient rag2-mutant D. rerio harbored CD45-expressing cells, above that seen in non-transplanted rag2-mutant controls, suggesting engraftment of ALLSIL cells. One limitation of this assay is that CM-Dil fluorescence is temporary, and does not increase as cells multiply. To alleviate this, we created a Jurkat T-ALL line stably-transfected with green fluorescent protein (GFP). We are currently optimizing conditions to transplant GFP-tagged Jurkat into rag2-mutant D. rerio. Stably xenografting Jurkat would demonstrate that human cancers can survive in rag2 fish, opening the door to patient-derived xenografts. The improved feasibility and cost of in vivo drug trials in zebrafish position rag2-mutant xenografts as a potential alternative for personalized testing.
VAPE SHOP LOCATION: NEIGHBORHOOD SOCIO-DEMOGRAPHIC CHARACTERISTICS AND PROXIMITY TO SCHOOLS
Presented by: Raees Shaikh

Raees Shaikh, Dana Mowls, Eleanor L. Leavens, Amelia Wedel, Neil Molina, Laura Beebe, Theodore L. Wagener

Oklahoma University Health Science Center- Oklahoma Tobacco Research Center

Objective: The rising prevalence of e-cigarette use in the US, especially among adolescents, has been accompanied by a surge in the number of vape shops. Unlike tobacco stores, little research has focused on the geographic locations of these vape shops in terms of factors like socio-demographic characteristics and their proximity to schools. Our study seeks to address this gap.

Methods: Names and addresses of vape shops, stores that primarily sell vaping products, in a Midwestern metro city area were obtained using online search. Seventy-four vape shops were confirmed to be operational via personal visits and telephone calls. ArcGIS, a geographic information system, was used to identify census tracts and to map vape shop proximity to middle, junior, and high schools within a 1-mile radius. The 2014 American Community Survey 5-year estimates were used to describe socio-demographic characteristics of census tracts containing the 74 vape shops.

Results: More than two-thirds (68%) of vape shops were located within a 1-mile radius of a school. Population of census tracts had a median age of 35.74 years, were predominantly Non-Hispanic White (69%), had higher proportion of ‘some college degree or more’ educational attainment (42%) than ‘less than high school’ (24.32%), more likely to be employed (50.62%) than unemployed or not in labor force (28.88%). There were also more households with annual income of $25,000 to $100,000 (65%) than those making less than $25,000 in the vape shop neighborhoods.

Conclusion: Vape shops seem to be located in census tracts with high SES, old and White population, and in close proximity to schools. It is important to investigate the reasons behind vape shop location preferences, both from a research and policy point-of-view in order to understand whether vape shops are targeting a different population than the tobacco industry or is it simply a business decision.
Objective: The number of vape shops in the US has increased considerably in the recent years. However, unlike tobacco retail stores, research on the point-of-sale (POS) marketing and other important sale practices of vape shops has been scant. The current study aims to fill this gap.

Methods: Names and addresses of seventy-four vape shops, currently operating in a Midwestern metro city area were obtained using online search. Trained researchers audited all 74 vape shops and assessed both exterior and interior POS marketing. Audits focused on presence of advertisements, displays and promotions as well as important products and services offered at the point-of-sale.

Results: 80% of vape shops carried external advertisements and 96% featured advertisements inside the stores. Majority of advertisement, both exterior (56%) and interior (96%) were for e-juices. 92% of vape shops had e-cigarette displays inside the shops. 60% of vape shops offered some type of price promotion on their products, most commonly offering dollars or cents off on purchases. 64% shops offered free e-juice sampling, 60% had a self-serve e-juice bar and 72% offered in-house e-juice mixing. 98% of the vape shops carried flavored e-juice with tobacco, fruit/candy and menthol being the most common flavors available. 48% had age of sale warning displayed inside the shop.

Conclusion: POS marketing is prevalent in vape shops and its effects on uptake and maintenance of vaping needs to be investigated. Such investigation might help strengthen policies such as the recently enacted FDA deeming regulations by drawing attention to the unique features and POS marketing practices at vape shops.
WHAT DIFFERENTIATES CIGARETTE SMOKERS, E-CIGARETTE USERS AND POLYTOBACCO USERS AMONG ADOLESCENTS: RESULTS FROM A NATIONAL SAMPLE
Presented by: Raees Shaikh

Raees Shaikh, Dana Mowls, Eleanor L. Leavens, Laura Beebe, Theodore L. Wagener
Oklahoma University Health Science Center- Oklahoma Tobacco Research Center

Objective: Rising e-cigarette use among adolescents in recent years has raised the question whether e-cigarettes are adding to the pool of future smokers or whether they are appealing only to the adolescents who are already at higher risk of becoming smokers or tobacco users. Our aim was to examine the characteristics that distinguish cigarette smokers, e-cigarette users and polytobacco users among adolescents.

Methods: Data from the 2014 National Youth Tobacco Survey, of US middle and high school students, was analyzed. Current users (past 30 days, n=2355), were grouped as ‘cigarette smokers’ if they had only used cigarettes, ‘e-cigarette users’ if they had only used e-cigarettes, and ‘polytobacco users’ if they had used one or more tobacco products in addition to cigarettes or e-cigarettes. Associations of product use with demographic and smoking-related characteristics (e.g. age of initiation, quit intention etc.) were examined using multinomial logistic regression.

Results: Compared to cigarette and polytobacco users, e-cigarette users were more likely to be younger (p<0.001), more likely to be studying in lower grades (p=0.033), less likely to have initiated nicotine/tobacco use with a cigarette (p=0.0009), more likely to have initiated at a later age (p=<0.001), have smoked fewer cigarettes (p<0.001), less likely to purchase products at a gas station (p=<0.001), and less likely to believe e-cigarettes are harmful (p=0.001). Cigarette smokers were more likely to have an intention to quit than e-cigarette or polytobacco users (p=0.010). Polytobacco users were more likely than cigarette or e-cigarette users to believe smokeless tobacco (p=<0.001) and second hand smoke (p=0.012) were harmless.

