



CANCER RESEARCH SYMPOSIUM

FRIDAY, JAN. 29, 2016

Samis Family Education Center
Stephenson Cancer Center
Oklahoma City, Oklahoma



Stephenson
CANCER CENTER

The UNIVERSITY of OKLAHOMA

The Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Settlement Endowment Trust (TSET) for co-sponsoring the 2016 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 15 Highlights

With support from the Oklahoma TSET Cancer Research Program the Stephenson Cancer Center accomplished the following in FY 15:

- Increased cancer center membership by 23% (183 to 226 members) at ten academic institutions across Oklahoma
- Recruited seven new cancer researchers to Oklahoma
- Secured \$31.1 million in total grant funding related to cancer and tobacco prevention and control research
- Funded 13 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 32 research seminar speakers
- Hosted its 4rd 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 142 new cancer clinical trials
- Enrolled 565 patients to interventional clinical trials
- Enrolled 480 patients to cancer treatment trials
- Opened 24 new Phase I and Phase I/II clinical trials
- Enrolled 133 patients to Phase I clinical trials

Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Research Center (OTRC) for co-sponsoring the 2016 Stephenson Cancer Research Symposium.

About the Oklahoma Tobacco Research Center:

The mission of the Oklahoma Tobacco Research Center (OTRC) is to build a robust, inter-disciplinary center that will reduce the burden of tobacco-related cancers and other diseases in Oklahoma's most vulnerable populations. To achieve this mission, the OTRC engages local, state, tribal and national partners to address the following goals:

1. Build and sustain a research program that spans the entire translational research continuum and includes: 1) the development of novel interventions through engagement with community partners; 2) the elucidation of key mechanisms underlying tobacco dependence; and 3) the dissemination and implementation of research findings to high need communities in Oklahoma.
2. To efficiently and effectively deliver evidence-based tobacco treatment to smokers in Oklahoma.
3. To provide tobacco policy expertise to help inform decision makers in Oklahoma.
4. To develop and sustain a robust comprehensive tobacco research training program for undergraduate, graduate, and medical students and postdoctoral fellows.

In addition, the OTRC provides tobacco cessation services across the state through its Tobacco Dependence Treatment Program, and educates and trains health providers in state-of-the-art cessation services.

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

OTRC Director: Jennifer Vidrine, PhD
OTRC Associate-Directors: Steven Gillaspay, PhD
D. Robert McCaffree, MD, MSHA
Damon Vidrine, DrPH
Theodore Wagener, PhD



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Schedule & Agenda

Cancer Research Symposium Schedule at a Glance

7:30 - 8:30 a.m.	Registration, Continental Breakfast and Poster Set Up
8:20 - 8:30 a.m.	Welcome and Opening Remarks
8:30 - 8:40 a.m.	Break
8:40 - 9:40 a.m.	Concurrent Session I
9:40 - 10:40 a.m.	Concurrent Session II
10:40 - 10:50 a.m.	Break
10:50 - 11:50 a.m.	Stephenson Cancer Center Update
11:50 - 1:30 p.m.	Lunch and Poster Viewing
1:30 - 2:30 p.m.	Concurrent Session III
2:30 - 3:30 p.m.	Concurrent Session IV
3:30 - 3:45 p.m.	Break
3:45 - 4:45 p.m.	Concurrent Session V
4:45 - 5:00 p.m.	Break
5:00 - 5:15 p.m.	Awards and Closing Remarks
5:15 - 6:30 p.m.	Reception

Cancer Research Symposium Concurrent Session Agenda

Basic / Translational / Clinical Track (B / T / C)

Cancer Health Disparities and Control Track (CHD)

8:40-9:40 a.m. CONCURRENT SESSION I

B / T / C	CELL SIGNALING Moderator: Ralf Janknecht, PhD & Jie Wu, PhD	Level Two Auditorium
8:40-8:55	MICROVESICLES IN B CELL CHRONIC LYMPHOCYTIC LEUKAMIA- IMPLICATION IN DISEASE PROGRESSION Asish Ghosh, PhD Department of Pathology University of Oklahoma Health Sciences Center	
8:55-9:10	THE ROLE OF TMEFF2 IN PROSTATE CANCER HETEROGENEITY AND TUMOR BIOLOGY Maria Ruiz-Echevarria, PhD Department of Pathology University of Oklahoma Health Sciences Center	
9:10-9:25	DNA METHYLATION ANALYTICAL TOOLBOX FOR STUDIES OF VIRAL- INDUCED CANCERS Willard Freeman, PhD Department of Physiology University of Oklahoma Health Sciences Center	
9:25-9:40	MODELING RET FUSION IN LUNG ADENOCARCINOMA Jie Wu, PhD Department of Pathology University of Oklahoma Health Sciences Center	
CHD	CANCER HEALTH DISPARITIES KEYNOTE ADDRESS Moderator: Mark Doescher, MD, MSPH	Level B B3
8:40-9:40	ADVANCING TOBACCO CONTROL POLICY TO REDUCE CANCER HEALTH DISPARITIES: PROGRESS AND PROMISE Scott J. Leischow, PhD Professor Co-Director, Cancer Prevention and Control, Mayo Clinic Cancer Center Director, Research on Healthy Equity and Community Health, Office of	

Health Disparities Research

9:40-10:40 a.m. CONCURRENT SESSION II

B / T / C	CANCER NANOMEDICINE Moderator: Rajagopal Ramesh, PhD & Priyabrata Mukherjee, PhD	Level Two Auditorium
9:40-10:00	AN OPTICAL IMAGE-GUIDED PRODRUG STRATEGY USING A COMBINATION OF PHOTODYNAMIC THERAPY AND SITE –SPECIFIC CHEMOTHERAPY Youngjae You, PhD Department of Pharmacy University of Oklahoma Health Sciences Center	
10:00-10:20	MOLECULAR-TARGETED IMAGING TO ASSESS EITHER ANGIOGENESIS, EARLY DETECTION OF METASTASIS IN DIFFERENT PRE-CLINICAL CANCER MODELS Rheal Towner, PhD Advanced Magnetic Resonance Center Oklahoma Medical Research Foundation	
10:20-10:40	PHAGE-ENABLED CANCER DIAGNOSIS AND THERAPY Chuanbin Mao, PhD Department of Chemistry and Biochemistry University of Oklahoma	
CHD	CANCER HEALTH DISPARITIES GUEST SPEAKERS Moderation: Mark Doescher, MD, MSPH	Level B B3
9:40-10:10	THE ECONOMICS OF TOBACCO TAXATION IN OKLAHOMA Frank Chaloupka, PhD Director, Health Policy Center University of Illinois – Chicago	
10:10-10:40	CALIFORNIA HIGH TECH CIGARETTE TAX STAMP: PROCESS AND BENEFITS William P. Kimsey, CPA Business Taxes Administrator California State Board of Equalization	
10:50-11:50	STEPHENSON CANCER CENTER UPDATE Robert Mannel, MD Director, Stephenson Cancer Center	Level Two Auditorium

1:30-2:30 p.m. CONCURRENT SESSION III

B / T / C	PANCREATIC CANCER Moderator: Min Li, PhD	Level Two Auditorium
1:30-1:42	OVEREXPRESSION OF DCLK1 IN PANCREATIC CANCER ACTIVATES KRAS/PI3K/mTOR PATHWAY SIGNALING AND SUPPORTS TUMORIGENESIS, INVASIVENESS, AND STEMNESS Dongfeng Qu, PhD Department of Medicine University of Oklahoma Health Sciences Center	
1:42-1:54	ENHANCED PANCREATIC TUMOR PROGRESSION IS REGULATED BY NATURAL KILLER T (NKT) CELLS DEPENDENT ON mPGES-1 IN TUMOR-ASSOCIATED MACROPHAGES Naveena Janakiram, PhD Department of Hematology and Oncology University of Oklahoma Health Sciences Center	
1:54-2:06	REPRESSION OF p38 PATHWAY AND CACHEXIA UNDERLIES ZIP4 REGULATION OF POST-SURGICAL SURVIVAL OF PANCREATIC CANCER Jingxuan Yang, PhD Department of Internal Medicine University of Oklahoma Health Sciences Center	
2:06-2:18	PROTOCOL FOR A TRANSLATIONAL RTC: PREOPERATIVE EXERCISE AND NUTRITION TO IMPROVE PANCREATIC CANCER OUTCOMES BY TARGETING SARCOPENIA Elizabeth Hile, PhD, PT Department of Rehabilitation Sciences University of Oklahoma Health Sciences Center	
2:18-2:30	MACROPINOCYTOSIS AND PANCREATIC CANCER Xunhao Xiong, PhD Department of Pathology University of Oklahoma Health Sciences Center	
CHD	IMPROVING TRIBAL FOOD ENVIRONMENTS Moderator: Damon Vidrine, DrPH	Level B B3

1:30-2:15 POLICY AND ENVIRONMENTAL STRATEGIES TO IMPROVE TRIBAL FOOD ENVIRONMENTS: THE THRIVE STUDY
Valerie Blue Bird Jernigan, DrPH, MPH
College of Public Health
University of Oklahoma Health Sciences Center

2:15-2:30 QUESTION AND ANSWER PANEL
Bobby Saunkeah, Chickasaw Nation
Michael T. Peercy, Choctaw Nation

2:30-3:30 p.m. CONCURRENT SESSION IV

B / T / C **TRANSLATIONAL CANCER BIOLOGY - PART I** Level Two Auditorium
Moderator: Xin Zhang, MD, PhD

2:30-2:50 TARGETING INFLAMMATION BLOCKS TUMOR INITIATING STEM CELLS AND PANCREATIC CANCER PROGRESSION
Altaf Mohammed, PhD
Department of Medicine
Center for Cancer Prevention and Drug Development
University of Oklahoma Health Sciences Center

2:50-3:10 NEXT GENERATION IMAGE GUIDED DRUG DELIVERY USING ULTRASOUND IMAGEABLE LIPOSOMES AND HIGH INTENSITY FOCUSED ULTRASOUND FOR ENHANCED CHEMOTHERAPY PENETRATION IN SOLID TUMORS
Ashish Ranjan, PhD
Department of Physiological Sciences
Oklahoma State University

3:10-3:30 PANCREATIC CYSTIC NEOPLASMS: A SINGLE INSTITUTION EXPERIENCE
Alessandra Landmann, MD
Department of Surgery
University of Oklahoma Health Sciences Center

CHD **USING mHEALTH TO REACH UNDERSERVED POPULATIONS** Level B B3
Moderator: Damon Vidrine, DrPH

2:30-3:30 USING mHEALTH TO ADDRESS CANCER RELATED HEALTH DISPARITIES
Michael Businelle, PhD & Darla Kendzor, PhD
Department of Family and Preventative Medicine
University of Oklahoma Health Sciences Center

3:45-4:45 p.m. CONCURRENT SESSION V

B / T / C	TRANSLATIONAL CANCER BIOLOGY – Part II Moderator: Zhizhuang (Joe) Zhao, PhD	Level Two Auditorium
3:45-4:05	TRANSCRIPTIONAL REARRANGEMENT OF RETINAL DEGENERATION PROTEIN 3 (RD3) ORCHESTRATES MYCN INDEPENDENT NEUROBLASTOMA EVOLUTION Natarajan Aravindan, PhD Department of Radiation Oncology University of Oklahoma Health Sciences Center	
4:05-4:25	UNCOVERING THE ROLE OF XRN2 IN GENOMIC INSTABILITY AND THE DNA DAMAGE RESPONSE Julio Morales, PhD Department of Neurosurgery University of Oklahoma Health Sciences Center	
4:25-4:45	INHIBITION OF BMI1 INDUCED AUTOPHAGY MEDIATED NECROPTOSIS Anindya Dey, PhD Department of Obstetrics and Gynecology University of Oklahoma Health Sciences Center	
CHD	SELECTED RESEARCH PRESENTATIONS Moderator: Damon Vidrine, DrPH	Level B B3
3:45-4:05	THE ASSOCIATION OF WNT/BETA-CATENIN SIGNALING ACTIVATION AND MODIFIABLE RISK FACTORS IN OROPHARYNGEAL CANCER Lacy Brame Departments of Otorhinolaryngology and Biostatistics and Epidemiology University of Oklahoma Health Sciences Center	
4:05-4:25	TRENDS IN LUNG AND BRONCHOUS, PROSTATE, FEMALE BREAST, AND COLON AND RECTUM CANCERS INCIDENCE AND MORTALITY IN OKLAHOMA AND THE UNITED STATES FROM 1999-2012 C. Larry Hill, Jr. Department of Biostatistics and Epidemiology University of Oklahoma Health Sciences Center	
4:25-4:45	NALOZONE ADMINISTRATION AMONG CANCER PATIENTS BY EMS IN OKLAHOMA, 2011 TO 2014 Johnnie L. Gilpen, Jr. MS, NREMT-I, GISP Oklahoma State Department of Health	

**Cancer Health Disparities
Keynote and Guest Speakers
Biographies**

Scott J. Leischow, PhD

Professor

Co-Director, Cancer Prevention and Control, Mayo Clinic Cancer Center

Director, Research on Health Equity and Community Health, Office of Health Disparities Research

Scott J. Leischow, Ph.D. joined the Mayo Clinic in 2012, where he leads Risk Reduction Research within the Mayo Clinic Cancer Center and Research on Health Equity and Community Engagement Program at the Mayo Clinic Arizona. He was formerly *Associate Director* at the University of Arizona Cancer Center, and before that served as *Senior Advisor for Tobacco Policy* in the US Department of Health and Human Services and *Chief* of the Tobacco Control Research Branch at the National Cancer Institute of NIH. Dr. Leischow completed his doctorate in Health Education from the University of Maryland, and a postdoctoral fellowship in Behavioral Pharmacology from Johns Hopkins University. Dr. Leischow has received several awards, including the NIH Director's Award. Most of Dr. Leischow's research and publications focus on pharmacologic and behavioral treatments for tobacco dependence, systems and network approaches to public health, and the analysis of social media regarding tobacco control. He also created the Arizona Smokers Helpline, and played a leadership role in establishing the national network of smoking cessation quitlines in the United States. Dr. Leischow is past President of the Society for Research on Nicotine and Tobacco (SRNT).

Frank Chaloupka, PhD

Director
Health Policy Center
University of Illinois-Chicago

Frank J. Chaloupka is a Distinguished Professor at the University of Illinois at Chicago, where he has been on the faculty since 1988. He is currently Director of the UIC Health Policy Center and holds appointments in the College of Liberal Arts and Sciences' Department of Economics and the School of Public Health's Division of Health Policy and Administration. He is a Fellow at the University of Illinois' Institute for Government and Public Affairs, and is a Research Associate in the National Bureau of Economic Research's Health Economics Program and Children's Program. Dr. Chaloupka is Director of the WHO Collaborating Centre on The Economics of Tobacco and Tobacco Control, Director of ImpacTeen: A Policy Research Partnership for Healthier Youth Behavior and Co-Director of the International Tobacco Evidence Network. An economist, Dr. Chaloupka earned his B.A. from John Carroll University in 1984 and his Ph.D. from the City University of New York Graduate School and University Center.

Numerous professional publications and presentations have resulted from Dr. Chaloupka's research on the effects of prices and substance control policies on cigarette smoking and other tobacco use, alcohol use and abuse, and illicit drug use, as well as on various outcomes related to substance use and abuse. Much of this research has focused on youth and young adults. This research has been funded by the National Cancer Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, the Centers for Disease Control and Prevention, The Robert Wood Johnson Foundation, the Rockefeller Foundation, the Bloomberg Philanthropies, the Bill and Melinda Gates Foundation, and others. Dr. Chaloupka contributed a section on the effects of cigarette taxes and prices on youth smoking for the 1994 Surgeon General's report, and a lengthy chapter on the economics of tobacco for the 2000 Surgeon General's report on which he was Consulting Scientific Editor. In addition, he co-authored the World Bank's policy report: *Curbing the Epidemic: Governments and the Economics of Tobacco Control* and co-edited the volume *Tobacco Control in Developing Countries* containing the background papers prepared for the report. He is currently updating this work as lead editor for the forthcoming NCI and WHO monograph on *The Economics of Tobacco and Tobacco Control*, was part of the editorial team for the 2012 Surgeon General's report on *Preventing Tobacco Use Among Youth and Young Adults*, and chaired the International Agency for Research on Cancer's working group that produced the 2011 IARC Handbook *Effectiveness of Tax and Price Policies for Tobacco Control*. Over the past few years, Dr. Chaloupka's research on the policy and economic determinants of health behaviors has expanded to include a focus on healthy eating, physical activity, and obesity. Some of this research is highlighted in the October 2007 supplement to the *American Journal of Preventive Medicine* for which Dr. Chaloupka was the lead editor.

Dr. Chaloupka is on the editorial boards of *American Journal of Preventive Medicine*, *JAMA Pediatrics*, and *Contemporary Economic Policy*, is the economics editor for *Tobacco Control*, an Assistant Editor for *Addiction*, and an Associate Editor for *Nicotine & Tobacco Research*. He is a consultant to numerous governmental agencies, private organizations, and businesses. In 1996 Dr. Chaloupka received the

University Scholar Award from the University of Illinois for his research on the economic analysis of substance use and abuse, in 2009 received UIC's first Researcher of the Year in the Social Sciences and Humanities award for his work on the economic, policy and environmental determinants of health behavior, in 2011 received the Society for Research on Nicotine and Tobacco's John Slade Award, and in 2015 received the American Cancer Society's Luther Terry Award for Exemplary Leadership in Tobacco Control for Outstanding Research Contribution.

William P. Kimsey, CPA

Business Taxes Administrator
California State Board of Equalization

Bill Kimsey has worked for the Board of Equalization for over 35 years in audit. Of those 36 years, he worked in management for 26 years in the Special Taxes and Fees Department. Mr. Kimsey was directly involved in the State's transition to the new alternative cigarette tax stamp that is encrypted with security features and has significantly decreased California's problems with counterfeit cigarette tax stamps. Currently, as a Branch Manager in the Appeals and Data Analysis Branch, Mr. Kimsey oversees all Appeals and Data Analysis functions for 28 taxes and fees programs, including excise taxes, fuel taxes, and environmental fees. These functions include processing various types of petitions, administrative protests, and refunds and analyzing external data for audit purposes. He also oversees the branch's responsibilities for the current California cigarette tax stamp and for the Master Settlement Agreement in preparing various reports for the California State Attorney General's Office.

**Concurrent Sessions:
Information
&
Abstracts**

Concurrent Session I – Basic / Translational / Clinical

8:40 a.m. – 9:40 a.m.

Level Two, Auditorium

CELL SIGNALING

Moderator: Ralf Janknecht, PhD & Jie Wu, PhD

- | | |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8:40 a.m. – 8:55 a.m. | MICROVESICLES IN B CELL CHRONIC LYMPHOCYTIC LEUKEMIA:
IMPLICATION IN DISEASE PROGRESSION
Asish Ghosh, PhD
Department of Pathology
University of Oklahoma Health Sciences center |
| 8:55 a.m. – 9:10 a.m. | THE ROLE OF TMEFF2 IN PROSTATE CANCER HETEROGENEITY
AND TUMOR BIOLOGY
Maria Ruiz-Echevarria, PhD
Department of Pathology
University of Oklahoma Health Sciences Center |
| 9:10 a.m. – 9:25 a.m. | DNA METHYLATION ANALYTICAL TOOLBOX FOR STUDIES OF
VIRAL-INDUCED CANCERS
Willard Freeman, PhD
Department of Physiology
University of Oklahoma Health Sciences Center |
| 9:25 a.m. – 9:40 a.m. | MODELING RET FUSION IN LUNG ADENOCARCINOMA
Jie Wu, PhD
Department of Pathology
University of Oklahoma Health Sciences Center |

MICROVESICLES IN B CELL CHRONIC LYMPHOCYTIC LEUKEMIA-IMPLICATION IN DISEASE PROGRESSION

PRESENTER: Asish Ghosh

Asish K. Ghosh, PhD

Department of Pathology, University of Oklahoma Health Sciences Center

Microvesicles (MVs) released by malignant cancer cells constitute an important part of the tumor microenvironment. They can transfer various messages to target cells and may be critical to disease progression. Here, we demonstrate that MVs circulating in plasma of B-cell chronic lymphocytic leukemia (CLL) patients exhibit a phenotypic shift from predominantly platelet derived in early stage to leukemic B-cell derived at advanced stage. Furthermore, the total MV level in CLL was significantly greater compared with healthy subjects. To understand the functional implication, we examined whether MVs can interact and modulate CLL bone marrow stromal cells (BMSCs) known to provide a “homing and nurturing” environment for CLL B cells. We found that CLL-MVs can activate the AKT/mammalian target of rapamycin/p70S6K/hypoxia inducible factor-1 α axis in CLL- BMSCs with production of vascular endothelial growth factor, a survival factor for CLL B cells. Moreover, MV-mediated AKT activation led to modulation of the β -catenin pathway and increased expression of cyclin D1 and c-myc in BMSCs. We found MVs delivered phospho-receptor tyrosine kinase Axl directly to the BMSCs in association with AKT activation. This study demonstrates the existence of separate MV phenotypes during leukemic disease progression and underscores the important role of MVs in activation of the tumor microenvironment.

THE ROLE OF TMEFF2 IN PROSTATE CANCER HETEROGENEITY AND TUMOR BIOLOGY

PRESENTER: Maria J. Ruiz-Echevarría

Joshua M. Corbin, Sandra Thibivilliers, Maria J. Ruiz-Echevarría

Department of Pathology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Prostate cancer (PCa) is the second leading cause of cancer death in American men. Although the majority of PCa cases remain indolent, 10% of the cases progress to lethality with metastases and the subsequent emergence of therapy-resistant disease. Identifying those cancers that require aggressive treatment and developing lasting therapies for advanced disease are therefore the most crucial needs in the clinical management of PCa. The failure of current prognostic indicators to accurately stratify disease risk reflects, in part, the genomic heterogeneity of this disease; patients with similar pathological outcomes (Gleason score, PSA level) may demonstrate disparate therapeutic responses/mortality rates. Importantly, this intertumor variability has proven valuable in identifying cancer-related driver genes in other cancers, which are either upregulated or downregulated, and therefore demonstrate a higher variation across tumors.

TMEFF2 has recently been identified as one of the most variably expressed genes in PCa, a finding that suggests that its expression may correlate with the variable clinical outcome of this disease. Our laboratory has identified TMEFF2 as a tumor suppressor in PCa that functions as a modulator of one-carbon metabolism, and of cell motility. Here we further explore the clinical relevance of TMEFF2 and its role in PCa. Using bioinformatics analysis of existing databases, we found that low TMEFF2 expression is associated with significantly shorter disease-free survival (median of 20 vs. 110 months; logrank test $P=6.5 \times 10^{-4}$). Also, loss of TMEFF2 expression appears more prevalent in metastatic disease as compared with primary tumors, raising the possibility that its downregulation may predispose and perhaps predict the development of metastatic disease. Importantly, studies in cell lines indicate that, related to its role in modulating one-carbon metabolism, low TMEFF2 levels sensitize the cell to methotrexate, an anti-folate chemotherapeutic drug. Relevant to its role in PCa, expression of TMEFF2 is regulated by the androgen-receptor (AR), a nuclear receptor essential in prostate homeostasis and PCa development and progression. TMEFF2 affects the transcriptional activity of the AR, indicating that TMEFF2 is not only a target but also a co-regulator of the AR. In support of this role, results obtained with a transgenic TMEFF2 mouse model developed in our lab indicate that TMEFF2 modulates prostate branching morphogenesis during regeneration, a developmental process controlled by AR/androgen signaling. Together these data support the clinical significance of TMEFF2 and its potential as a biomarker, and validate the need to further understand its role in PCa. These studies provide new potential avenues for PCa therapeutic intervention and risk stratification.

DNA METHYLATION ANALYTICAL TOOLBOX FOR STUDIES OF VIRAL-INDUCED CANCERS

PRESENTER: Willard Freeman

Willard M. Freeman, PhD
Donald W. Reynolds Chair in Aging Research
Associate Professor of Physiology
Adjunct Associate Professor of Geriatric Medicine
Member, Harold Hamm Diabetes Institute
Associate Member, Stephenson Cancer Center

The concept that cancer is a disease of epigenetic as well as genetic abnormalities has been well validated. Alterations in the epigenetic patterns of genomes including 5-methylcytosine in CG and non-CG dinucleotide contexts is a common hallmark of human cancer and may be a key regulator of oncogenes. Viral DNA CpG methylation, as well as host genetic, epigenetic, transcriptome and oncogene alterations are observed with HPV infections. While significant advances have been made in the next generation sequencing methods for analysis of DNA modifications, bringing these to practice requires another generation of method development. We have developed a three tiered approach for absolute, base- and strand-specific analysis of DNA methylation of small viral and large host genomes. This approach uses whole genome bisulfite sequencing (WGBS), Bisulfite Oligonucleotide Capture Sequencing (BOCS), and Bisulfite Amplicon Sequencing (BSAS) for analysis of gigabases, megabases, and kilobases of genomes respectively. Examples of each of these methods will be presented. These tools are available to the entire SCC research community.

MODELING RET FUSION IN LUNG ADENOCARCINOMA

PRESENTER: Jie Wu

Jie Wu, PhD

Department of Pathology, University of Oklahoma Health Sciences Center

Recurrent RET fusions have been found lung adenocarcinoma. Among them KIF5B-RET fusion is the most prevalent. To develop an animal model for evaluation of KIF5B-RET fusion in lung adenocarcinoma, we generated transgenic mice containing a doxycycline-inducible tetO-KIF5B-RET transgene. Induction of CCSP-rtTA/tetO-KIF5B-RET bitransgenic mice with doxycycline resulted in MRI- and CT-detectable lung adenocarcinoma in 4-5 months. KIF5B-RET-induced lung adenocarcinoma is characterized by desmoplastic reaction. Desmoplasia is associated with invasive lung adenocarcinoma and is found in human RET-fusion-positive lung adenocarcinoma, but it has not been observed in transgenic mouse models of EGFR^{L858R}-, Kras^{G12D}-, or PTPN11^{E76K}-induced lung adenocarcinoma. Using MRI, CT, and histological examinations, we evaluated oncogene dependency and the response to the multikinase RET inhibitor ponatinib in KIF5B-RET-induced lung tumors. Tumors regressed one month after Dox withdrawal or ponatinib treatment. Thus, we have established a transgenic mouse model of KIF5B-RET-induced lung adenocarcinoma. The KIF5B-RET-induced lung tumors are associated with desmoplasia, depend on KIF5B-RET for maintaining the malignant phenotype, and respond to ponatinib treatment.

Concurrent Session I – Cancer Health Disparities

8:40 a.m. – 9:40 a.m.

Level B, Room B3

KEYNOTE ADDRESS

ADVANCING TOBACCO CONTROL POLICY TO REDUCE CANCER HEALTH DISPARITIES: PROGRESS AND PROMISE

Scott J. Leischow, PhD

Professor

Co-Director, Cancer Prevention and Control, Mayo Clinic Cancer Center

Director, Research on Health Equity and Community Health, Office of Health Disparities Research

This presentation will discuss the relationship between tobacco related and cancer related health disparities in the United States. Considerable evidence shows that disparities exist regarding tobacco use in areas related to, ethnicity, socioeconomic status, mental health status and sexual orientation. For example, American Indians have the highest prevalence of tobacco use relative to other ethnic minorities, and American Indian lung cancer mortality is highest in those regions of the US where American Indian smoking rates are highest. Similar cancer health disparities also exist, evidenced by higher rates of lung cancer mortality among African American men than men of other racial/ethnic groups. This presentation will explore both tobacco and cancer related health disparities, and explore factors that impact them both. In addition, potential policy and practice interventions to reduce tobacco-related health disparities, and the effect these could have on cancer-related health disparities, will also be discussed.

Concurrent Session II – Basic / Translational / Clinical

9:40 a.m. – 10:40 a.m.

Level Two, Auditorium

CANCER NANOMEDICINE

Moderator: Rajagopal Ramesh, PhD & Priyabrata Mukherjee, PhD

9:40 a.m. – 10:00 a.m.

AN OPTICAL IMAGE-GUIDED PRODRUG STRATEGY USING A COMBINATION OF PHOTODYNAMIC THERAPY AND SITE – SPECIFIC CHEMOTHERAPY

Youngjae You, PhD

Department of Pharmacy

University of Oklahoma Health Sciences Center

10:00 a.m. – 10:20 a.m.

MOLECULAR-TARGETED IMAGING TO ASSESS EITHER ANGIOGENESIS, EARLY DETECTION OR METASTASIS IN DIFFERENT PRE-CLINICAL MODELS

Rheal Towner, PhD

Advanced Magnetic Resonance Center

Oklahoma Medical Research Foundation

10:20 a.m. – 10:40 a.m.

PHAGE-ENABLED CANCER DIAGNOSIS AND THERAPY

Chuanbin Mao, PhD

Department of Chemistry and Biochemistry

University of Oklahoma

AN OPTICAL IMAGE-GUIDED PRODRUG STRATEGY USING A COMBINATION OF PHOTODYNAMIC THERAPY AND SITE –SPECIFIC CHEMOTHERAPY

PRESENTER: Youngjae You

Youngjae You, PhD

Department of Pharmaceutical Sciences, University of Oklahoma Health Sciences Center

A non-invasive or minimally invasive tumor ablation regimen is an attractive tool with which to control local and regional tumors. This approach is complementary to primary treatment options without causing systemic side effects or severe physical burdens from the treatment itself. Clinically approved photodynamic therapy (PDT) is one such regimen. In PDT, photosensitizers are activated by visible and near IR light to destroy tumors. However, the therapeutic efficacy of PDT is limited due to the spatial and temporal restrictions of the effector of PDT, singlet oxygen. We recently developed a new prodrug strategy that can overcome these limits by using a unique combination of PDT and site-specific chemotherapy. The prodrug is composed of photosensitizer and anticancer drug via a singlet oxygen-cleavable linker. In particular, we designed the prodrugs using fluorescent photosensitizers. Thus, the prodrugs can be detected using optical imaging both *in vitro* and *in vivo*. Upon illumination, the prodrugs cause immediate PDT damage and simultaneously release anticancer drugs, which cause slow and sustained damage, only at the illuminated target area. The followings will be presented: the concept of our prodrug strategy, proof of its concept using *in vitro* and *in vivo* models, and the recent progress toward targeted multifunctional prodrugs.