Conclusion: Adolescent smokers, e-cigarette users and polytobacco users differ from each other in important demographic and product-use related characteristics. These finding imply a need for longitudinal investigation into the effects of these differences on future tobacco use in order to guide tobacco control policies and programs that could be implemented at an earlier stage in life.
DEVELOPMENT OF PBPK/PD MODEL TO CHARACTERIZE RELATIONSHIPS OF DOSE-EXPOSURE-BIOMARKER MODULATION OF SHETAV2, AN ORAL CHEMOPREVENTION AGENT

Presented by: Ankur Sharma

Ankur Sharma1, Elangovan Thavathiru2, Satish K Ramraj2, Vishal Chandra2, Doris M Benbrook2, Sukyung Woo1

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SHetA2, a sulfur-containing heteroarotinoid, selectively inhibits cancer cell growth and induces apoptosis without activation of nuclear retinoic acid receptors. SHetA2 shows great potential with respect to preclinical efficacy and a safety profile suitable for an oral chemoprevention agent. Currently, SHetA2 is under development for a Phase 0 clinical trial to determine if an oral formulation of SHetA2 can achieve physiological concentrations shown to exert in vitro chemoprevention activity. The objectives of this study are to assess 1) tissue distribution of SHetA2 in tumor bearing mice after multiple oral dose administration and 2) dynamics of drug-induced apoptosis by measuring caspase-cleaved cytokeratin-18 (CK-18) released from the apoptotic carcinoma cells into the blood as a pharmacodynamic (PD) biomarker.

An orthotopic xenograft mouse model of ovarian cancer was chosen to most accurately mimic the ovarian cancer tumor biology and microenvironment in peritoneal cavity. This model involves intraperitoneal injection of SKOV3-luc human ovarian cancer cell lines. Blood and/or tissue samples were collected at 1, 4, 6, 8, 12, 24 hr after the first dose; at 48, 72, 96, and 120 hr before daily subsequent doses for troughs; and at 0.25, 0.5, 1, 2, 2.5, 4, 6, 8, 12 and 24 hr after the last seventh dose. The blood/tissue samples from control animals were also collected at corresponding time points. Plasma and tissue concentrations of SHetA2 were analyzed by a validated HPLC/UV method. The caspase cleaved CK-18 in plasma was measured using M30-Apoptosense® ELISA. The time profiles of SHetA2 concentrations and apoptosis biomarker were characterized by a physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) model.

Daily oral administration of 60 mg/kg SHetA2 for seven days showed no significant accumulation in plasma/tissues of tumor bearing mice, which was expected based on the estimated elimination half-life from a single oral dose study (t1/2=4.5h). The mean trough concentrations of SHetA2 in the plasma were 18.8±6.6 ng/ml. The concentrations in the tumor tissues during 0.25-4 hr after the last dose was greater than the IC50 values (1600 ng/mL) required for growth inhibition in ovarian cancer cell lines. The plasma concentrations of caspase cleaved CK-18 were significantly higher at 72 hr (903.4 U/L, p<0.05) and further elevated upto 96 hr (984.3 U/L, p<0.05), as compared to the baseline (693.9 U/L) from control animals.

The developed PBPK/PD model well depicted tumor SHetA2 levels and its apoptotic effect which was characterized by quantifying the caspase cleaved CK-18 in plasma from tumor-bearing mice. The findings from this study and the developed preclinical PBPK/PD model will assist in designing dosing regimen and sample collections and understanding of SHetA2 efficacy following administration of SHetA2 in the planned clinical studies.
In dividing cells, DNA replication occurs in a precise order, but many questions remain regarding the mechanisms of replication timing establishment and regulation. We now have generated genome-wide, high-resolution replication timing maps throughout zebrafish development. Unexpectedly, in the rapid cell cycles preceding the midblastula transition, a defined timing program was present that predicted the initial wave of zygotic transcription. Replication timing was thereafter progressively and continuously remodeled across the majority of the genome, and epigenetic changes involved in enhancer activation frequently paralleled developmental changes in replication timing. Strikingly, the long arm of chromosome 4 underwent a dramatic developmentally regulated switch to late replication during gastrulation, reminiscent of mammalian X chromosome inactivation. This study reveals that replication timing is dynamic and tightly linked to epigenetic and transcriptional changes throughout early zebrafish development. These data provide insight into the regulation and functions of replication timing and will enable further mechanistic studies.
DEVELOPING URINE EXOSOME-BASED BIOMARKER SCREENING TOOL FOR PREDICTING TREATMENT OUTCOMES IN ENDOMETRIAL CANCER PATIENTS

Presented by: Akhil Srivastava

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Introduction. The ability to successfully predict treatment outcomes will aid oncologists in offering personalized medicine to cancer patients. Recent studies have shown nano-sized (50-120 nm) extracellular vesicles (EV) called “exosomes” play a role in cancer progression, metastasis and drug resistance. Studies have shown that the exosomes’ lumen is enriched with lipids, proteins, DNA, mRNA, and miRNAs. Based on these reports we hypothesized that the luminal contents of the exosomes before, during and after chemotherapy will present “unique signatures” or “bar codes” that can predict treatment outcomes. To test our hypothesis we isolated exosomes from the urine of endometrial cancer patients and focused on micro (mi) RNA profile.

Methods. Urine was collected from patients (n=22) diagnosed with endometrial cancer. Urine collected from patients (n=5) mimicking the symptoms of endometrial cancer but not having cancer was used as controls. Exosomes were isolated and subjected to physical and biological characterization. Subsequently, the exosomes were used for miRNA profiling by quantitative PCR-based miRNA array. The miRNA results were then subjected to hierarchical listing based on the fold difference between cancer exosomes over control exosomes. The top three highly expressed miRNAs in cancer exosomes were identified and validated by conducting miRNA-specific quantitative (q) PCR. Subsequently, miRNA-targets were identified and their expression tested by PCR and/or western blotting.