MOLECULAR-TARGETED IMAGING TO ASSESS EITHER ANGIOGENESIS, EARLY DETECTION OR METASTASIS IN DIFFERENT PRE-CLINICAL CANCER MODELS

PRESENTER: Rheal Towner

Rheal A. Towner, PhD
Associate Member,
Director, Advanced Magnetic Resonance Center
Oklahoma Medical Research Foundation (OMRF)

Molecular-targeted magnetic resonance imaging (MRI) approaches will be discussed to assess angiogenesis, early tumor detection or metastasis in rodent models for various cancers including gliomas, bladder cancer and metastatic breast cancer. High-resolution pre-clinical MRI systems can provide spatial information at 50 μm resolution. Tumor-specific molecular imaging probes that consist of either gadolinium-based or iron oxide nanoparticle-based constructs are used to visualize the in vivo and in situ levels of molecular targets associated with tumor growth, angiogenesis or metastasis. In rodent and human xenograft glioma models, a probe for VEGFR2 (vascular endothelial growth factor receptor 2) was used to assess different glioma grades (rat C6 and RG2) as well as therapeutic response (e.g. OKN-007 (mouse GL261) and Epsin inhibitor (human U87 xenografts in SCID mice)). VEGFR2 is highly expressed in most malignant vascular tumors. VEGFR2 levels were found to be significantly higher in gliomas of rodents given the VEGFR2 probe compared to non-specific IgG controls (rat C6 and RG2, mouse GL261). Heterogeneous VEGFR2 levels were also found to be significantly different in glioma models that varied in tumor grades (C6 vs. RG2). Anti-cancer treatment was also found to alter VEGFR2 levels in gliomas. OKN-007, a small molecule nitron-based compound was found to significantly decrease VEGFR2 levels (mouse GL261), whereas a tumor endothelium-targeting chimeric peptide (UPI) (Epsin inhibitor) was found to significantly increase extracellular VEGFR2 levels (human U87 xenografts), compared to untreated tumors. A nine amino acid peptide bladder tumor-binding MRI probe for early detection of tumors in mice was developed and found to be significantly increased in a MB49-TR model, when compared to a scrambled peptide MRI probe of similar molecular weight (MW). In rodent models for breast cancer metastasis (rat DMBA D1, mouse 4T1), a CD44v6-specific MRI probe was found to be significantly higher in primary and secondary lymph nodules, compared to tumor-bearing animals administered a non-specific IgG MRI contrast agent of similar MW. CD44v6 is highly expressed in metastatic tumors. Molecular-targeted MRI can provide useful in vivo and in situ information on the heterogeneous distribution of tumor growth molecular markers associated with cell proliferation, angiogenesis or metastasis, and also assess effective molecular-targeted therapeutic response in different tumor models.

PHAGE-ENABLED CANCER DIAGNOSIS AND THERAPY

PRESENTER: Chuanbin Mao

Chuanbin Mao, PhD

Department of Chemistry & Biochemistry, University of Oklahoma

Phage is a human-safe non-toxic virus that specifically infects bacteria. It is a biological nanostructure made of a protein capsid encapsulating DNA that genetically encodes the protein capsid. In contrast to traditional non-biogenic nanostructures, its DNA can be genetically modified so that it can display foreign peptides or proteins on the protein capsid. A tumor-homing peptide can be identified by collecting phages always associated with tumor. The peptide can then be conjugated with photothermal gold nanorods to achieve targeted cancer therapy. Phage can also be engineered to display functional proteins and show physical properties. It can then form a complex with inorganic nanoparticles. Once the complex captures cancer biomarker molecules from the biological samples, the number of phage nanoparticles will be commensurate with the number of biomarker molecules. Thus quantifying phage nanoparticles will lead to the ultrasensitive detection of the biomarkers.

Concurrent Session II – Cancer Health Disparities

9:40 a.m. – 10:40 a.m.

Level B, Room B3

GUEST SPEAKERS

Moderator: Mark Doescher, MD, MSPH

9:40 a.m. – 10:10 a.m.

THE ECONOMICS OF TOBACCO TAXATION IN OKLAHOMA

Frank Chaloupka, PhD

Director, Health Policy Center

Distinguished Professor of Economics

University of Illinois at Chicago

10:10 a.m. – 10:40 a.m.

CALIFORNIA HIGH TECH CIGARETTE TAX STAMP: PROCESS AND
BENEFITS

William P. Kimsey, CPA

Business Taxes Administrator

California State Board of Equalization

THE ECONOMICS OF TOBACCO TAXATION IN OKLAHOMA

PRESENTER: Frank Chaloupka

Frank J. Chaloupka, PhD
Distinguished Professor of Economics
University of Illinois at Chicago

This presentation will provide an overview of the history of tobacco taxation in the United States, as well as the history of tobacco taxation in Oklahoma. The evidence on the impact of tobacco taxes and prices on tobacco use, including overall sales, prevalence of use, initiation and cessation, will be reviewed. The impact on tobacco tax revenues will also be discussed. Finally, evidence on the misleading and often false arguments made by opponents of increased tobacco taxes will be reviewed.

CALIFORNIA HIGH TECH CIGARETTE TAX STAMP: PROCESS AND BENEFITS

PRESENTER: Bill Kimsey

William P. Kimsey, CPA
Business Tax Administrator
Special Taxes and Fees Department
Appeals and Data Analysis Branch
California State Board of Equalization

The presentation will discuss the process and benefits of implementing the California's new high tech cigarette tax stamp. With the support and participation from the cigarette distributors and industry, new legislation was passed in the State of California that mandated a new high tech cigarette tax stamp be implemented. The discussion will include the bidding process along with the costs associated with the implementation of the new high tech cigarette tax stamp. Other topics included in the presentation will cover some of the enhancements made to the stamp after implementation. Along with the overall results and benefits of the new high tech cigarette tax stamps; such as, revenue retention, improved compliance from the industry, and improved compliance to the State's reporting requirements for the Master Settlement Agreement. The presentation will conclude with a discussion about the future of tax stamping and the lessons learned by the State of California.

Concurrent Session III – Basic / Translational / Clinical

1:30 p.m. – 2:30 p.m.

Level Two, Auditorium

PANCREATIC CANCER

Moderator: Min Li, PhD

- 1:30 p.m. – 1:42 p.m.** OVEREXPRESSION OF DCLK1 IN PANCREATIC CANCER ACTIVATES KRAS/PI3K/mTOR PATHWAY SIGNALING AND SUPPORTS TUMORIGENESIS, INVASIVENESS, AND STEMNESS
Dongfeng Qu, PhD
Department of Medicine
University of Oklahoma Health Sciences Center
- 1:42 p.m. – 1:54 p.m.** ENHANCED PANCREATIC TUMOR PROGRESSION IS REGULATED BY NATURAL KILLER T (NKT) CELLS DEPENDENT ON mPGES-1 IN TUMOR-ASSOCIATED MACROPHAGES
Naveena Janakiram, PhD
Department of Hematology and Oncology
University of Oklahoma Health Sciences Center
- 1:54 p.m. – 2:06 p.m.** REPRESSION OF p38 PATHWAY AND CACHEXIA UNDERLIES ZIP4 REGULATION OF POST-SURGICAL SURVIVAL OF PANCREATIC CANCER
Jingxuan Yang, PhD
Department of Internal Medicine
University of Oklahoma Health Sciences Center
- 2:06 p.m. – 2:18 p.m.** PROTOCOL FOR A TRANSLATIONAL RTC: PREOPERATIVE EXERCISE AND NUTRITION TO IMPROVE PANCREATIC CANCER OUTCOMES BY TARGETING SARCOPENIA
Elizabeth Hile, PhD, PT
Department of Rehabilitation Sciences
University of Oklahoma Health Sciences Center
- 2:18 p.m. – 2:30 p.m.** MACROPINOCYTOSIS AND PANCREATIC CANCER
Xunhao Xiong, PhD
Department of Pathology
University of Oklahoma Health Sciences Center

OVEREXPRESSION OF DCLK1 IN PANCREATIC CANCER ACTIVATES KRAS/PI3K/mTOR PATHWAY SIGNALING AND SUPPORTS TUMORIGENESIS, INVASIVENESS, AND STEMNESS

PRESENTER: Dongfeng Qu

Dongfeng Qu¹, Nathaniel Weygant¹, William L. Berry², James J. Tomasek², Randal May¹, Prthasarathy Chandrakesan¹, Sripathi Sureban¹, Courtney W. Houchen^{1*}

¹Department of Medicine, ²Department of Cell Biology, University of Oklahoma Health Sciences Center

Doublecortin-line kinase 1 (DCLK1), a marker of gastrointestinal and pancreatic tuft cells, is overexpressed and marks a population of tumor-initiating cells in pancreatic ductal adenocarcinoma (PDAC). It regulates key oncogenes, pluripotency factors, angiogenic factors, and epithelial mesenchymal transition (EMT) related transcription factors. It is suggested that “driver” mutations, such as *KRAS* mutation, in the tumor-initiating cells may be the root cause of PDAC. In this study we evaluated the role of DCLK1 in *KRAS*-mediated signaling in PDAC. Human pancreatic cancer cells (AsPC-1 and MiaPaCa-2) were infected with Lentivirus containing DCLK1 cDNA to overexpress DCLK1 or red fluorescent protein (RFP) cDNA as control. The proliferative and invasive potential of these cells were compared using a MTT assay for proliferation, wound healing assay for migration, soft agar assay for clonogenicity, and Matrigel coated transwell assay for invasion. Analysis of PDAC was performed using the TCGA PAAD dataset. Here we report that overexpressing DCLK1 protein resulted in activation of *KRAS* which was reversible by DCLK1-inhibitor XMD8-92. Compared to RFP control cells, AsPC-DCLK1 and MP2-DCLK1 cells exhibited a more than 20% increase in proliferation, 30% increase in colony formation, 20% increase in migration, and a 2-fold increase in invasion. Evidence from TCGA PAAD demonstrated that pancreatic tumors expressing high levels of DCLK1 had activated PI3K/AKT/mTOR-pathway signaling suggesting greater *KRAS* activity. These data taken together suggest that DCLK1 promotes *KRAS*-driven p13K/AKT/mTOR signaling in PDAC leading to increased migratory, invasive, anti-apoptotic effects, stem-like and tumorigenic properties.

**ENHANCED PANCREATIC TUMOR PROGRESSION IS REGULATED BY NATURAL KILLER T (NKT) CELLS
DEPENDENT ON mPGES-1 IN TUMOR-ASSOCIATED MACROPHAGES**

PRESENTER: Naveena Janakiram

Naveena B. Janakiram, Altaf Mohammed, Taylor Bryant, Rebekah Ritchie, Lydgia Jackson, Stan Lightfoot, Doris M. Benbrook, Mark L. Lang, and Chinthalapally V. Rao

Department of Hematology and Oncology, University of Oklahoma Health Sciences Center

Pancreatic cancer (PC) is highly lethal. It is difficult to diagnose early, and diagnosis is often made late in the disease course. Recent evidence indicates that inflammation and immune cells in the tumor microenvironment play major roles in PC development and progression. Dysfunction or loss of innate immune Natural Killer (NK) cells is linked to aggressive tumor growth and poor survival in patients with pancreatic cancer (PC). We first show that increased NK cells are associated with reduced PC and IL-6 pathway activity, suggesting an inhibitory role of NKs through regulation of inflammation. Role of unique T cell population, Natural Killer T (NKT) cells which have similar functions like NK cells in PC is not yet evaluated. In order to address the regulatory roles of NKT cells on tumor progression through tumor-associated macrophages (TAM) and their production of microsomal prostaglandin E synthase-1 (mPGES-1) in (Kras)-driven pancreatic tumor (KPT) progression, we used CD1d^{-/-} mice deficient in both iNKT and vNKT cells. Loss of NKT cells significantly increased pancreatic intra epithelial lesions (PanINs) and also increased mPGES-1 expression in M2 type macrophages and cancer stemness in pancreatic tumors. Pharmacological inhibition of mPGES-1 in M2 macrophages with specific inhibitor YS-121 in KPT-CD1d^{-/-} mice decreased PanINs and suppressed tumor growth in association with elevated levels of active NKs and CD8a cells. Hence, NKT cells regulate PC by modulating TAMs (M2) through mPGES-1 and absence of NKT cells leads to aggressive development of PC. Hence, the development of agents to enhance NKTs function or to inhibit mPGES-1 for clinical PC prevention or treatment is warranted.

REPRESSION OF p38 PATHWAY AND CACHEXIA UNDERLIES ZIP4 REGULATION OF POST-SURGICAL SURVIVAL OF PANCREATIC CANCER

PRESENTER: Jingxuan Yang

¹Jingxuan Yang, ¹Yuqing Zhang, ²Guohua. Zhang, ¹Yiping Li, and ¹Min Li

¹Department of Internal Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, ²Department of Integrative Biology & Pharmacology, University of Texas Medical School at Houston, Houston, TX

Cancer cachexia and muscle wasting are hallmarks of pancreatic cancer. Chemo- and radiotherapies provide little benefit in improving patient survival or quality of life, highlighting the importance of understanding the mechanism of cancer cachexia and developing new adjuvant therapies. Here we described a novel surgical xenograft mouse model and a new signaling pathway through which a cancer-promoting zinc transporter ZIP4 regulates pancreatic cancer cachexia and muscle wasting. Our results demonstrate that surgical removal of tumors combined with lowering ZIP4 levels in pancreatic cancer cells significantly improved survival and reduced body weight loss and muscle wasting. Mechanistically, we demonstrated that reduced ZIP4 levels in pancreatic cancer cells limits muscle wasting due to attenuated p38 MAPK activation and subsequent atrogen1/MAFbx upregulation, which was shown previously to mediate the muscle catabolism induced by other types of tumor cells. These data suggests that ZIP4 could mediate pancreatic cancer-induced muscle wasting through enhanced activation of the p38 MAPK/atrogen1/MAFbx pathway. In addition, the mouse model we developed provides a unique resource to test future adjuvant therapies in combination with surgery to develop more effective treatments for pancreatic cancer.

**PROTOCOL FOR A TRANSLATIONAL RTC:
PREOPERATIVE EXERCISE AND NUTRITION TO IMPROVE PANCREATIC CANCER OUTCOMES BY
TARGETING SARCOPENIA
PRESENTER: Elizabeth Hile**

Elizabeth Hile PhD PT¹, Min Li PhD², Russell Postier MD², Leah Hoffman PhD, RD/LD³, Kai Ding PhD⁴

OUHSC Departments of ¹Rehabilitation Sciences, ²Surgery, ³Nutritional Sciences ⁴Biostatistics and Epidemiology

Background/Aims: Pancreatic cancer (PanC) survival remains below 7%. Surgery is the only cure, yet 60% of patients have post-op complications as serious as death. Loss of weight (cachexia) and muscle (sarcopenia), seen in >80% at diagnosis, predict worse quality of life (QoL), surgical outcomes, chemotherapy response, and ultimately survival. Evidence suggests that pre-surgical exercise and nutrition (prehabilitation) improves post-op outcomes in colorectal and bladder cancers, but the limited evidence in PanC is preclinical. This translational double-blinded pilot RCT is designed to quantify the impact of moderate intensity muscle strengthening (SPRE) when added to a pancreatic cancer aerobic exercise and nutrition presurgical 'prehab' program aimed at improving PanC outcomes. This study aims to 1) quantify the impact of muscle strengthening on post-op outcomes (surgical complications, QoL, physical performance), 2) determine whether novel serum, tumor and muscle biomarkers of cachexia and sarcopenia explain any benefits of SPRE, 3) determine which pre-op biomarkers and/or physical performance tests predict post-op outcomes, allowing more evidence-based determination of surgical candidacy in the future. **Methods:** In this double-blinded pilot RCT, 130 adults with PanC categorized as clearly approved or 'borderline' for surgical resection will be randomized to receive 3 weeks of protein supplementation combined with one of two home-based exercise strategies distinguishable only by the presence or absence of SPRE. Randomization will be stratified by 'clear' vs 'borderline' surgical candidacy. Patients who are unsafe to exercise, or who already exercise regularly at moderate intensity will be excluded. All participants receive a single nutritional counseling session and provision of supplements, followed by 1-on-1 physical therapist-led instruction in a home exercise program (with or without SPRE based on randomization group), and follow-up phone calls for adherence and progression. Blinded data collection will occur at baseline, 1-2 days pre-op, and approximately 1- and 3-months post-op. Outcomes include QoL (Functional Assessment of Cancer Therapy scales), functional performance (Six Minute Walk Test, dynamometry), nutrition (clinical labs), body composition (by BMI, bioimpedance, CT, muscle biopsy), and surgical outcomes (length of stay, hospital readmissions, surgical complications). Additionally, novel biomarkers of sarcopenia from serum, (Hsp70/90) tumor (Zip4) and muscle (p38 MAPK-activated catabolic mediators) will be analyzed as potential mediators and/or predictors of clinical outcomes.