Results. The isolated exosomes were 83-100 nm in size, and exhibited spherical structure. The presence and purity of the exosomes was confirmed by demonstrating the presence of the membrane proteins, tetraspanins CD63 and CD81, but not Hsp90B1 (Grp94) cytosolic protein and fulfilled the International Society of Extracellular Vesicle (ISEV) consortium criteria. MiRNA profiling showed the top three miRNA that were abundant in cancer exosomes were 200c-3p > 23b-3p > 100-5p. Validation of 200c-3p by qPCR exhibited increased expression in cancer exosomes compared to control exosomes confirming the miRNA array results. TCGA data showed miR-200c-3p expression was altered in 2.1% of endometrial cancer patients and patients with miR-200c-3p alterations had poor survival. starBase 2.0 Pan-Cancer Project Analysis showed approximately a two-fold increase in miR-200c-3p miRNA expression in endometrial cancer patients over normal. Finally, miR target analysis using TarBase showed Zeb1, Zeb2 and BMI-1 as molecular targets of miR200c-3p. Zeb1 and Zeb2 are known to play an important role in epithelial-mesenchymal transition (EMT) and metastasis while BMI-1 in drug resistance. The presence of Zeb1, Zeb 2 and BMI-1 miRNA and protein in the cancer exosomes is currently being investigated.

Conclusions. Our study demonstrates urine exosomes can serve as potential source for biomarker screening and exosomal miRNAs offer unique “Bar Codes” that can be used to predict disease progression and treatment outcomes. Further, the “Bar Codes” offer new therapeutic targets for endometrial cancer treatment.

Acknowledgments. The study was supported in part by funds received from the Stephenson Cancer Center (SCC) Seed Grant, SCC Multi-PI Grant, Presbyterian Health Foundation Seed Grant, Chapman Foundation, and Jim and Christy Everest Endowed Chair in Cancer Developmental Therapeutics, the University of Oklahoma Health Sciences Center.
NANOSOMES CARRYING DOXORUBICIN EXHIBIT POTENT ANTICANCER ACTIVITY AGAINST HUMAN LUNG CANCER CELLS
Presented by: Akhil Srivastava

Akhil Srivastava a,h,+, Narsireddy Amreddya,h,+, Anish Babua,h, Janani Panneerselvama,h, Meghna Mehta b,h, Ranganayaki Muralidharana,h, Allshine Chenf, Yan Daniel Zhaoch, Mohammad Razaqd,h, Natascha Riedingerd, Hogyoung Kimf, Shaorong Liu b,h, Si Wug,h, Asim B. Abdel-Mageed, Anupama Munshib,h, Rajagopal Ramesha,h,+

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Introduction. Successful chemotherapeutic intervention for management of lung cancer requires an efficient drug delivery system. Gold nanoparticles (GNPs) can incorporate various therapeutics; however, GNPs have limitations as drug carriers. Nano-sized cellular vesicles like exosomes (Exo) can ferry GNP-therapeutic complexes without causing any particle aggregation or immune response. In the present study, we describe the development and testing of a novel Exo-GNP-based therapeutic delivery system –‘nanosomes’- for lung cancer therapy. This system consists of GNPs conjugated to anticancer drug doxorubicin (Dox) by a pH-cleavable bond that is physically loaded onto the exosomes (Exo-GNP-Dox).

Methods. Exosomes were purified and characterized followed by loading of the exosomes with Dox-conjugated GNPs to create “nanosomes”. The therapeutic efficacy of Dox in nanosomes was assessed in H1299 and A549 non-small cell lung cancer cells, normal MRC9 lung fibroblasts, and Dox-sensitive human coronary artery smooth muscle cells (HCASM). Efficacy was assessed by cell viability, western blotting, fluorescence microscopy, and COMET assays

Results. Nanosomes exhibited enhanced rate of drug release under acidic conditions. Further, cell uptake studies showed successful uptake of the nanosomes by the recipient cells and the cell viability assays demonstrated that nanosomes exhibit preferential cytotoxicity towards cancer cells and have minimal activity on non-cancerous cells. Finally, we showed nanosome-mediated cytotoxicity involved ROS-mediated DNA damage.

Conclusions. Our study results mark the establishment of an amenable drug delivery vehicle and highlight the advantages of a natural drug carrier that demonstrates reduced cellular toxicity and efficient delivery of therapeutics to cancer cells. Further improvements in nanosome are currently underway for achieving tumor-targeted nanosome delivery.

Acknowledgments. The study was supported in part by a grant received from the National Institutes of Health (NIH), R01 CA167516, an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences (P20 GM103639) of the National Institutes of Health, and by funds received from the Stephenson Cancer Center Seed Grant, Presbyterian Health Foundation Seed Grant, Chapman Foundation, and Jim and Christy Everest Endowed Chair in Cancer Developmental Therapeutics, the University of Oklahoma Health Sciences Center.
The ability to personalize therapeutic administration of anti-cancer compounds would be extremely beneficial to both patients and doctors. In order to develop personalized care and determine the effectiveness of the drug, the anti-cancer compound’s interactions with cancer cells must be explored at the single-cell level. We have developed a method utilizing the Single-probe, which is a miniaturized, multifunctional device that can be coupled to a mass spectrometer for the analysis of live, single cells under ambient conditions. We have used single cell mass spectrometry (SCMS) to detect a variety of anti-cancer compounds in a various cell lines, including T24 and SW780. One major goal of this project includes single-cell quantification of anti-cancer compounds by utilizing an internal standard in the sampling solvent. Another major goal is the adaptation of a suspension cell analysis system for the SCMS determination of anti-cancer compounds in the urine of bladder cancer patients.
DETERMINATION OF CALIBRATION FACTOR FOR TWO REAL-TIME DETECTION INSTRUMENTS USED IN E-CIGARETTE RESEARCH
Presented by: Tyler Watson

Tyler Watson, Theodore Wagener, David Johnson, Evan Floyd

Objective: Real-Time Detection Instruments (RTDIs) are convenient for measuring aerosol concentration in environments with high variability and/or aerosol that is particularly difficult to capture by traditional means, as is the case with liquid aerosols. Several studies have utilized the TSI SidePak with PM2.5 impaction inlet to covertly estimate PM2.5 in various venues but did not first determine the accuracy of these instruments for measuring e-Cigarette (e-Cig) aerosol. The purpose of this study was to determine the calibration factor necessary for accurate e-Cig aerosol measurement by two common RTDIs, the TSI SidePak and the Grimm Portable Aerosol Spectrometer (Grimm).

Methods: e-Cig aerosol was delivered 1-4 times per minute at varied power into a well-mixed exposure chamber, using an automated puffing machine. The e-juice was “chocolate” 70:30 VG:PG, 24 mg/mL nicotine, confirmed by density analysis. e-Cig aerosol was simultaneously sampled with six devices, 3 RTDIs and 3 filter based samplers: SidePak-PM2.5, SidePack-PM10, Grimm, and PM2.5, PM10 and Respirable cyclones. RTDIs were set to calibration factor of 1, i.e. no correction from manufacturer calibration. Filters were equilibrated at 27°C and 50% RH until stable pre-weight and post-weighed immediately after each trial to minimize evaporation. Linear regression of RTDI data on filter results determined the RTDI specific calibration factors.

Results: The R² of RTDI regression was 0.98 - 0.995. The SidePak-PM2.5 and SidePak-PM10 overestimated by 98% and 86%. The Grimm underestimated PM2.5 by 15%, but overestimated PM10 and Respirable mass by 14% and 6%. The corresponding calibration factors are: SidePak-PM2.5, 0.51; SidePak-PM10, 0.54; Grimm PM2.5, 1.18; Grimm PM10, 0.88; Grimm Respirable, 0.94.

Conclusions: Estimation of e-Cig aerosol concentration with RTDI is a good application of this technology, especially when considering the potential for sample loss during real life conditions where aerosol concentration may become very low and collected sample may evaporate. However, use of aerosol-specific calibration factors is necessary for obtaining accurate measurement.

Funding Sources: This project was funded in part by the Oklahoma Tobacco Research Center (OTRC) Summer Scholars Program.
BRAIN REACTIVITY TO CIGARETTE RELATED AND EMOTIONAL VISUAL STIMULI WHEN SMOKERS ARE TAKING VARENICLINE, BUPROPION, OR PLACEBO

Presented by: Elise M. Stevens


Background: Varenicline and bupropion are two of the most effective smoking cessation pharmacotherapies. Researchers have hypothesized that these medications might be effective, in part, because they reduce cue-induced craving, one of the most commonly reported causes of smoking relapse. However, studies that measured physiological responses to cigarette-related cues in smokers taking varenicline or bupropion yielded mixed results. Here, we used event-related potentials (ERPs) to directly measure brain reactivity to cigarette-related, pleasant, neutral, and unpleasant pictures in smokers attempting to quit while taking varenicline, bupropion, or placebo.

Method: Participants were smokers involved in a 12-week placebo-controlled double blind clinical trial of smoking cessation medications (varenicline, bupropion, placebo). For each participant, the target quit date was scheduled after 2 weeks of treatment. We collected ERPs at 2 time points: 24 hours after the quit date (Time 1, 140 participants) and 4 weeks after the quit date (Time 2, 176 participants). We measured the motivational relevance of cigarette-related, pleasant, neutral, and unpleasant pictures using the amplitude of the Late Positive Potential (LPP). We measured self-reported tonic craving with the Questionnaire of Smoking Urges (QSU-B).

Analyses: We analyzed the LPPs obtained at each visit using a 3 x 2 x 4 ANOVA with drug type (varenicline, bupropion, placebo) and smoking abstinence (abstainer, non-abstainer) as between-subjects factors, and picture category (cigarette-related, pleasant, neutral, unpleasant) as a within-subjects factor. The results from the QSU-B collected at each visit were analyzed using a 3 x 2 ANOVA with drug type (varenicline, bupropion, placebo) and smoking abstinence (abstainer, non-abstainer) as between-subjects factors.

Results: At both visits, emotional and cigarette-related images evoked larger LPPs than neutral pictures, as evidenced by a main effect of picture category (Time 1: $F[3, 136] = 55.21, p < .001$; Time 2: $F[3, 172] = 59.37, p < .001$). Post-hoc pairwise comparisons indicated that, cigarette-related pictures evoked significantly ($p < .0005$) larger LPPs than neutral images at Time 1 and Time 2. Neither drug type nor smoking abstinence altered this effect of picture category at either visit ($ps > .25$). At both visits, varenicline and bupropion significantly reduced self-reported tonic craving relative to the placebo condition (Time 1: $p < .01$; Time 2: $p < .001$).

Conclusion: While both varenicline and bupropion reduced tonic craving intensity, neither medication altered brain reactivity to cigarette-related or emotional stimuli in smokers attempting to quit. This suggests that these medications may influence abstinence by means other than reduced cue reactivity and that unattenuated cue reactivity could influence relapse after medication is withdrawn.
N-MYC NON-AMPLIFIED HIGH-RISK NEUROBLASTOMA: IDENTIFICATION OF A NOVEL MOLECULAR SWITCH AND ITS FUNCTIONAL RESPONSE IN PROGRESSIVE DISEASE
Presented by: Karthikeyan Subramanian

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N-MYC amplification is restricted to ~30% of the high-risk neuroblastoma (NB), while the remaining 70% is N-MYC non-amplified (N-MYC-NA), yet still has a poor outcome with only 37% 5 Year OS and a miserable 9% 10Y OS. Recently, we demonstrated, Retinal Degeneration Protein 3 (RD3) regulates metastatic state of NB cells and its loss associates with poor prognosis. Herein, utilizing bed-to-bench approach coupled with in vitro, in vivo and ex vivo NB models, we investigated the role of RD3 reprogramming in the evolution of N-MYC-NA-NB. Assessing 15 different human derived stage-4 N-MYC-NA-NB cell lines demonstrated: transcriptional/translational loss of RD3 compared to neural crest cells; cell specific loss and; association of RD3 loss to cellular progressive disease, cellular therapy resistance and disease relapse. Further, in silico analysis demonstrated that RD3-loss was intrinsically associated with reduced OS and abridged relapse-free survival in N-MYC-NA-NB patient cohorts. We also demonstrated the complete loss of RD3 in metastatic site-derived aggressive cells (regardless of CSC status) ex vivo and in reproducible aggressive disease models in vivo. RD3-loss correlated with the heightened metastatic state (tumor cell migration, invasion and tumorosphere formation) of the N-MYC-NA-NB cells. Further, re-expressing RD3 in aggressive cells reverted their metastatic potential both in vitro and in vivo. These results demonstrate the loss of RD3 in high-risk N-MYC-NA-NB, its novel tumor evolution stabilization function and further imply that continuous ongoing acquisition of RD3-loss in therapy resistant cells may directly relate to tumor progression and poor clinical outcomes.
MUTATION SELECTIVITY OF AN ALLOSTERIC SHP2 INHIBITOR
Presented by: Xiaojun Sun