MACROPINOCYTOSIS AND PANCREATIC CANCER

PRESENTER: Xunhao Xiong

Xunhao Xiong, Sounik Saha, Resham Bhattacharya, Priyabrata Mukherjee

Department of Pathology, Stephenson Cancer Center, University of Oklahoma Health Science Center

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies with a notoriously dismal prognosis. Accumulating researches in tumor metabolism have led to the emergence of aberrant signaling pathways as critical factors modulating central metabolic networks that fuel pancreatic tumors. Therefore, targeting PDAC-specific metabolic pathways represents a novel strategy to explore for the development of innovative therapies. As a major process of endocytosis, macropinocytosis plays a crucial role in cellular physiology by facilitating uptake of nutrients and communication with the microenvironment. Recent evidences suggest that due to their high metabolic demand cancer cells utilize macropinocytosis as a preferred mode of nutrient uptake to support growth and survival. Hence, identifying new molecular machineries that regulate macropinocytosis in cancer cells is crucial to understand the biology of tumor progression and metastasis and provides innovative means to inhibit it. Here, I will discuss our research effort to understand micropinocytosis and its role in pancreatic cancer growth.

Concurrent Session III – Cancer Health Disparities

1:30 p.m. – 2:30 p.m.

Level B, Room B3

IMPROVING TRIBAL FOOD ENVIRONMENTS

Moderator: Damon Vidrine, DrPH

1:30 p.m. – 2:15 p.m.

POLICY AND ENVIRONMENTAL STRATEGIES TO IMPROVE TRIBAL
FOOD ENVIRONMENTS: THE THRIVE STUDY

Valerie Blue Bird Jernigan, DrPH, MPH

College of Public Health

University of Oklahoma Health Sciences Center

2:15 p.m. – 2:30 p.m.

QUESTION AND ANSWER PANEL

Bobby Saunkeah, Chickasaw Nation

Michael T. Percy, Choctaw Nation

**POLICY AND ENVIRONMENTAL STRATEGIES TO IMPROVE TRIBAL FOOD ENVIRONMENTS:
THE THRIVE STUDY**

PRESENTER: Valerie Blue Bird Jernigan

Valerie Blue Bird Jernigan, DrPH, MPH
College of Public Health, University of Oklahoma Health Sciences Center

Poor access to healthy food increases the risk for obesity, diabetes, hypertension, and cancer. These conditions are highly prevalent among American Indian (AI) adults in Oklahoma, whose burdens of obesity (42%), diabetes (15%), and hypertension (38%) exceed those of the general U.S. population. Although many tribes have implemented individual-level efforts to prevent and control obesity, few studies have assessed the environmental correlates of obesity in tribal communities, and none have developed interventions to improve the food environments of Oklahoma tribal nations. We provide an overview of current efforts underway nationally to address obesity through policy in tribal communities. We then present methods and selected results of the THRIVE study – Tribal Health and Resilience in Vulnerable Environments – a NHLBI funded randomized trial implementing healthy "makeovers" within tribal convenience stores in the Chickasaw and Choctaw Nations of Oklahoma.

Concurrent Session IV – Basic / Translational / Clinical

2:30 p.m. – 3:30 p.m. Level Two, Auditorium

TRANSLATIONAL CANCER BIOLOGY – PART I

Moderator: Xin Zhang, MD, PhD

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|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2:30 p.m. – 2:50 p.m. | TARGETING INFLAMMATION BLOCKS TUMOR INITIATING STEM CELLS AND PANCREATIC CANCER PROGRESSION
Altaf Mohammed, PhD
Department of Medicine
Center for Cancer Prevention and Drug Development
University of Oklahoma Health Sciences Center |
| 2:50 p.m. – 3:10 p.m. | NEXT GENERATION IMAGE GUIDED DRUG DELIVERY USING ULTRASOUND IMAGEABLE LIPOSOMES AND HIGH INTENSITY FOCUSED ULTRASOUND FOR ENHANCED CHEMOTHERAPY PENETRATION IN SOLID TUMORS
Ashish Ranjan, PhD
Department of Physiological Sciences
Oklahoma State University |
| 3:10 p.m. – 3:30 p.m. | PANCREATIC CYSTIC NEOPLASMS: A SINGLE INSTITUTION EXPERIENCE
Alessandra Landmann, MD
Department of Medicine, Department of Surgery
University of Oklahoma Health Sciences Center |

TARGETING INFLAMMATION BLOCKS TUMOR INITIATING STEM CELLS AND PANCREATIC CANCER PROGRESSION

PRESENTER: Altaf Mohammed

Altaf Mohammed¹, Naveena B. Janakiram¹, Venkateshwar Madka¹, Misty Brewer¹, Rebekah L. Ritchie¹, Stan Lightfoot¹, Gaurav Kumar¹, Michael Sadeghi¹, Jagan Mohan R. Patlolla¹, Zobeida Cruz-Monserrate², Courtney Houchen¹, Vernon E. Steele³ and Chinthalapally V. Rao¹

¹Center for Cancer Prevention and Drug Development, Department of Medicine, Hem-Onc Section & Digestive Diseases Section, PC Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. ²Department of Cancer Biology, University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA ³Division of Cancer Prevention, Chemoprevention Agent Development Research Group, National Cancer Institute, Bethesda, MD, USA

Pancreatic cancer (PC) is a deadly disease with the lowest survival of all cancers. Recent development of genetically engineered mouse models (GEMs) for PC that recapitulate human disease progression has enabled development of new strategies to delay or inhibit pancreatic cancer and testing of experimental interventions in preclinical trials. Pancreatic tumor-initiating or cancer stem cell (CSC) populations contribute to tumor growth, metastasis, and resistance to therapy. We first found that expression of the CSC marker DclK1 occurs at an early stage of PC in both early and late pancreatic intraepithelial neoplasia (PanINs) and increases as the disease progresses. Genome-wide next generation sequencing of pancreatic ductal adenocarcinoma (PDAC) from GEMs revealed significantly increased DclK1 along with inflammatory genes compared to normal pancreas. Genetic ablation of cyclo-oxygenase (COX)-2 decreased the DclK1 in GEMs. Induction of inflammation with cerulein induced pancreatitis in GEMs increased DclK1, and DclK1 was reduced by the novel anti-inflammatory dual COX/5-lipoxygenase (5-LOX) inhibitor licofelone. We investigated the long term pharmacologic inhibitory efficacy of licofelone on PDAC in vivo using a GEM model. GEM (n=86) and wild type mice (n=24) were fed a diet containing different doses of licofelone for 300 days and evaluated for formation of PanINs and for their progression to PDAC. Dietary licofelone at tested doses significantly inhibited the incidence of PDAC (60-90%; p<0.0001) with a profound suppression of carcinoma in situ (35-60%; p<0.001) in male and female GEMs. Licofelone caused a dose-dependent suppression of pancreatic tumor COX-2 and 5-LOX activities and modulated miRNAs for inflammation markers and CSCs, including DclK1, CD133, CD44, and Lgr5 (p<0.001) in correlation with the PDAC inhibition. Licofelone also inhibited inflammation-induced CSCs in vitro. These studies provide the first evidence that modulation of inflammation with a dual COX-LOX inhibitor effectively blocks CSCs and inhibits pancreatic tumorigenesis. In summary, our preclinical data indicate that licofelone has potential for chemoprevention of PC and should be evaluated in other PDAC models in anticipation of future clinical trials. {Supported by NCI-CN-53300}

NEXT GENERATION IMAGE GUIDED DRUG DELIVERY USING ULTRASOUND IMAGEABLE LIPOSOMES AND HIGH INTENSITY FOCUSED ULTRASOUND FOR ENHANCED CHEMOTHERAPY PENETRATION IN SOLID TUMORS

PRESENTER: Ashish Ranjan

Ashish Ranjan^{*}, Danny Maples, Joshua VanOsdol, Selvarani Ramasami, Kalyani Ektate

Laboratory of Nanomedicine and Targeted Therapy, Department of Physiological Sciences, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater

Cancer chemotherapy typically employs systemic delivery of antitumor drugs having limited specificity, causing toxic side effects in normal tissues, and also inefficient and insufficient drug delivery to tumors. To overcome these barriers, we have developed a ultrasound imageable heat-activated liposome (E-LTSL)-based drug delivery system that provides 2 major advantages: 1) an echogenic tracking agent (Perfluoropentane, PFP) to permit in vivo tracking of liposome distribution and improve/fine-tune real-time control of drug delivery, and 2) locally-inducible drug release, using heat-activated liposomes (low temperature-sensitive liposomes; LTSL) that are sensitive to mild, non-destructive temperature elevations above normal body temperature, achieved by precise external warming of the tumor-containing region using ultrasound (US)-guided High-Intensity Focused Ultrasound (HIFU).

Data suggest that E-LTSLs can be efficiently co-loaded with PFP and doxorubicin. Phantom and transmission electron microscopy study clearly showed that E-LTSLs are echogenic. Temperature vs. size increase and drug release kinetics of E-LTSL demonstrated no difference with control (LTSL alone). Doxorubicin release in physiological buffer was <5% in 1 hr at baseline (25°C) and body temperatures (37°C), vs. >99% release with hyperthermia (~41°C). In vivo studies in mouse model of colon cancer showed that E-LTSL enhanced tumor imaging (~15-20 min.). Additionally, a combination of E-LTSL with hyperthermia delivered by US-guided HIFU resulted in significantly greater Dox delivery (~2-4fold) to tumors and heated muscle compared to E-LTSL, free Dox, and non-thermosensitive echogenic liposomes (E-NTSL) in mouse model of colon cancer.

In conclusion, an US imageable heat sensitive liposome formulation co-loaded with doxorubicin and an US contrast agent was developed for clinical translation. Stability, imageability, and US monitoring of contrast agent and doxorubicin release suggest that US-guided HIFU and E-LTSL may assist physicians in enhancing real-time tumor drug delivery.

PANCREATIC CYSTIC NEOPLASMS: A SINGLE INSTITUTION EXPERIENCE

PRESENTER: Alessandra Landmann

A Landmann MD, T Garwe PhD, Z Shakir BS, MM Bonds MD; N Bhandari MPH, JL Calisto MD, RG Postier MD

Background

Cystic lesions of the pancreas, once an uncommon pathology, are increasing in frequency; many are diagnosed incidentally after abdominal imaging, with a cited prevalence in the literature of 2.5%-13.5%. These neoplasms present a diagnostic and management challenge to the general surgeon, as the treatment is constantly evolving. This study describes demographic and clinical characteristics of patients diagnosed with cystic neoplasms.

Methods

A retrospective chart review of 866 patients who underwent pancreatic resection at a single institution from January 2002-December 2013 was conducted. Patients were included in the study if they had pathology confirmed cystic neoplasms. Means and proportions were used to summarize the data. Univariate analysis comparing the different cystic neoplasm pathologies was performed using analysis of variance (ANOVA) for continuous variables and chi-square/Fisher's Exact tests for categorical variables.

Results

The prevalence of CNPs in our patient cohort was 14.6% (127/866). Of the 127 patients included in our study, intraductal papillary mucinous neoplasm (IPMN) was present in 71 patients (56%, national average 27-48%), 25 patients had mucinous cystic neoplasm (MCN) (20%, national average 11-23%), and 31 patients had serous cystic adenoma (SCA) (24%, national average 12-23%). These lesions were identified based on CT imaging in the majority of patients (50%, 43%, 69% respectively). Ductal dilation and chronic pancreatitis were more common in IPMN than other neoplasms ($p < 0.05$). There was a male and older patient predominance for IPMN ($p < 0.05$). Of the IPMNs, 18% were malignant and 48% were borderline malignant. MCN demonstrated 11% malignancy, 37% borderline malignancy, while the majority of SCNS are benign (87%). The most common postoperative complications were intra abdominal abscess (11%) and delayed gastric emptying (3%). Non-infectious complications were more common in the IPMN cohort, and infectious complications were more common in the remainder.

Conclusion

Pancreatic cystic neoplasms represent an increasing cohort of patients presenting for pancreatic resection. While many lesions are diagnosed based on imaging characteristics, we demonstrate that a large cohort of patients harbor lesions with malignant potential.

Concurrent Session IV – Cancer Health Disparities

2:30 p.m. – 3:30 p.m.

Level B, Room B3

USING mHEALTH TO REACH UNDERSERVED POPULATIONS

Moderator: Damon Vidrine, DrPH

2:30 p.m. – 3:30 p.m.

USING mHEALTH TO ADDRESS CANCER RELATED HEALTH
DISPARITIES

Michael Businelle, PhD & Darla Kendzor, PhD
Department of Family and Preventative Medicine
University of Oklahoma Health Sciences Center

USING mHEALTH TO ADDRESS CANCER RELATED HEALTH DISPARITIES

PRESENTERS: Michael Businelle and Darla Kendzor

Michael S. Businelle, Ph.D.^{1,2} and Darla E. Kendzor, Ph.D.^{1,2}

¹Stephenson Cancer Center, Oklahoma Tobacco Research Center

²Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center

Studies have indicated that traditional assessment methodologies provide biased and inaccurate estimates due to recall bias and errors in memory. Recent technological advances now offer the potential to study “life as it is lived” through real-time assessment of psychosocial, physiological, and geolocation data. Ecological momentary assessment (EMA), in which handheld devices (e.g., smart phones) are used to capture moment-to-moment experience, is currently the most accurate way to measure phenomena in real-time in natural settings. EMAs can be used to assess variables of interest at multiple times throughout the day and can simultaneously capture geolocation data and mobility patterns that may influence behavior. Thus, momentary changes in key variables can be tracked and potentially used to initiate real-time interventions and re-engage patients in treatment. EMA, wearable sensors (e.g., heart rate monitors, accelerometers, glucose monitors), and geolocation data can improve our understanding of the mechanisms that drive health behavior and health behavior change in difficult to reach populations, and can pave the way toward more effective, cost-effective, and highly disseminable interventions.

The presenters will describe their research which has incorporated EMAs, wearable sensors, and geolocation technology for assessment and intervention in vulnerable populations. Michael Businelle will discuss his research which has used EMAs to identify predictors of imminent smoking relapse among individuals receiving smoking cessation treatment at a safety-net hospital. He will then describe features of a novel smartphone based tailored smoking cessation app that accesses risk for smoking relapse in real-time and automatically delivers treatment messages that are tailored to the situation and individual. Darla Kendzor will describe the short-term impact of a mobile phone intervention that targeted sedentary behavior in real-time within a diverse community sample. The session will conclude with a brief description of the developing interdisciplinary OTRC mHealth Core. The Core will offer resources to enable Oklahoma researchers to create innovative web and mobile based applications that identify and intervene upon environmental, cognitive, affective, physiological, and behavioral antecedents of modifiable risk factors linked to cancer and other diseases.

Concurrent Session V – Basic / Translational / Clinical

3:45 p.m. – 4:45 p.m. Level Two, Auditorium

TRANSLATIONAL CANCER BIOLOGY – PART II

Moderator: Zhizhuang (Joe) Zhao, PhD

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|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3:45 p.m. – 4:05 p.m. | TRANSCRIPTIONAL REARRANGEMENT OF RETINAL DEGENERATION PROTEIN 3 (RD3) ORCHESTRATES MYCN INDEPENDENT NEUROBLASTOMA EVOLUTION
Natarajan Aravindan, PhD
Department of Radiation Oncology
University of Oklahoma Health Sciences Center |
| 4:05 p.m. – 4:25 p.m. | UNCOVERING THE ROLE OF XRN2 IN GENOMIC INSTABILITY AND THE DNA DAMAGE RESPONSE
Julio Morales, PhD
Department of Neurosurgery
University of Oklahoma Health Sciences Center |
| 4:25 p.m. – 4:45 p.m. | INHIBITION OF BMI1 INDUCED AUTOPHAGY MEDIATED NECROPTOSIS
Anindya Dey, PhD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center |

**TRANSCRIPTIONAL REARRANGEMENT OF RETINAL DEGENERATION PROTEIN 3 (RD3) ORCHESTRATES
MYCN INDEPENDENT NEUROBLASTOMA EVOLUTION**

PRESENTER: Natarajan Aravindan

Natarajan Aravindan, PhD

Department of Radiation Oncology, University of Oklahoma Health Science Center

Clinical outcomes for high-risk neuroblastoma patients remains poor, with <10% overall survival (OS) and almost no long-term survival. MYCN is amplified in 20% of neuroblastomas, and has been shown to play multiple roles in malignancy and maintenance of stem-like state with poor prognosis. However, tumors without MYCN amplification also may have a poor outcome. This study recognized the loss of RD3 in MYCN-independent aggressive neuroblastoma, its influence in better clinical outcomes and defined its novel metastasis suppressor function. The results showed ubiquitous expression of RD3 in healthy tissues, complete-loss and significant TNM-stage association of RD3 in clinical samples. RD3-loss was intrinsically associated with reduced OS, abridged relapse-free survival, aggressive stage etc., in neuroblastoma 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*. 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 neuroblastoma, its novel tumor evolution stabilization function and further imply that RD3-loss independent of MYCN amplification status may directly relate to tumor aggressiveness and poor clinical outcomes.

Acknowledgements: Stephenson Cancer Center – Experimental Therapeutics Program, NIH COBRE 1P20GM103639-01.

UNCOVERING THE ROLE OF XRN2 IN GENOMIC INSTABILITY AND THE DNA DAMAGE RESPONSE

PRESENTER: Julio Morales

Julio C. Morales, PhD

Department of Neurosurgery, University of Oklahoma Health Sciences Center

The role of transcriptional by-products as a source of genomic instability and initiating the DNA damage response is becoming more apparent. Several studies have found that factors classically viewed in context of RNA metabolism are also intimately involved in the DNA damage response (DDR), with the best examples being factors involved in transcription termination. Transcription termination is a process that involves a number of different proteins. Several transcription termination factors have been shown to have direct roles in regulating double strand break (DSB) repair or the DDR response to transcriptional by-products. In this study we examine the role of the transcription termination factor XRN2 in the DDR. XRN2 is a 5'-3' ribo-exonuclease involved in several RNA degradation pathways. We find that XRN2 responds to multiple forms of DNA damage by undergoing nuclear transcription dependent relocalization and co-localizes with transcriptional by-products, in particular RNA:DNA hybrids (R-loops). The loss of XRN2 also leads to increased sensitivity to several forms of DNA damaging lesions, increased genomic instability, increased amounts of replication stress, and R-loop formation. Interestingly, loss of XRN2 leads to the initiating of the DDR signaling and an accumulation of factors involved in repairing DSBs at the 3' end of genes that undergo poly-A mediated transcription termination. Loss of XRN2 also leads to delayed DNA damage repair kinetics in response to ionizing radiation. Importantly, we find that the difference in DNA repair kinetics in cells that have lost XRN2 is due to active transcription and formation of R-loops. This suggest that XRN2 is involved in regulating transcription after DNA damage and that this regulation is important for repairing DSBs in a timely manner.

INHIBITION OF BMI1 INDUCES AUTOPHAGY MEDIATED NECROPTOSIS

PRESENTER: Anindya Dey

Anindya Dey¹, Soumyajit Banerjee Mustafi¹, Sounik Saha², Shailendra Kumar Dhar Dwivedi¹, Priyabrata Mukherjee² and Resham Bhattacharya^{1,3*}

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The clonal self-renewal property conferred by BMI1 is instrumental in maintenance of not only normal stem-cells but also cancer initiating cells from several different malignancies that represent a major challenge to chemotherapy. Realizing the immense pathologic significance, PTC-209, a small molecule inhibitor of BMI1 transcription has recently been described. While targeting BMI1 in various systems significantly decreases clonal growth, the mechanisms differ, are context dependent and somewhat unclear. We report here that, genetic or pharmacologic inhibition of BMI1 significantly impacts clonal growth without altering CDKN2A/INK4/ARF or CCNG2 and induces autophagy in ovarian cancer (OvCa) cells through ATP depletion. While autophagy can promote survival or induce cell death, targeting BMI1 engages the PINK1/PARK2 dependent mitochondrial pathway and induces a novel mode of non-apoptotic, necroptosis mediated cell death. In OvCa, necroptosis is potentiated by activation of the RIPK1-RIPK3 complex that phosphorylates its downstream substrate, MLKL. Importantly, genetic or pharmacologic inhibitors of autophagy or RIPK3 rescue clonal growth in BMI1 depleted cells. Thus, we have established a novel molecular link between BMI1, clonal growth, autophagy and necroptosis. In chemo-resistant OvCa where apoptotic pathways are frequently impaired, necroptotic cell death modalities provide an important alternate strategy that leverage overexpression of BMI1.

Concurrent Session V – Cancer Health Disparities

3:45 p.m. – 4:45 p.m.

Level B, Room B3

SELECTED RESEARCH PRESENTATIONS

Moderator: Mark Doescher, MD, MSPH & Damon Vidrine, DrPH

- | | |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3:45 p.m. – 4:05 p.m. | <p>THE ASSOCIATION OF WNT/BETA-CATENIN SIGNALING ACTIVATION AND MODIFIABLE RISK FACTORS IN OROPHARYNGEAL CANCER</p> <p>Lacy Brame
Department of Otorhinolaryngology, Biostatistics & Epidemiology
University of Oklahoma Health Sciences Center</p> |
| 4:05 p.m. – 4:25 p.m. | <p>TRENDS IN LUNG AND BRONCHOUS, PROSTATE, FEMALE BREAST, AND COLON AND RECTUM CANCER INCIDENCE AND MORTALITY IN OKLAHOMA AND THE UNITED STATES FROM 1999-2012</p> <p>C. Larry Hill, Jr.
Department of Biostatistics & Epidemiology
University of Oklahoma Health Sciences Center</p> |
| 4:25 p.m. – 4:45 p.m. | <p>NALOZONE ADMINISTRATION AMONG CANCER PATIENTS BY EMS IN OKLAHOMA, 2011 TO 2014</p> <p>Johnnie L. Gilpen, Jr. MS, NREMT-I, GISP
Oklahoma State Department of Health</p> |

THE ASSOCIATION OF WNT/BETA-CATENIN SIGNALING ACTIVATION AND MODIFIABLE RISK FACTORS IN OROPHARYNGEAL CANCER

PRESENTER: Lacy Brame

Lacy Brame^{1,2}, Ilangovan Ramachandran¹, Ryan Raju¹, Eva Brabcova¹, Matt Naifeh¹, Casey Buttler¹, Basil Mathews¹, Janis Campbell², Daniel Zhao², Greg A. Krempf¹, Liu Z. Cheng³, and Lurdes Queimado^{1,4-7}

Departments of ¹Otorhinolaryngology, ²Biostatistics and Epidemiology, ³Pathology, ⁴Pediatrics, ⁵Cell Biology; ⁶The Oklahoma Tobacco Research Center; ⁷Stephenson Cancer Center, and The University of Oklahoma Health Sciences Center, Oklahoma.

Background: Modifiable risk factors such as tobacco consumption are known to be associated with head and neck cancers including oropharyngeal squamous cell carcinoma (OPSCC). Additionally, the activation of WNT/beta-catenin signaling is associated with the progression of many cancers including OPSCC. Previous studies have not evaluated the effect of modifiable risk factors such as tobacco on the activity of the WNT/beta-catenin pathway, which is of interest in our study.

Aims: To determine whether WIF-1, WNT1, beta-catenin, and tobacco usage are associated with oropharyngeal cancer. Additionally, to determine if covariates are significantly predictive of case status among cases and controls.

Methods: Paraffin-embedded tissue samples were obtained from 48 patients with OPSCC as well as 51 controls. Participants were identified from the annotated tumor registry at the University of Oklahoma Health Sciences Center. Patient characteristics and smoking status were obtained from electronic medical records. WIF-1, WNT1, and beta-catenin expression were evaluated by immunohistochemistry. SAS PROC NPAR1WAY was used to conduct univariate analyses. ROC curves and logistic regression were used to evaluate if covariates were predictive of OPSCC. Data were analyzed using SAS and JMP software. Approval for this study was obtained from the OUHSC Institutional Review Board.

Results: Cases that smoked were observed to have significantly higher WNT1 and beta-catenin expression in tumor cells compared to adjacent epithelial cells. Moreover, cases that smoked were observed to have significantly lower WIF-1 tumor expression compared to non-smokers. Additionally, controls who smoked were observed to have significantly lower WIF-1 expression in normal epithelium compared to non-smokers. Controls who smoked had significantly higher WNT1 and beta-catenin expression in normal epithelium compared to non-smokers. Using ROC analysis, we found that beta-catenin and WIF-1 were significantly predictive of case status among cases and controls (AUC = 0.93).

Conclusion: Our study demonstrated for the first time that smoking is associated with a significant activation of the Wnt/beta-catenin pathway in both cancer and non-cancer patients. We also found that both WIF-1 and beta-catenin were useful in predicting case status and may be useful as potential biomarkers that aide in the prediction of OPSCC. Our findings have major clinical implications as they suggest a novel mechanism by which smoking can increase the risk of cancer development and increase the progression of established tumors.

Grant support: This work was supported by the Oklahoma Center for the Advancement of Science and Technology and the American Academy of Otolaryngology – Head and Neck Surgery. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology. Lacy Brame was funded through a graduate research assistantship through the Biostatistics and Epidemiology Research Design and Analysis Center (BSE-RDAC).

TRENDS IN LUNG AND BRONCHUS, PROSTATE, FEMALE BREAST, AND COLON AND RECTUM CANCERS INCIDENCE AND MORTALITY IN OKLAHOMA AND THE UNITED STATES FROM 1999 TO 2012

PRESENTER: C. Larry Hill, Jr.

Quyen Duong, C. Larry Hill, Jr., Amanda E. Janitz, Janis E. Campbell

Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center

Introduction: Cancer is the second-leading cause of death in the United States (US) and Oklahoma ranks near the top with the highest rates of mortality from cancer. In 2012, cancer was responsible for 582,623 deaths in the US accounting for 22.9% of all mortality. Oklahoma had 8,040 deaths due to cancer accounting for 21.8% of all deaths in the state. The top four major sites of cancer were prostate, female breast, lung and bronchus, and colon and rectum.

Methods: State and national-level age-adjusted incidence and mortality rates data were obtained from the United States Cancer Statistics: 1999-2012 Incidence and Mortality Report. Joinpoint software was used to examine changes in the incidence and mortality for prostate, female breast, lung and bronchus, and colon and rectum cancers over time from 1999-2012 for both the US and Oklahoma.

Results: Prostate cancer, female breast cancer, lung and bronchus cancer, and colon and rectum cancer sites make up more than half of the cancer cases and deaths due to cancer in both the US and Oklahoma. In the 1999 to 2012 time period, the highest cancer incidence was observed in prostate cancer, followed by female breast cancer, lung and bronchus cancer, and colon and rectum cancer in the US but in Oklahoma, the highest cancer incidence was observed in lung and bronchus cancer, followed by female breast cancer, prostate cancer, and colon and rectum cancer. Incidence and mortality rates declined from 1999-2012 for the four cancer sites. The average annual, age-adjusted incidence rate was higher in the US than Oklahoma for prostate cancer, but higher in Oklahoma for female breast, lung and bronchus, and colon and rectum cancer sites.

Conclusions: Over the course of 14 years from 1999-2012, the age-adjusted incidence and mortality rates of prostate cancer, female breast cancer, lung and bronchus cancer, and colon and rectum cancer decreased over time nationally and in Oklahoma. Rates in Oklahoma were higher than the US, which indicates the state has to continue to monitor lung and bronchus cancer and promote smoking cessation and prevention. By using the Joinpoint software, we identified differences between the US and Oklahoma regarding trends in mortality and incidence of all four cancers. Understanding cancer incidence and mortality time trends is important for understanding the health of Oklahomans related to modifiable factors, making screening available, and verifying treatment of the cancers are available and used in a similar manner to the United States.

**NALOXONE ADMINISTRATION AMONG CANCER PATIENTS BY EMS
IN OKLAHOMA, 2011-2014**

PRESENTER: J.L. Gilpen MS NREMT-I GISP

J.L. Gilpen MS¹ NREMT-I GISP, M.Q. Lansdale MPH¹, Y. Wan PhD¹, K.E. Stewart PhD², A.S. Sheikhh MPH², R.E. Espinoza MPH²

¹Emergency Systems, Protective Health Services, & ²Oklahoma Central Cancer Registry, Chronic Disease Services, Oklahoma State Department of Health

BACKGROUND & OBJECTIVE: In 2013, Cancer is the second leading cause of deaths in the United States. Cancer-related pain is described as one of the most serious health-issues cancer patients’ face. Opioid prescriptions has increased considerably among cancer patients. With the increase in opioid use there has been a directly proportional increase in opioid-related deaths. To decrease opioid-related mortality, efforts are being made to increase opioid antagonist’s availability among emergency first responders and third-party individuals (e.g., family members). The Oklahoma State Department of Health’s (OSDH) Emergency Systems (ES) has developed a base-line description of suspected opioid-related toxicity and the subsequent administration of naloxone by EMS providers. In an effort to distinguish between individuals who were prescribed narcotics and those abusing opioids, ES teamed with the Oklahoma Central Cancer Registry (OCCR) to identify cancer patients who were given naloxone by EMS. Our objective was to identify cancer patients who received naloxone – naloxone administration events (NAE’s) during an emergency service call between 2011 and 2014. Study subjects were identified by matching individuals in OCCR with emergency service calls from OSDH’s Oklahoma EMS Information System (OKEMIS) database.

RESULTS: (See Table 1.) Among the 15,149 naloxone administration events, 690 cancer patients were associated with 820 (5.4%) NAE’s. Among these, 104 (15.1%) were individuals treated on more than one occasion. The mean age was 66 years; the proportions for gender were similar. Half of all NAE’s occurred with the 1st year after diagnosis, 20.3% between 1st and 3rd year post-diagnosis, 20.1% between 4th and 5th year, and 9.6% after the 5th year. The largest group of patients by primary site of cancer was in the prostate but they only comprised 11.9% of the 690 individuals. Almost a quarter of the patients had adenocarcinoma followed by squamous cell carcinoma.

Table 1: Cancer Patients Descriptive Statistics

# of Repeated NAE’s	Age Distribution (%) (22-97 y/o)	Gender (%)	Time Since Diagnosis (%)	Cancer Histology (%)
586 – 1x	11.4 (55-59 y/o)	50.7 (M)	50.0 (≤ 1 yr)	24.3 (Adenocarcinoma)
88 – 2x	14.0 (60-64 y/o)	49.1 (F)	20.3 (1-3 yrs)	8.0 (Squamous cell)
9 – 3x	13.3 (65-69 y/o)		20.1 (4-5 yrs)	
1 – 7x	11.8 (70-79 y/o)		9.6 (6-10 yrs)	
	10.3 (≥ 90 y/o)			

CONCLUSION: Additional studies are needed to identify risk-factors associated with opioid toxicity in cancer patients. In the interim, the data presented here supports the need for the development of an education program for cancer patients, family members, and associated healthcare team regarding the risks associated with taking opioid-based pain medications.

Poster Presentation Abstracts

Cancer Research Symposium Poster Session

12:00 p.m. – 1:30 p.m.