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SHP2 (PTPN11) is a protein tyrosine phosphatase (PTP) activated by oncogenic protein tyrosine kinases (PTKs) to mediates oncogenic signaling and tumor growth. Moreover, gain-of-function PTPN11 mutants are oncogenes found in hematological malignancies and solid tumors. In particular, PTPN11 is the most frequently mutated oncogene in juvenile myelomonocytic leukemia (JMML), accounting for ~35% of JMML cases. Recently, an allosteric SHP2 inhibitor SHP099 has been identified that inhibits the PTK-activated, wildtype SHP2 in cancer cells [Nature (2016) 535, 148-152]. However, it is unclear if the allosteric SHP2 inhibitor SHP099 can also inhibit oncogenic SHP2 mutants. In this study, we synthesized SHP099 and compared its activities in inhibiting oncogenic SHP2 mutants. In vitro SHP2 PTP assay showed that SHP099 did not inhibit the non-activated wildtype SHP2. SHP099 selectively inhibited bisphophotyrosine GAB1 peptide-activated wildtype SHP2 and the SHP2E69K mutant, but it was 5-fold less potent in inhibiting the SHP2E76K mutant. In SHP2E76K- and SHP2E69K-transformed TF1 myeloid leukemic cells, SHP099 inhibited SHP2E69K- and SHP2E76K-dependent survival and growth of these cells with IC₅₀ of 1.6 µM and 26 µM, respectively. Immunoblot analysis showed that SHP099 inhibited SHP2E69K-activated MEK1/2 and ERK1/2, suppressed SHP2E69K-induced BCL-XL, and induced apoptosis in TF1/SHP2E69K cells in low µM concentrations. Together, these results show that the SHP099 activity can be affected by different SHP2 oncogenic mutations and demonstrate that the allosteric inhibitor selectively inhibits PTK-activated wildtype SHP2 and the SHP2E69K mutant.
Background: Macrophage chemoattractant protein-1 (MCP-1), also known as CC-motif ligand (CCL2), is a chemokine which recruits monocytic macrophages to the site of inflammation. This chemokine also contributes to cancer progression by causing infiltration of macrophages into tumors, and activating those macrophages toward the M2 phenotype that supports tumor growth and angiogenesis. In ovarian cancer, increased CCL2 levels were associated with increased tumor macrophage content and chemotherapy resistance. Basal and chemotherapy-induced CCL2 expression is induced by interleukin-6 (IL-6). IL-6 neutralizing antibodies reduced IL-6, CCL2 and macrophage markers in chemotherapy-resistant ovarian cancer patients. We hypothesized that single nucleotide polymorphisms (SNPs) in the CCL2 gene are associated with CCL2 expression and ovarian cancer patient survival.

Methods: Ovarian cancer patient samples and cell lines were evaluated for germline CCL2 SNPs using PCR, and for CCL2 and IL-6 protein levels using ELISAs. Associations with clinical data were evaluated using Kaplan Meier Survival Analysis, Cox proportional hazard regression model, Kruskal-Wallis test and Spearman Correlation. GATA expression and binding were evaluated by Western blot and ChIP.

Results: The rs1860190 SNP was significantly associated with progression free survival (PFS) and overall survival (OS) of ovarian cancer patients. Patients homozygous for the A allele had significantly longer PFS in comparison to patients homozygous for T, while heterozygous AT patients had intermediate PFS. Multivariate analysis found a significant OS benefit of AA over TT (hazard ratio: 0.317, 95% CI: 0.113-0.892 for TT over AA). This SNP is upstream of the CCL2 coding sequence and may affect promoter activation. CCL2 serum levels measured in an independent set of specimens were higher in patients homozygous for T in comparison to patients with the AT or AA genotypes. We discovered that the T allele creates a previously unidentified GATA transcription factor DNA binding site in the 5’ region of the CCL2 gene. GATA transcription factors are induced by IL-6. Using an independent set of 85 ovarian cancer specimens, we observed a positive association of serum CCL2 and IL-6 levels in patients homozygous for T, and not in AT heterozygotes or AA homozygotes. Our mechanistic studies in cell cultures confirmed that GATA transcription factors are expressed in ovarian cancer and bind to the rs1860190 T allele, and that IL-6 induced CCL2 transcription in an ovarian cancer cell line harboring the TT genotype.

Conclusion: The AA allele of the rs1860190 CCL2 SNP in germline DNA is associated with improved survival of ovarian cancer patients. The worse outcome in patients harboring the T allele may be caused by the creation of a GATA site in the CCL2 gene promoter that is induced by IL-6 to increase CCL2 levels and support tumor growth. Regulation of autophagy by the IL-6 – CCL2 axis may contribute to these associations.
GTSE1 IS A NOVEL REGULATOR OF CHROMOSOME ALIGNMENT DURING MITOSIS
Presented by: Aaron Tipton

Aaron Tipton, Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation

Defects in the movement or distribution of chromosomes during meiosis and mitosis are major causes of congenital birth defects and a contributor to increased malignancy in cancer. Mitotic spindle assembly and function are regulated by multiple microtubule-associated proteins. We have identified the microtubule-binding protein, GTSE1 (G2 and S phase expressed protein 1), as a novel mitotic regulator required for chromosome alignment during prometaphase. GTSE1 expression is highly regulated during the cell cycle. The protein appears during G2, peaks during mitosis then is completely degraded following entry into G1. GTSE1 interacts with EB1 and exhibits plus end tip-tracking before mitosis, but loses tip-tracking and becomes bound to the microtubule lattice from late prophase to metaphase. At anaphase onset tip-tracking abruptly reemerges. Cells depleted of GTSE1 fail to properly align chromosomes, form multipolar spindles, are delayed in mitotic progression, and aberrantly exit from mitosis. GTSE1 depletion reduces levels of the chromokinesin, Kif4A, on mitotic chromosomes and reduces kinetochore to pole distances in monopolar spindles induced by treating cells with Monastrol. These results suggest that GTSE1 regulates microtubule interaction with chromosome arms through Kif4A. GTSE1 depletion results in a significant decrease of Histone H3 phosphorylation on S10 on chromosome arms indicating that GTSE1 regulates Aurora B kinase activity or a counteracting phosphatase on chromosome arms. Photobleaching and photoactivation experiments show that GTSE1 depletion results in microtubule stabilization in mitotic spindles. In anaphase, microtubule interactions with chromosome arms may be attenuated to promote anaphase chromosome movement consistent with the return of GTSE1 to tip tracking. These results suggest a model whereby GTSE1 is recruited to the microtubule lattice during prometaphase to regulate microtubule interaction with Kif4A on chromosome arms and promote chromosome alignment at the spindle equator at metaphase.
TUMOR TARGETED ENZYME-PRODRUG THERAPY FOR METASTATIC OVARIAN CANCER
Presented by: Needa Virani