Level 1

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TRANSCRIPTIONAL REARRANGEMENT OF RETINAL DEGENERATION PROTEIN 3 (RD3) ORCHESTRATES MYCN INDEPENDENT NEUROBLASTOMA EVOLUTION Aravindan, Natarajan	B/T/C Board 3
EFFECTS OF IGF-1 DEFICIENCY ON LIFESPAN AND PATHOLOGY IN MALE AND FEMALE MICE Ashpole, Nicole	B/T/C Board 4
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EXPRESSION OF LIVER- AND CANCER-TYPE-ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3 IN CANCERS AND NON-MALIGNANT TISSUES

PRESENTER: Khondoker Alam

Khondoker Alam¹, Wei Zheng², Kar-Ming Fung² and Wei Yue¹

¹Department of Pharmaceutical Sciences, ²Department of Pathology, University of Oklahoma Health Sciences Center

Purpose: Organic anion transporting polypeptide (OATP) 1B3 is localized to the basolateral membrane of hepatocytes in the liver under normal physiological conditions. Expression of OATP1B3 has also been reported in various cancer tissues. Over-expression of the liver type (Lt)-OATP1B3 in ovarian cancer cell lines results in increases cytotoxicity in cell after treatment with paclitaxel, which can be efficiently influxed into ovarian cancer cell lines via OATP1B3. Recently, a cancer type (Ct)-OATP1B3 variant was identified, which lacks 28 amino acids at the N-terminus of liver-type (Lt)-OATP1B3 and exhibits minimal transport activity. Although it is promising that expression of Lt-OATP1B3 could be a potential bio-marker for patient responsiveness to paclitaxel treatment, to date, the expression of Lt-OATP1B3 mRNA has only been specifically detected in lung cancer tissues. In the majority of the studies, methods used to detect mRNA levels of OATP1B3 did not distinguish Lt- from Ct-OATP1B3. Current studies were designed to determine the specific Lt- and Ct-OATP1B3 mRNA expression in cancer and non-malignant tissues from ovary, breast, prostate, and bladder.

Methods: 23-25 cancerous and normal tissues were each collected from the ovary, breast, prostate, and bladder. TaqMan real time RT-PCR was designed to distinguish the Lt- from Ct-OATP1B3 based on a previous publication. Lt-OATP1B3-over-expressing HEK293 cell line and colon cancer cell line DLD-1, which has been reported to express Ct-OATP1B3 but not Lt-OATP1B3, were used positive controls of Lt- and Ct-OATP1B3, respectively. A rabbit polyclonal OATP1B3 antibody is developed. The specificity of OATP1B3 antibody for immunoblot, immunofluorescence staining in OATP1B3-overexpressing cells and immunohistochemistry (IHC) in human liver tissues were determined. The expression of OATP1B3 in normal and cancer tissues were determined by IHC through the SCC Tissue Pathology Core.

Results: In cancer tissues, Lt-OATP1B3 and Ct-OATP1B3 mRNA were detected in 56% and 28% of prostate cancers, 12% and 12% of breast cancers, 8.7% and 47.8% of bladder cancers, and 29.2% and 67.7% of ovarian cancers, respectively. In non-malignant tissues, Lt-OATP1B3 and Ct-OATP1B3 mRNA were detected in 36% and 20% of prostate tissues, 4% and 0% in breast tissues, 8% and 20% in bladder tissues and 4% and 8% of ovarian tissues, respectively. Positive OATP1B3 IHC staining was observed in ovarian cancer tissues expressing Lt-OATP1B3.

Conclusion: Our results report, for the first time, that Lt-OATP1B3 can be detected in all four cancer types from ovary, breast, prostate, and bladder tissue origins. The Lt-OATP1B3 may play a role in the influx of anti-cancer drugs, such as paclitaxel, into cancer tissues. Different expression levels of Lt-OATP1B3 in cancers among patients may explain the different responsiveness of cancer patients to paclitaxel treatment. Studies are ongoing to determine the expression of Lt-OATP1B3 in other cancer tissues by IHC.

DEFINING THE UNIQUE ROLES OF Esco1 AND Esco2 ACETYLTRANSFERASES IN CHROMOSOME COHESION AND DNA REPAIR

PRESENTER: Reem Alomer

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Sister chromatid cohesion is a central process in maintaining genomic integrity through its roles in ensuring equal chromosome segregation and DNA repair. Cohesion is mediated by a protein complex called cohesin. Cohesin plays critical roles in DNA repair, chromatin structure organization, and gene expression regulation. Cohesin is thought to be differentially modified during these different functions. One modification is mediated by the Eco family of acetyltransferases. In yeast, Establishment of Cohesion (Eco1) acetylates subunits of cohesin during DNA replication or in G2 in response to DNA damage. This acetylation is indispensable for proper cohesin function. Interestingly, vertebrates express two homologs of Eco1, called Esco1 and Esco2. Both enzymes are required for proper mitotic cohesion and some studies suggest they are both important for DNA repair. Their specific contributions to cohesin function during the DNA damage response are not known. Our goal is to delineate the mechanisms that specify Esco1 and Esco2 unique functions, and to characterize the crosstalk between cohesin regulation and the DNA damage response.

In this study, we characterized the phenotypes conferred by depletion of Esco1 and Esco2, both separately and together. We assessed both mitotic cohesion and kinetics of DSB repair. In complementary experiments, we characterized the phenotypes of patient-derived cells that are genetically deficient in Esco2 function. Collectively, our data suggest that Esco1 and Esco2 make unique contributions to replication-dependent and damage-induced cohesion. Because DNA repair pathways are critical to both the development and drug sensitivity of tumors, the Esco enzymes provide uniquely attractive chemotherapeutic targets.

OBESITY, DIABETES, AND BIRTH OUTCOMES AMONG AMERICAN INDIANS AND ALASKA NATIVES

PRESENTER: Kermyt Anderson

Kermyt G. Anderson, Paul Spicer, Michael Peercy

Department of Anthropology, University of Oklahoma; Center for Applied Social Research

The link between cancer and obesity suggests that disparities on body mass index (BMI) may contribute to disparities in cancer, as well as other adverse health conditions. American Indians and Alaska Natives (AI/AN) have the highest rates of diabetes, and among the highest rates of obesity, among American ethnic groups. This study examines the relationship between prepregnancy diabetes mellitus (DM) and gestational diabetes mellitus (GDM), and overweight (BMI of 25.0 – 30.0) and obesity (BMI \geq 30.0), with several adverse birth outcomes: preterm delivery ($<$ 37 weeks), low birth weight ($<$ 2500 g), and macrosomia ($>$ 4500 g). All of these birth outcomes are associated with increased risk of obesity and its sequelae.

We use 44,570 AI/AN singleton first births drawn from the 2000-2013 U.S. natality (birth certificate) files. Adjusted odds ratios control for calendar year, maternal age, education and marital status, Kotelchuck prenatal care index, and child's sex. Controlling for maternal diabetes status, being underweight predicted preterm delivery among AI/AN (OR = 1.20, 95%CI = 1.03–1.38) but overweight and obesity did not. Low birth weight was predicted by underweight (OR = 1.62, 95%CI = 1.38 – 1.90), overweight (OR = 0.81, 95%CI = 0.73-0.90) and, if preterm births are excluded, obesity (OR = 0.80, 95%CI = 0.68 – 0.93). Macrosomia was predicted by underweight (OR = 0.45, 95%CI = 0.34 – 0.59), overweight (OR = 1.47, 95%CI = 1.35 – 1.61) and obesity (OR = 1.99, 95%CI = 1.83 – 2.16). Controlling for maternal BMI, preterm delivery was predicted by DM (OR = 1.65, 95%CI = 1.32 – 2.06) and GDM (OR = 1.17, 95%CI = 1.02 – 1.34), while low birth weight was not predicted by diabetes status. Macrosomia was also associated with DM (OR = 2.21, 95%CI = 1.75 – 2.79) and GDM (OR = 1.49, 95%CI = 1.30 – 1.71). This study, the first study to examine pregnancy outcomes as a function of both overweight/obesity and diabetes simultaneously among AI/AN, found that both maternal BMI and diabetes have independent effects on adverse birth outcomes in this population. This implies an intergenerational transfer of health disparities, with obese and diabetic AI/AN mothers more likely to have obese or diabetic offspring.

**TRANSCRIPTIONAL REARRANGEMENT OF RETINAL DEGENERATION PROTEIN 3 (RD3) ORCHESTRATES
MYCN INDEPENDENT NEUROBLASTOMA EVOLUTION**

PRESENTER: Natarajan Aravindan

Natarajan Aravindan, PhD

Department of Radiation Oncology, University of Oklahoma Health Science Center

Clinical outcomes for high-risk neuroblastoma patients remains poor, with <10% overall survival (OS) and almost no long-term survival. MYCN is amplified in 20% of neuroblastomas, and has been shown to play multiple roles in malignancy and maintenance of stem-like state with poor prognosis. However, tumors without MYCN amplification also may have a poor outcome. This study recognized the loss of RD3 in MYCN-independent aggressive neuroblastoma, its influence in better clinical outcomes and defined its novel metastasis suppressor function. The results showed ubiquitous expression of RD3 in healthy tissues, complete-loss and significant TNM-stage association of RD3 in clinical samples. RD3-loss was intrinsically associated with reduced OS, abridged relapse-free survival, aggressive stage etc., in neuroblastoma 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*. 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 neuroblastoma, its novel tumor evolution stabilization function and further imply that RD3-loss independent of MYCN amplification status may directly relate to tumor aggressiveness and poor clinical outcomes.

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EFFECTS OF IGF-1 DEFICIENCY ON LIFESPAN AND PATHOLOGY IN MALE AND FEMALE MICE

PRESENTER: Nicole Ashpole

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Studies have reported that early-life deficiency of IGF-1 affects lifespan in rodent models, likely due to decreased cancer risk. However, a deficiency in IGF-1 during early development impairs body growth and the development of specific organs, which may bias the results of the lifespan studies. Here, we describe the initial findings of a comprehensive study on the effects of IGF-1 deficiency, induced at several time-points, on lifespan and pathology in male and female C57BL/6 mice. IGF-1 production in the liver was reduced in *Igf^{fl/fl}* at post-natal day 15 (LID_{15d}), 5 months of age (LID_{5m}), or 15 months of age (LID_{15m}) using genetic or viral liver-specific Cre recombinase. In each group, IGF-1 knockdown reduced IGF-1 levels by at least 50% compared to controls. IGF-1 knockdown mice, both males and females, exhibited a significant decrease in body weight, fat mass, and lean mass compared to littermate controls. Cross-sectional pathology (at 27 months of age, the median lifespan of the shortest-lived group), lifespan, and post-mortem pathology were compared.

We found that lifespan is significantly increased in the LID_{15d} and LID_{5m} female mice. Analysis of the Cox Proportional Hazard Ratio in these mice indicates the hazard of death is 40% lower for the LID_{5m} females than controls, suggesting that the early-life loss of IGF-1 is beneficial for survival in females. There was an association between IGF-1 levels at 15 months of age with lifespan, as increasing one unit of IGF-1 decreased lifespan 0.5327. No effect of IGF-1 on male lifespan was observed. Post-mortem pathology indicated that pituitary adenomas were significantly reduced in the female LID_{15d}, LID_{5m}, and LID_{15m} mice, with no difference in the males. These data were consistent with our cross-sectional pathology, in which 26% of control females exhibited pituitary tumors compared to only 8% of the IGF-1 deficient females. Thus, 75% of observed pituitary tumors occurred in IGF-1 replete females ($p=0.028$).

Early-life decreases in IGF-1 also resulted in decreased levels of glomerular nephritis and adrenal subscapular hyperplasia in the females. In males, despite the minimal effect on lifespan, early-life decreases in IGF-1 resulted in decreased numbers of testicular cysts and reduced low-grade lymphoma. Despite the benefits of increased lifespan, the reduction in IGF-1 did increase the odds of hepatocarcinoma in both the male and female mice, likely due to increased growth hormone stimulation in the liver when IGF-1 levels are reduced. Thus, the effects of IGF-1 deficiency are diverse, with reduced risk for pituitary and kidney pathologies in females and not males. Together, our study suggests that the effects of IGF-1 deficiency are the result of interactions of circulating IGF-1 levels and pathologies specific for strain and sex.

USING MEDIATION ANALYSES TO IDENTIFY THE NEURAL BASIS OF POSITIVE ALLIESTHESIA IN NICOTINE ADDICTION

PRESENTER: Jason Avery

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*All research was conducted at The Laureate Institute for Brain Research, Tulsa, OK.

Smoking-cessation efforts depend upon a smoker's ability to overcome the influence of nicotine cues in their environment that prompt them to continue smoking. However, the strength of that influence varies greatly, depending upon the internal state of the body. For cigarette smokers, nicotine withdrawal results in aversive physiological and interoceptive changes that increase the motivational salience of cigarettes. This process, known as positive alliesthesia, is thought to result from homeostatic computations in the brain that modify the reward value of drug-related stimuli, motivating drug-seeking behavior. Given the centrality of this process to nicotine addiction, we sought to characterize the specific brain processes that underlie the shift in nicotine cue valuation as a function of shifting interoceptive experience. Cigarette smokers were asked to rate the pleasantness of cigarette pictures when they were nicotine-sated or nicotine-abstinent. On both sessions, smokers also underwent fMRI scanning while performing an interoceptive attention (IA) task. Before scanning, subjects' levels of exhaled carbon monoxide (eCO) were measured. Hemodynamic, physiological, and behavioral parameters were compared between sated and abstinent scans. The relationship between the changes in each of these parameters across sessions was also examined.

Smokers rated cigarette pictures as significantly more pleasant while nicotine-abstinent than while nicotine-sated. This increase in pleasantness ratings was significantly correlated with the decrease in exhaled carbon monoxide between scans. Comparing abstinent to sated scans, smokers also exhibited significantly decreased mid-insula activity while attending to interoceptive signals from the body. Using mediation analyses, we demonstrated that the change in interoceptive activity within the left mid-insula not only predicted the increase in smoker's pleasantness ratings, but also partially mediated the relationship between change in exhaled carbon monoxide and change in pleasantness ratings. These findings suggest that the processing of interoceptive withdrawal signals in the mid-insular cortex underlies the relationship between reduced cigarette consumption and increased reward value for cigarette cues. The identification of this relationship between nicotine reward and interoceptive activity in the insula may serve to identify specific neural targets for future smoking-cessation interventions.

DEVELOPMENT OF BIOPOLYMER NANOPARTICLE SYSTEM FOR TARGETED HuR-RNAi THERAPY OF LUNG CANCER

PRESENTER: Anish Babu

Anish Babu^{#§}, Narsireddy Amreddy^{#§}, Ranganayaki Muralidharan^{#§}, Akhil Srivastava^{#§}, Anupama Munshi^{†§}, Rajagopal Ramesh^{#§}

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RNA interference (RNAi) therapeutics has shown promise in mitigating the challenges of current treatment strategies of lung cancer. We have previously shown that siRNA based knockdown of an RNA-binding protein, 'HuR', results in downregulation of HuR-regulated oncogenic mRNAs and proteins resulting in antitumor activity against human cancer cells. To accomplish the goal of improving the therapeutic potential of HuR-RNAi therapy, our attempt was to design a nanoparticle system that can not only carry HuR-siRNA (siHuR) but also multiple therapeutics/small molecule inhibitor(s) as payload. As the first step towards this goal, the present study focuses on synthesis and evaluation of a biocompatible polymer nanoparticle (NP) system for HuR siRNA delivery in lung cancer cells.

Firstly, siHuR was complexed with protamine and encapsulated in polylacticacid-co-glycolic acid (PLGA) nanocapsule using a double emulsion-solvent evaporation technique. The surface of nanoparticle was then modified with chitosan (CS), a cationic biopolymer. The siHuR carrying nanoparticles were thoroughly characterized for physico-chemical properties. *In vitro* cell uptake and efficacy studies of siHuR loaded nanoparticles (siHuR-PLGA-CSNP) were carried out in lung cancer cell lines (A549, H1299) and compared with appropriate controls.