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Ovarian cancer accounts for most deaths associated with gynaecological cancers and nearly 80% is detected after the tumor has spread to the peritoneal cavity. Due to the lack of effectiveness of current therapies novel approaches need to be investigated and implemented. One such approach is an enzyme-prodrug treatment which utilizes a mutant cythathionine-γ-lyase (mCGL) fused with annexin V (AV) for tumor targeting. The mCGL enzyme converts selenomethionine prodrug into 200-1000X more toxic methylselenol that generates reactive oxygen species leading to apoptosis. The AV binds to phosphatidylserine (PS) which has been shown to be normally internalized on healthy cells but externalized on tumor cells and vasculature. The proposed approach ensures tumor specific delivery of a highly cytotoxic agent with minimum side effects to the surrounding healthy tissue.

Mouse ovarian cancer cells (ID8) have been tested in vitro to validate this therapy. A binding study found the dissociation constant to be 18.53 ± 6.1 nM, indicating strong affinity. Fluorescence microscopy confirmed the binding the mCGL-AV fusion protein to the tumor cells and previous studies have shown that mCGL-AV also binds non-confluent endothelial (HAAE-1) cells, which mimic endothelial cells in the tumor vasculature. This therapy can therefore cut off the blood supply to the tumor leading to minimized tumor growth as well diffuse through the leaky vasculature and directly attack the tumor cells for regression. In addition, the fusion protein injected into the peritoneum where the ovarian cancer has spread will bind directly to the tumor cells. A cytotoxicity study was conducted to confirm complete tumor cell death after only 2 days of enzyme-prodrug treatment. These results shed a promising light on the potential for this therapy in animal studies and beyond.

To demonstrate the effectiveness of this therapy for treating peritoneum metastatic ovarian cancer, tests in immune-competent mice are planned to determine the optimum dosage cycle which maximizes effectiveness while minimizing drug required. Currently, clinical therapies often utilize combinatorial approaches to attack the tumor from multiple pathways which will be implemented here to achieve the final objective of tumor erradication. The enzyme prodrug therapy will be combined with pairs of immunostimulants (selected from anti-PD-1, anti-CD73, and anti-OX40), along with carboplatin (alkylating agent to sustain the DNA damage caused and lead to apoptosis) and/or rapamycin (prevent hypoxic response survival).
NEAR-INFRARED LIGHT ABLATION OF BLADDER CANCER USING PHOSPHATIDYLserINE TARGETED CARBON NANOTUBES
Presented by: Needa Virani

Needa Virani¹, Carole Davis², Paul Hauser², Robert Hurst², Joel Slaton², Roger Harrison¹
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Approximately 80% of bladder cancer patients have recurrent tumors starting with Stage I superficial and quickly progressing towards more muscle invasive and metastatic malignancies with each recurrence. The high incidence of reappearance is believed to be due to the residual tumor left behind in at least 27-62% of patients. The current form of treatment is a transurethral resection for lower grade tumors with a minimum number of treatments, ideally one. Toward this goal, this study focuses on treating superficial bladder cancer via thermal ablation using annexin V (AV) surface-modified single-walled carbon nanotubes (SWNTs). Phosphatidylserine (PS) is normally internalized in healthy cells; however it has proven to be a surface marker for solid tumors and can be targeted by AV. SWNTs absorb near infrared (NIR) light at 980 nm and dissipate most of their generated heat into the surrounding substrate, such as cancerous tissue. This study provides a means to target and treat tumor cells all along the bladder wall, thus reducing the risk of recurrence and potential development into higher grade tumors.

In vitro binding studies confirmed a strong binding affinity of AV to MB49 (Kd = 4.14 ± 1.28 nM) and J82 (Kd = 0.38 ± 0.20 nM) cells. Combining SWNT-AV heating via NIR confirmed significant cell death as compared to untreated controls for both cell lines which provided validation for the potential of this targeted ablation therapy.

In vivo testing on C57BL-6 mice was conducted to confirm the efficacy of this treatment. A biodistribution study of intravesically delivered SWNT-AVs in MB49 orthotropic models was conducted and analyzed via FT-Raman. The study verified that no non-specific accumulation of SWNT-AVs had occurred. NIR power tolerance tests with a 360° radiating fiber confirmed that no healthy tissue damage occurred at 50 J/cm². Preliminary in vivo treatment of MB49 bladder cancer bearing mice with SWNT-AV and NIR combination therapy resulted in significant decrease in tumor size. A large scale study confirmed similar results with minimum tumor presence after therapy.

SWNT-AVs have proven to preferentially target bladder cancer cells and in conjunction with NIR to cause significant cytotoxicity in vitro as well as in vivo. The results of this study show promise for NIR thermally heated SWNT-AVs as a viable global, therapeutic option for recurrent superficial bladder cancers.
MACROPHAGE-INDUCED BYSTANDER EFFECT ACTIVATES WNT/β-CATENIN SIGNALING AND INDUCES CELLULAR DEDIFFERENTIATION

Presented by: Xingmin Wang

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Cancer stem cells (CSCs) in colorectal cancer (CRC) help maintain tumor heterogeneity, promote tumor growth, invasion, and metastasis, and produce resistance to therapeutic agents. The origin of colorectal CSCs, however, is unclear. Our recent studies showed that a macrophage-induced bystander effect (MIBE) induced gene expression of stem/progenitor cell markers including Ly6A/E and Dclk1 in murine colonic epithelial cells, implying that MIBE helps induce colorectal CSCs.