The siHuR-PLGA-CSNP had spherical structure and had an average hydrodynamic size of 250 nm with cationic surface charge (~30 mV). Gel retardation assay revealed that the NPs were able to protect the siRNA in the *in vitro* conditions. The NPs allowed slow and controlled release of siHuR in physiological pH and in fetal bovine serum containing media. The PLGA-CSNPs carrying fluorescently labelled control siRNA (siGLO) were internalized in lung cancer cells over time as observed by fluorescence microscopy and quantitated using Envision Multilabel[®] reader. The uptake of siHuR-PLGA-CSNP resulted in significant downregulation of HuR mRNA levels and its effect was reflected in HuR and HuR-regulated proteins such as Cyclin E and p27 expression levels in lung cancer cell lines. HuR knockdown using siHuR-PLGA-CSNP resulted in significant cell growth inhibition and G1 phase cell cycle arrest when compared to siC-PLGA-CSNP and untreated control cells. It is evident from our preliminary studies that PLGA-CSNP could be a promising gene delivery vector for RNAi therapy for lung cancer. Our current efforts are on modifying the PLGA-CSNP using RGD peptide to achieve targeted siHuR delivery in integrin ($\alpha_v\beta_3$) overexpressing lung cancer cells. Future directions include the addition of multiple therapeutic payloads and/or small molecule inhibitors and testing it in both *in vitro* and *in vivo* lung cancer models.

PREVALENCE AND MORTALITY OF MELANOMA IN OKLAHOMA AMONG RACIAL GROUPS, 2000-2008

PRESENTER: Jonathan Baldwin

Jonathan Baldwin, BSRT CNMT; Amanda E. Janitz, PhD; Julie Erb-Alvarez, MPH CPH; Cuyler Snider, MPH, Janis E. Campbell, PhD, GISP

This work was completed at the University of Oklahoma Health Sciences Center, College of Public Health, Department of Biostatistics and Epidemiology.

Introduction:

Disparities in melanoma incidence, stage, and mortality are evident in the literature among racial groups in the US.¹⁻¹¹ Few studies have focused on the disparities in the prevalence and mortality of melanoma among racial groups in a single state with large numbers of American Indian and Alaska Native (AI/AN) individuals, like Oklahoma. This study assessed the period prevalence (2000-2008) and mortality rates of melanoma, in Oklahoma, among different racial/ethnic strata.

Methods:

We included incident cases of melanoma from the Oklahoma Central Cancer Registry from 2000-2008. Melanoma disease duration was estimated by Kaplan-Meier survival analysis. We estimated prevalence using information on incidence and duration for race/ethnic groups. To determine differences in prevalence by race/ethnicity and mortality in Oklahoma compared to the US, we used a series of Chi-Square Tests.

Results:

White non-Hispanics in Oklahoma had the highest period prevalence ($p < 0.0001$) among the racial strata. AI/AN individuals have the second highest period prevalence of melanoma in Oklahoma ($p < 0.0001$). Furthermore, white non-Hispanics ($p < 0.0001$) and AI/AN individuals ($p = 0.0001$) in Oklahoma had higher mortality rates compared to those in the US.

Conclusions:

This study was the first study to estimate the prevalence of melanoma in a state with a high proportion of AI/AN individuals. We observed higher prevalence of melanoma among the AI/AN population than other non-white racial groups. Also, melanoma mortality rates in white non-Hispanic and AI/AN individuals in Oklahoma were higher than national mortality rates. Prevention and education programs should focus on the AI/AN and white non-Hispanic populations in Oklahoma to attempt to reduce the prevalence and mortality of melanoma.

**EFFECTS OF PULSE PARAMETERS ON REDUCTION OF CARCINOGENS IN METAL INERT GAS (MIG)
WELDING FUME**

PRESENTER: Marcio Bezerra

Marcio Bezerra, Jun Wang, James Regens

Department of Occupational and Environmental Health, College of Public Health, University of Oklahoma Health Sciences Center (OUHSC)

Metal inert gas (MIG) welding fume contains various inhalation carcinogens such as hexavalent chromium and nickel. Occupational exposure to welding fume can cause various adverse health effects. The high-temperature welding process creates high concentrations of ultrafine metallic aerosols composed of toxic metals. Pulse welding targets on reducing the heat input to the welding arc zone by high-frequency current fluctuation, in opposed to the steady voltage in non-pulse welding. Pulse welding was hypothesized to improve the weld quality, while decreasing the metal vaporization thus leading to less fume emission. The objective of this study is to investigate the pulse parameters (voltage, frequency, and percentage) on formation and characteristics of carcinogens in the particulate fume. A pulse metal inert gas welder was placed in a metal fume chamber. Welding with different combinations of pulse parameters as well as baseline (non-pulsed) welding were conducted through beading on 308L stainless steel plates. Particle size distribution was measured by a scanning mobility particle sizer and an aerodynamic particle sizer for fine and coarse particles, respectively. Respiratory deposition fractions for head airways (HA), tracheobronchial (TB), and alveolar (AL) regions were estimated based on a simplified International Commission on Radiological Protection (ICRP) model. Carcinogens such as hexavalent chromium (Cr^{6+}) were analyzed by an ion chromatograph. Morphology of the pulsed welding fume aerosols was imaged through transmission electron microscopy. The results indicated the dominant parameter of particle emission characteristics was pulse current. Pulse welding did not drastically change the geometric distribution of the particle sizes comparing to the non-pulse welding. However, pulse welding reduced the particle emissions in both fine and coarse regimes, without compromising the weld quality. Use low pulse voltage can produce the least particle number concentrations ($3.0\text{E}7 \text{ \#/cm}^3$ fine particles and $0.7\text{E}4 \text{ \#/cm}^3$) and in favor of more upper respiratory tract deposition. In addition, the reduction in heat input results in less metal oxidation and hexavalent chromium formation. Hence, we suggest the welder should operate at a low pulse voltage to minimize the potential particle exposures.

THE ASSOCIATION OF WNT/BETA-CATENIN SIGNALING ACTIVATION AND MODIFIABLE RISK FACTORS IN OROPHARYNGEAL CANCER

PRESENTER: Lacy Brame

Lacy Brame^{1,2}, Ilangovan Ramachandran¹, Ryan Raju¹, Eva Brabcova¹, Matt Naifeh¹, Casey Buttler¹, Basil Mathews¹, Janis Campbell², Daniel Zhao², Greg A. Krempf¹, Liu Z. Cheng³, and Lurdes Queimado^{1,4-7}

Departments of ¹Otorhinolaryngology, ²Biostatistics and Epidemiology, ³Pathology, ⁴Pediatrics, ⁵Cell Biology; ⁶The Oklahoma Tobacco Research Center; ⁷The Peggy and Charles Stephenson Cancer Center, and The University of Oklahoma Health Sciences Center, Oklahoma

Background: Modifiable risk factors such as tobacco consumption are known to be associated with head and neck cancers including oropharyngeal squamous cell carcinoma (OPSCC). Additionally, the activation of WNT/beta-catenin signaling is associated with the progression of many cancers including OPSCC. Previous studies have not evaluated the effect of modifiable risk factors such as tobacco on the activity of the WNT/beta-catenin pathway, which is of interest in our study.

Aims: To determine whether WIF-1, WNT1, beta-catenin, and tobacco usage are associated with oropharyngeal cancer. Additionally, to determine if covariates are significantly predictive of case status among cases and controls.

Methods: Paraffin-embedded tissue samples were obtained from 48 patients with OPSCC as well as 51 controls. Participants were identified from the annotated tumor registry at the University of Oklahoma Health Sciences Center. Patient characteristics and smoking status were obtained from electronic medical records. WIF-1, WNT1, and beta-catenin expression were evaluated by immunohistochemistry. SAS PROC NPAR1WAY was used to conduct univariate analyses. ROC curves and logistic regression were used to evaluate if covariates were predictive of OPSCC. Data were analyzed using SAS and JMP software. Approval for this study was obtained from the OUHSC Institutional Review Board.

Results: Cases that smoked were observed to have significantly higher WNT1 and beta-catenin expression in tumor cells compared to adjacent epithelial cells. Moreover, cases that smoked were observed to have significantly lower WIF-1 tumor expression compared to non-smokers. Additionally, controls who smoked were observed to have significantly lower WIF-1 expression in normal epithelium compared to non-smokers. Controls who smoked had significantly higher WNT1 and beta-catenin expression in normal epithelium compared to non-smokers. Using ROC analysis, we found that beta-catenin and WIF-1 were significantly predictive of case status among cases and controls (AUC = 0.93).

Conclusion: Our study demonstrated for the first time that smoking is associated with a significant activation of the Wnt/beta-catenin pathway in both cancer and non-cancer patients. We also found that both WIF-1 and beta-catenin were useful in predicting case status and may be useful as potential biomarkers that aide in the prediction of OPSCC. Our findings have major clinical implications as they suggest a novel mechanism by which smoking can increase the risk of cancer development and increase the progression of established tumors.

Grant support: This work was supported by the Oklahoma Center for the Advancement of Science and Technology and the American Academy of Otolaryngology – Head and Neck Surgery. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology. Lacy Brame was funded through a graduate research assistantship through the Biostatistics and Epidemiology Research Design and Analysis Center (BSE-RDAC).

GIANT CYSTADENOCARCINOMA: A REPORT OF A CASE AND REVIEW OF TREATMENT RECOMMENDATIONS

PRESENTER: Cressilee Butler

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Intro: Serous cystadenomas (SCA) are rare accounting for 1% of all pancreatic tumors and 15% of cystic tumors. Giant serous cystadenocarcinomas refer to intrapancreatic tumors measuring greater than 10 centimeters. Giant SCA's are more likely to be symptomatic presenting with abdominal pain, fullness, and jaundice.

Methods: We present the case of a 60-year-old female who presented with a large pancreatic head mass concerning for serous cystadenoma. Abdominal CT revealed 10.2 x 6.8 cm multi-cystic pancreatic head lesion with central calcifications and scarring causing significant mass effect upon the common bile duct. She complained of symptoms of nausea and abdominal pain and was offered resection. She underwent pylorus-preserving pancreaticoduodenectomy. Pathology revealed a 12 x 8 x 7.5 cm encapsulated cystic mass with diffuse calcifications within the head of the pancreas consistent with a SCA. Post-operative course was complicated by early delayed gastric emptying.

Results: Cystic neoplasms represent 10-15% of all pancreatic cysts. SCAs account for 15% of cystic neoplasms of the pancreas and are commonly seen in women over the age of 60. Often incidentally found on imaging, SCA's have a microcystic appearance with numerous small well-defined cystic loculations, central calcifications and larger cysts on the periphery of the mass. Emphasis must be placed on differentiating these lesions from the malignant cystic neoplasms of the pancreas. Lesions that are large, symptomatic, or harboring potential malignancy should undergo surgical resection. Giant SCAs exhibit greater than average annual growth and are more likely to be symptomatic due to size.

Conclusion: Giant serous cystadenomas are often incidentally found on imaging. While expectant management for smaller, asymptomatic SCA's is reasonable, surgical resection is indicated for giant SCA's due to their size, presence of symptoms and potential to be harboring malignancy.

FIVE YEAR CANCER SURVIVAL RATES IN OKLAHOMA FROM 1997 TO 2008

PRESENTER: Janis Campbell

Janis Campbell, PhD, Krupa Gandhi, MPH, Anne Pate, PhD, MPH, Amanda Janitz, PhD, Amber Anderson, BS, Robin Kinnard, DrPH, MHA, Kai Ding, PhD

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Introduction: This study evaluated the five-year observed survival rates of American Indians/Alaskan Native, African American, and white cancer patients among various demographic characteristics in Oklahoma focusing on lung and bronchus, colon and rectum, female breast, and prostate for the cancer patients diagnosed between 1997 and 2008.

Methods: The five year observed survival rates were calculated for overall cancer and specific cancer sites, using Kaplan-Meier method with data from the Oklahoma Central Cancer Registry.

Results: Overall, 51.5% patients diagnosed with cancer survived for five years. For specific sites we found: 79.2% for female breast cancer survived; 77.5% for prostate cancer; 12.9% for lung and bronchus cancer; and 49.9% for colorectal cancer.

Conclusions: The five year observed survival rates in Oklahoma were consistent with national trends. Overall, cancer survival seems to be improving over time, but there remains disparity with the AA and AI/AN populations in contrast to whites in Oklahoma.

IDENTIFICATION OF BREAST CANCER STEM CELL-BINDING PEPTIDES BY PHAGE DISPLAY TECHNIQUE

PRESENTER: Binrui Cao

Binrui Cao and Chuanbin Mao

Department of Chemistry and Biochemistry, University of Oklahoma,

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. However, to date, no drug has been developed that can target BCSCs specifically and kill them efficiently. Here we identified the BCSC-specific peptides by selecting a phage-displayed random peptide library (a 15-mer peptide library) against BCSCs derived from MCF-7 breast cancer cells. Our affinity selection results show that peptides GRVPSMFGGHFFSR and RWVFTAYAFSRMVA have high BCSC surface binding affinity and peptide GRGLSAWVRSVRYAY can internalize into BCSCs. Then phage capture ELISA and peptide-inhibition affinity assay were performed respectively and the results also confirmed the high BCSC-binding affinity of the identified peptides. At last, we applied these three peptides to functionalize the surface of up-conversion nanoparticle (UCNP), a type of nanoparticle that absorbs near infrared light and emits visible light, and found that the selected peptide labeled UCNPs can bind to BCSCs for cell imaging. Our results identify some new BCSC-binding domains and thus shed light into the development of anti-BCSC cancer therapies.

**SYNERGISTIC EFFECTS OF GLYCATE4D CHITOSAN WITH HIGH-INTENSITY FOCUSED ULTRASOUND
ON SUPPRESSION OF METASTASES IN SYNGENEIC BREAST TUMOR MODEL**

PRESENTER: Wei Chen

Feifan Zhou, Wei R. Chen

Biophotonics Research Laboratory, Center for Interdisciplinary Biomedical Education and Research,
University of Central Oklahoma

Stimulation of the host immune system is crucial in cancer treatment. In particular, nonspecific immunotherapies, when combined with other traditional therapies such as radiation and chemotherapy, may induce immunity against primary and metastatic tumors. In this study, we demonstrate that a novel, non-toxic immunoadjuvant, glycosylated chitosan (GC), decreases the motility and invasion of mammalian breast cancer cells in vitro and in vivo. Lung metastatic ratios were reduced in 4T1 tumor bearing mice when intratumoral GC injection was combined with local high-intensity focused ultrasound (HIFU) treatment. We postulate that this treatment modality stimulates the host immune system to combat cancer cells, as macrophage accumulation in tumor lesions was detected after GC-HIFU treatment. In addition, plasma collected from GC-HIFU-treated tumor-bearing mice exhibited tumor-specific cytotoxicity. We also investigated the effect of GC on epithelial–mesenchymal transition-related markers. Our results showed that GC decreased the expression of Twist-1 and Slug, proto-oncogenes commonly implicated in metastasis. Epithelial-cadherin, which is regulated by these genes, was also upregulated. Taken together, our current data suggest that GC alone can reduce cancer cell motility and invasion, whereas GC-HIFU treatment can induce immune responses to suppress tumor metastasis in vivo.