In current studies we show that commensal-triggered MIBE activates Wnt/β-catenin signaling and induces dedifferentiation of colonic epithelial cells during colorectal carcinogenesis, thus contributing to the origin of colorectal CSCs. Exposure of murine primary epithelial cells (YAMC) to commensal-polarized macrophages induced phosphorylated Gsk3β (Ser9), active β-catenin, and Tcf4, suggesting activation of Wnt/β-catenin signaling by MIBE. In vivo, active β-catenin was evident in both stromal and epithelial cells for colon biopsies from *E. faecalis*-colonized *Il10−/−* mice compared to sham-colonized mice. In addition, we showed that 4-hydroxynonenal (4-HNE), a byproduct of lipid peroxidation of ω6 polyunsaturated fatty acids, and tumor necrosis factor α (TNFα) mediated activation of Wnt/β-catenin signaling. Next, we showed that exposure of YAMC cells to 4-HNE and TNFα induced expression of c-Myc, Klf4, Oct4, and Sox2—factors essential for pluripotent stem cells. Immunofluorescent staining of colon biopsies from *E. faecalis*-colonized *Il10−/−* mice showed increased expression of these factors in colonic epithelial cells, suggesting dedifferentiation induced by MIBE. This was confirmed by qRT-PCR and Western blots that showed increased expression of Dclk1 and CD44, two markers for colorectal CSCs. Furthermore, increased expression of DCLK1 was noted in human tubular adenomas and invasive CRCs compared to hyperplastic polyps. Finally, inhibition of β-catenin/TCF4 using FH535, and by silencing CTNNB1, decreased DCLK1 expression in HCT116 human colon cancer cells, supporting the notion that Wnt/β-catenin signaling induces cellular dedifferentiation leading to colorectal CSCs.

In summary, these results demonstrate that commensal-polarized macrophages activate Wnt/β-catenin signaling and induce dedifferentiation of colonic epithelial cells through 4-HNE and TNFα-mediated bystander effects. These findings provide new evidence for the origin of CSCs in colorectal carcinogenesis and should lead to novel strategies for CRC prevention and therapy.
EXAMINING PREGNANT SMOKERS' INTEREST IN USING ELECTRONIC NICOTINE DELIVERY SYSTEMS, SMOKING CESSATION MEDICATIONS, AND NICOTINE REPLACEMENT DURING AND AFTER PREGNANCY TO REDUCE OR QUIT SMOKING

Presented by: Amelia Wedel

Amelia Wedel, Eleanor Leavens, Theodore Wagener, Neil Molina

Oklahoma Tobacco Research Center, University of Oklahoma Health Sciences Center

Significance: Research suggests that pregnant smokers believe electronic nicotine delivery systems (ENDS) may be successfully used for smoking reduction or cessation, but that they are unsure about potential harm to their baby, so it is unclear if they are using or interested in using ENDS for smoking cessation or reduction during pregnancy. The purpose of the present study was to assess pregnant smokers’ use and attitudes regarding ENDS, smoking cessation medications, and nicotine replacement therapy (NRT) during and after pregnancy.

Methods: A convenience sample of 86 pregnant smokers (65.9% White; mean age = 28) were recruited from a high risk pregnancy clinic. Each participant completed an anonymous survey and an exhaled CO measurement. The survey assessed their attitudes and beliefs toward medication, NRT, and ENDS as methods for smoking cessation or reduction during and after pregnancy. Data was examined using Pearson chi squares.

Results: Participants had significantly reduced their cigarettes per day from 17.5 to 8.6 since becoming pregnant (p<.05), with 40% reporting trying to quit smoking. Despite few participants (5.8%) reporting current ENDS use, the majority of the sample expressed an interest in vaping both during (50.6%) and after pregnancy (53.5%) in order to quit or reduce smoking. Compared to those who had never vaped, those who had ever vaped (62.4%) were significantly more interested in vaping both during (60.4% vs 35.5%) and after pregnancy (64.2% vs 37.5%; p<.05). Participants who had ever used any form of NRT (56.9%) were significantly more interested in using NRT both during (61.2% vs 16.7%) and after pregnancy (57.1% vs 25%; p< .01). Few participants had ever used a smoking cessation medication (10.6%) and few were interested in using them during (11.8%) or after pregnancy (20.9%).

Conclusions: Pregnant women are interested in using ENDS and NRT for smoking cessation. In general, they are more interested in product use after pregnancy than during pregnancy, and are more interested in using products they have used previously.
BIOMIMETIC SURFACE MODIFICATION PLATFORM FOR THE DEVELOPMENT OF IN VITRO TUMOR MODELS

Presented by: Cortes Williams

Cortes Williams¹, Patrick McKernan¹, Roger Harrison², and Vassilios Sikavitsas³.
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Traditional chemotherapy regimens put a high degree of emphasis on the use of historical data to predict a cancer patient’s response to a proposed therapy. Unfortunately for the patients, this often leads to continuous rounds of trial-and-error in the search for a compatible treatment, decreasing their chances for survival. Tumor engineering seeks to alleviate this issue by growing patient tumors outside of the body, providing a high throughput avenue for treatment discovery. Utilizing a variety of techniques for 3D culture, researchers have created models that more closely resemble and predict in vivo tumor drug responses; however, there is still more room for improvement. In particular, these in vitro models consistently exhibit poor cell proliferation and distribution, which severely limits their predictive capabilities.

The ability to seed and culture in vitro patient tumor cells on 3D scaffolds presents unique challenges due to the inert nature of commonly used polymeric or ceramic biomaterials. Mimicking the natural microenvironment of the target tissue can be of great benefit to not only improve the seeding efficiency, but also the drug response of the engineered tumor. The choice of scaffold used to support cells in culture plays a significant role in cell viability and ex vivo tumor development. Scaffold properties, such as rate of degradation, hardness, and biocompatibility must be manipulated to match desirable tissue properties and the rate of tissue growth to scaffold degradation. Surface modification primarily addresses the interface that the cells directly interact with, coating underlying material with undesirable properties (such as extreme hydrophilicity or hydrophobicity).

To combat this major issue, we have leveraged our novel biomimetic surface modification platform for tumor engineering applications. Initially we wanted to verify the existence of subpar cellular adhesion. We seeded various cell lines (PC3, MDA, and MB49) on unmodified poly(L-lactic acid) (PLLA) in both static and dynamic bioreactor conditions. Aligning with our previous statements, we saw very low attachment rates, consistently around 15%. In order to increase this adhesion rate, we have identified various moieties specific to certain tumors that are integral to cellular adhesion, and have used these to modify our scaffolds and trick the cancer cells into exhibiting higher rates of adhesion. For instance, in terms of prostate cancer, scaffolds were modified to express n-cadherin, which is a highly upregulated protein used for cellular adhesion. After cell seeding, we were able to significantly increase PC3 seeding efficiency and potentially improve cell physiology without compromising the mechanical and degradation properties of the underlying PLLA.
X-ray fluorescence imaging technique by using gold nanoparticles was demonstrated potentially improves diagnosis imaging specificity by targeting nanoparticles to tumor areas. The x-ray fluorescence detectability of low-concentration GNPs distribution determines the detecting ability and sensitivity of this technique. In this study, we measured the GNP k-shell fluorescence by using a 100 mm long scatter-eliminating collimator to further improve the detecting sensitivity compare to literatures. The GNPs were suspended in deionized water to acquire different concentrations. The emissions of the GNP fluorescence were measured by a spectrometer located with an angle of 90 degree as respect to the excitation beam. As a result, the k-shell fluorescence peaks, 66.99 keV and 68.80 keV, were measured and observed in 0.1, 0.2, 0.4, 0.8, 1.0, 2.0 and 4.0 mg/mL concentration modes. The resultant calibration curves performed linear relations between the GNP suspension concentrations and the number of photons of the fluorescence peaks. Therefore, the detection sensitivity of GNP fluorescence was successfully improved by an order of magnitude and observably reached 0.1 mg/mL (0.01 % in weight concentration).

As the fluorescent particles are excited, the whole volume of excited particles can be considered as a source of the fluorescence. The image of this source can be obtained by a pinhole camera associated with a CCD detector. Therefore, in this study a con-shape pinhole imaging system for imaging 2D GNP x-ray fluorescence was demonstrated. The GNP x-ray fluorescence excitation was performed by the same procedure as in fluorescence spectrum acquisitions. A cone-shape pinhole camera was designed based on the principle of single-pinhole gamma-ray camera employed in SPECT imaging. The incident pinhole was 0.8 mm in diameter. The GNP x-ray fluorescence pinhole images were acquired in GNP concentrations of 0.8, 1.6, 3.2, 6.4, 10.0, and 20.0 mg/mL. The acquisition time for each image was 1500 s. The resultant images were processed with background subtractions. As the results, the background subtracted GNP x-ray fluorescence images illustrated that the GNP k-shell x-ray fluorescence image can be potentially isolated from the background but the detectability was still limited.
SERUM EXOSOME MIR-1246 AND MIR-196A ARE POTENTIAL BIOMARKERS FOR EARLY DETECTION OF PANCREATIC CANCER
Presented by: Yi-Fan Xu

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Background: Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer death in the United States. The high mortality rate of PDAC is primarily attributed to a late stage diagnosis when treatment options are often limited and to the aggressive nature of PDAC. Circulating biomarkers for early detection or screening of PDAC are urgently needed in order to better manage this devastating disease. Recent development in cancer biology indicates that cancer exosome microRNAs (miRNAs) are potential circulating biomarkers for various types of malignancy due to their cancer specific expression profiles. However, circulating exosome miRNAs have not been well evaluated for early detection of PDAC.

Methods: Exosomes were collected by ultracentrifugation from the conditioned media of PDAC cell lines and plasma samples of PDAC patients (Stage 1-IIA, n=15), and age/gender matched healthy subjects (n=15). The isolated exosomes were verified by nanoparticle tracking analysis and western blot. Cellular and exosome miRNAs from PDAC cell lines were profiled by next-generation small RNA sequencing. Serum exosome miRNA expression was analyzed by real-time RT-PCR.

Results: Exosomes were successfully isolated from cultured media and human plasma samples. Small RNA sequencing and qRT-PCR analysis showed that miR-1246 is the highest enriched miRNA in PDAC exosomes, and miR-196a is the most differently expressed miRNA between PDAC exosomes and normal ductal epithelial cell exosomes. Consistent with the cell line study, serum exosome miR-1246 and miR-196a levels were found to be significantly elevated in PDAC patients versus healthy subjects. When serum exosome miR-1246 and miR-196a levels were combined, the sensitivity and specificity in detecting PDAC are further enhanced as indicated by Receiver Operating Characteristic curve (ROC) analysis.

Conclusions: Our results indicate that certain miRNAs are selectively enriched in PDAC exosomes and serum exosome miR-1246 and miR-196a are potential biomarkers for early detection of PDAC.

Acknowledgement: This work was supported by Presbyterian Health Foundation.
XZ-488 AS A NOVEL THERAPY AGAINST GLIOMAS  
Presented by: Jadith Ziegler

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High-grade gliomas such as Glioblastoma Multiforme (GBM) remain a deadly diagnosis that affect more than 14,000 new patients a year with few effective treatment options. XZ-488 is a novel bicyclic furo[2,3-d] pyrimidine that possesses both RTK (receptor tyrosine kinase) and tubulin inhibitory properties and other antitumor activities. Here, we investigate if XZ-488 can be an effective therapy against human G55 glioma xenografts.

Nude mice were implanted with the human G55 xenograft cells (10⁵). Once tumors reached 10-15 mm³, mice were either treated every 3 days with XZ488 or TMZ both at 30 mg/kg. Mice were also treated with anti-VEGF or nonspecific mouse immunoglobulin (Ig)G at 2 mg/kg. Mice were treated until the tumors reached 100-150 mm³, or for a total of 4 weeks. Magnetic resonance imaging was used to determine tumor volumes and tumor vascular perfusion. Additionally, immunohistochemistry (IHC) was conducted to determine microvessel density (MVD) of the tumor tissues.

We report that XZ-488 therapy helped significantly reduce tumor volumes, prolong percent survival, decrease microvessel density, as well as increase tumor perfusion, compared to untreated or IgG-treated mice. XZ-488 is a potential novel therapy against high-grade gliomas either used alone or in conjunction with another cytotoxic/anti-angiogenic drug.