THE CHARACTERIZATION OF TMEFF2 AS A NOVEL MODULATOR OF ANDROGEN SIGNALING IN PROSTATE CANCER

PRESENTER: Joshua Corbin

Joshua Corbin^{1*}, Tom Green^{2*}, Maria Ruiz-Echevarria^{1,3*}

1) Department of Pathology OUHSC; 2) Department of Biochemistry ECU; 3) Peggy and Charles Stephenson Cancer Center

* Some of these studies were completed while apart of Department of Oncology at East Carolina University

The goal of this study is to delineate the role of TMEFF2, a novel modulator of androgen signaling, in prostate cancer (PCa). The AR is a steroid nuclear receptor that serves a central function in both normal prostate cell homeostasis and in PCa. In fact, the vast majority of PCa cells require androgens for growth. While androgen deprivation therapy is initially a successful form of PCa treatment, the majority of patients relapse with castration-resistant PCa (CRPC), which is currently incurable.

TMEFF2 is an androgen responsive single pass transmembrane glycoprotein. Although overexpressed in PCa, multiple studies have suggested a tumor suppressor role for TMEFF2. By analyzing TMEFF2 expression in patient samples from public databases, we found that while TMEFF2 is overexpressed in primary PCa, TMEFF2 expression is down-regulated in metastatic PCa, suggesting that TMEFF2 may have unique functions at different stages of PCa. Additionally, we found that low TMEFF2 expression is associated with decreased disease-free survival. Next, we set out to determine the functional role of TMEFF2 in PCa. Using shRNA to stably knockdown TMEFF2 expression in androgen dependent PCa and CRPC cell lines (representing different stages of disease progression), we demonstrate that decreasing TMEFF2 expression inhibits the basal and androgen-induced expression of multiple androgen responsive genes, including prostate-specific antigen (PSA), at the mRNA and protein level. Importantly, the knockdown of TMEFF2 does not alter AR protein levels, indicating that TMEFF2 influences AR activity. Because the AR is a central regulator of PCa growth and disease progression, determining the involvement of TMEFF2 in androgen signaling will provide vital information for the role of this potential biomarker in PCa.

DESCRIPTIVE STUDY OF PERCEIVED PERSISTENT DECLINES IN MEMORY IN OLDER BREAST CANCER SURVIVORS

PRESENTER: Melissa Craft

Craft, M., Carlson, B., Wenger, M., Friedman, J., Benbrook, D., Razaq, W., Carlson, J., Curran, K., Mooney, E., Byerly, R., Daji, S., Crudden, G.

Fran and Earl Ziegler College of Nursing, University of Oklahoma Health Sciences Center

Purpose: This study aims to identify factors associated with self-reported declines in memory in breast cancer survivors.

Research Question/Hypothesis: In survivors who report declines in memory, what factors reportedly contribute to or accompany declines in memory, or lessen its impact on daytime function? How does self-reported declines in memory relate to other cognitive abilities?

Background: Aging and chemotherapy impact cognitive function during treatment by altering cerebral blood flow, and evoking inflammatory-oxidative stress pathways that over time, alter neural processing. Many breast cancer survivors complain about declines in memory during treatment, and up to a fourth report persistent declines 1-year post treatment. Survivor's perception of factors that impact memory, including strategies they use to compensate for declines in memory, will provide new avenues for intervention.

Methods: Twenty breast cancer survivors, aged 50+ years, completed a 4-day journal and questionnaires describing the impact of their treatment on their cognitive abilities and strategies they used to compensate to their perceived deficits. Correlational analyses examined associations between self-reported measures of memory abilities and sleep quality (Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Functional Outcomes of Sleep Questionnaire), ADL (Functional Assessment of Cancer Therapy-Breast) and other aspects of everyday cognition (Everyday Cognition Questionnaire).

Findings: Perceived difficulties were associated with problems sleeping and often occurred in situations with high stress and/or demands for multi-tasking. Both qualitative data from the journals and questionnaire data shows strong association between memory and executive function. Compensatory strategies included making lists, avoiding multitasking, taking sleep medications and reducing stressful situations.

Conclusions: Breast cancer survivors report persistent declines in many cognitive abilities and use a number of compensatory strategies to maintain function. These compensatory strategies, on the long run, may be metabolically taxing and thus, explains why they feel that they have greater difficulties performing tasks that are considered stressful and require a high level of cognitive demand.

CENTRAL LINE ASSOCIATED BLOOD STREAM INFECTIONS IN PEDIATRIC HEMATOLOGY/ONCOLOGY INPATIENTS AND OUTPATIENTS

PRESENTER: Amy Cruickshank

Cruickshank, A¹, Meyer, WH¹ and Carroll, TG².

1 University of Oklahoma Health Sciences Center, Department of Pediatric Hematology/Oncology

2 University of Oklahoma Health Sciences Center, Department of Pediatric Critical Care

Purpose:

Central venous access devices (CVADs) are required for care in pediatric hematology/oncology (ph/o) but may become infected. Central line associated blood stream infections (CLABSI) are a major source of unreimbursed costs and a serious cause of harm to patients. Typical inpatient CLABSI rates in ph/o are 2-3/1000 line days, but combined in/outpatient rates are not known. In a retrospective review we measured the incidence of in/outpatient CLABSIs and describe the first CLABSI.

Methods:

After IRB approval, charts of patients treated in the ph/o center from 1/1/2011 to 12/31/2013 who were 6mos-21yrs with CVAD placed and seen at least twice were reviewed. Data collected included demographics, diagnosis, type of line placed, dates of placement and removal, and positive blood cultures. Each culture was evaluated using CDC CLABSI criteria and only those meeting criteria were considered. The total number of CLABSIs was divided by the total number of line days to determine the overall incidence rate of CLABSIs. The frequency of demographics, timing, CVAD type, and cancer category were also analyzed for the first CLABSI.

Results:

During the study period, of 1783 unique patients seen during this 3-yr period, 312 had CVADs placed. There were 477 new CVADs with complete data and 113,717 central line days during the study period. There were 140 CLABSIs, and the overall incidence was 1.23/1000 central line days. The mean length of time a CVAD was in place was 236 days (95% CI 214, 262). The mean time to first CLABSI was 117 days (95% CI 89, 146). Patients with acute myeloid leukemia (AML), stem cell transplants (SCT) and those patients who had a double lumen (DL) broviac, peripherally inserted central catheter (PICC) had the highest incidence of an initial CLABSI (2.6, 2.4, 3.5, and 3.2/1000 central line days $p < 0.0001$ using chi-square). 35 patients had more than one CLABSI.

Conclusions:

To our knowledge, this is the second analysis of CLABSI in a combined in/outpatient ph/o population. DL broviacs, PICCs, patients with AML and SCT had the highest incidence of CLABSIs. Using this data, targeted efforts can be studied to prevent CLABSI in these high-risk populations.

APLIN/APJ PATHWAY FOR TARGETING OVARIAN TUMOR MICROENVIRONMENT

PRESENTER: Bharat Kumar Devapatla

Bharat Kumar Devapatla¹, Pharavee Jaiprasart¹, Samrita Dogra¹, Jihee Ha², Sanam Hussain³, Sukyung Woo^{1,2}

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Introduction: Ovarian cancer generates unique tumor microenvironment (TME) that promotes and enhances tumor progression and metastasis. Current therapy option for modulating ovarian TME is antiangiogenic therapy but its clinical benefit is limited; thus, alternative drug targets are needed for therapeutic durability. Apelin and its cognate receptor Apj is known to have roles in glucose metabolism, cardiovascular functions, and angiogenesis. We found that apelin/Apj are highly overexpressed in human ovarian tumors, but their functional role is unclear. We also found a significant upregulation of apelin/ Apj in tumors that progressed after antiangiogenic therapy in preclinical ovarian cancer models. Our objective is to determine the functional roles and mechanisms of apelin/Apj pathway on promoting ovarian tumor angiogenesis and progression.

Methods: We examined autocrine and paracrine functions of apelin/ Apj signaling on cell proliferation, migration, and tube formation using human ovarian cancer cells (SKOV3^{ApIn} and SKOV3^{Apj}) and endothelial cells (HUVEC^{Apj}). Phosphoproteome array was performed to evaluate the apelin/ Apj downstream signaling. We characterized the effect of apelin or Apj overexpression on tumor development and response to VEGFR inhibitor *in vivo*. To confirm the clinical relevance of apelin/Apj in ovarian TME, we measured soluble apelin levels in patients' ascites and Apj expressions in human ovarian tumors using an immunohistochemistry.

Results: Apelin (10-100 ng/ml) induced mitogenic and chemoattractant effects on both cancer and endothelial cells. These effects were more prominent under hypoxic condition, reflecting the significance of apelin/Apj axis in TME. The apelin-mediated proliferative and migratory effects were inhibited by a pharmacological Apj inhibitor (ML-221) in a dose-dependent manner. High Apj expression resulted in enhanced pro-angiogenic activity in HUVEC. Overexpression of apelin/Apj also led to reduced response to antiangiogenic treatment in both HUVEC and cancer cells. Apelin signaling induces phosphorylation of AKT, STAT, CREB, PRAS 40, and AMPK α 2 in SKOV3 cells. Our xenograft study indicates Apj-overexpressing tumors showed reduced response to sorafenib treatment compared to those control tumors. We found that Apj is mainly expressed in tumors and some extent in stromal component of human ovarian tumors. The median soluble apelin levels in ascites were 187 pg/ml (6.3 – 4,000 pg/ml).

Conclusions: Our results suggest that apelin/Apj may play an important role in promoting angiogenesis and progression in ovarian cancer and serve as an attractive pathway targeting ovarian TME.

INHIBITION OF BMI1 INDUCES AUTOPHAGY MEDIATED NECROPTOSIS

PRESENTER: Anindya Dey

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The clonal self-renewal property conferred by BMI1 is instrumental in maintenance of not only normal stem-cells but also cancer initiating cells from several different malignancies that represent a major challenge to chemotherapy. Realizing the immense pathologic significance, PTC-209, a small molecule inhibitor of BMI1 transcription has recently been described. While targeting BMI1 in various systems significantly decreases clonal growth, the mechanisms differ, are context dependent and somewhat unclear. We report here that, genetic or pharmacologic inhibition of BMI1 significantly impacts clonal growth without altering CDKN2A/INK4/ARF or CCNG2 and induces autophagy in ovarian cancer (OvCa) cells through ATP depletion. While autophagy can promote survival or induce cell death, targeting BMI1 engages the PINK1/PARK2 dependent mitochondrial pathway and induces a novel mode of non-apoptotic, necroptosis mediated cell death. In OvCa, necroptosis is potentiated by activation of the RIPK1-RIPK3 complex that phosphorylates its downstream substrate, MLKL. Importantly, genetic or pharmacologic inhibitors of autophagy or RIPK3 rescue clonal growth in BMI1 depleted cells. Thus, we have established a novel molecular link between BMI1, clonal growth, autophagy and necroptosis. In chemo-resistant OvCa where apoptotic pathways are frequently impaired, necroptotic cell death modalities provide an important alternate strategy that leverage overexpression of BMI1.

TRENDS IN LUNG AND BRONCHUS, PROSTATE, FEMALE BREAST, AND COLON AND RECTUM CANCERS INCIDENCE AND MORTALITY IN OKLAHOMA AND THE UNITED STATES FROM 1999 TO 2012

PRESENTER: Quyen Duong

Quyen Duong, C. Larry Hill, Jr., Amanda E. Janitz, Janis E. Campbell

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Introduction: Cancer is the second-leading cause of death in the United States (US) and Oklahoma ranks near the top with the highest rates of mortality from cancer. In 2012, cancer was responsible for 582,623 deaths in the US accounting for 22.9% of all mortality. Oklahoma had 8,040 deaths due to cancer accounting for 21.8% of all deaths in the state. The top four major sites of cancer were prostate, female breast, lung and bronchus, and colon and rectum.

Methods: State and national-level age-adjusted incidence and mortality rates data were obtained from the United States Cancer Statistics: 1999-2012 Incidence and Mortality Report. Joinpoint software was used to examine changes in the incidence and mortality for prostate, female breast, lung and bronchus, and colon and rectum cancers over time from 1999-2012 for both the US and Oklahoma.

Results: Prostate cancer, female breast cancer, lung and bronchus cancer, and colon and rectum cancer sites make up more than half of the cancer cases and deaths due to cancer in both the US and Oklahoma. In the 1999 to 2012 time period, the highest cancer incidence was observed in prostate cancer, followed by female breast cancer, lung and bronchus cancer, and colon and rectum cancer in the US but in Oklahoma, the highest cancer incidence was observed in lung and bronchus cancer, followed by female breast cancer, prostate cancer, and colon and rectum cancer. Incidence and mortality rates declined from 1999-2012 for the four cancer sites. The average annual, age-adjusted incidence rate was higher in the US than Oklahoma for prostate cancer, but higher in Oklahoma for female breast, lung and bronchus, and colon and rectum cancer sites.

Conclusions: Over the course of 14 years from 1999-2012, the age-adjusted incidence and mortality rates of prostate cancer, female breast cancer, lung and bronchus cancer, and colon and rectum cancer decreased over time nationally and in Oklahoma. Rates in Oklahoma were higher than the US, which indicates the state has to continue to monitor lung and bronchus cancer and promote smoking cessation and prevention. By using the Joinpoint software, we identified differences between the US and Oklahoma regarding trends in mortality and incidence of all four cancers. Understanding cancer incidence and mortality time trends is important for understanding the health of Oklahomans related to modifiable factors, making screening available, and verifying treatment of the cancers are available and used in a similar manner to the United States.

microRNA THERAPY IN OVARIAN CANCER

PRESENTER: Shailendra Dwivedi

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Treatment of chemo-resistant ovarian cancer (OvCa) remains clinically challenging and there is a pressing need to identify novel therapeutic strategies. Recent reports have underscored the importance of microRNA (miR) regulatory networks in the pathogenesis of OvCa; regulating epithelial to mesenchymal transition (EMT) and chemo-resistance. In addition, accumulating evidence implicates BMI1 as a clinically relevant therapeutic target based on its role in drug resistance and stem cell biology. We previously demonstrated that miR-15a and miR-16 directly targeted BMI1 but their expression was decreased in high grade serous (HGS) OvCa patients and cells. Here we show that multiple pathways that regulate OvCa progression and chemo-resistance could be targeted by miR-15a and miR-16. While data from the Cancer Genome Atlas (TCGA) supported correlations between low miR-16 expression, high BMI1 expression and shortened overall survival (OS), in vitro targeting with these microRNAs results in a) decreased growth rate; b) decreased anchorage independent clonal growth through BMI1; c) enhanced sensitivity to cisplatin; d) decreased expression of drug efflux transporters e) inhibited EMT and f) decreased degradation of the extra-cellular matrix (ECM) by OvCa cells. Also the combination therapy with miR-15a and miR-16 caused a striking reduction in tumor burden compared to cisplatin alone in a pre-clinical chemo-resistant orthotopic mouse model of OvCa. Thus, with the advent of miR replacement therapy some of which are in Phase 2 clinical trials, miR-15a and miR-16 represent novel ammunition in the anti-OvCa arsenal.

NOVEL TARGETS FOR BREAST CANCER STEM CELL INHIBITION

PRESENTER: Evan Fields

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The cancer stem cell theory was developed in response to the observation that only certain cells within a tumor, the cancer stem cells (CSCs), were able to generate tumors when transplanted. CSCs are thought to be responsible for tumor relapse and metastasis and are often difficult to eradicate due to their ability to enter a dormant phase in which they are generally drug resistant. We began this study to try to identify novel gene targets for CSC treatment. Carcinogenesis is driven by mutations to tumor suppressors and oncogenes that decrease the cells fidelity, leading to widespread genetic and epigenetic changes in the cell. The concept of oncogene addiction stemmed from the observation that – despite the variability of perturbations present – many cancers rely on overactive or mutated oncogenes to survive and maintain tumorigenicity. Pathways affected by activated oncogenes may offer new targets to cancer therapy. Using a bioinformatics algorithm called GAMMA, we predicted genes that were cancer stem cell specific, and manually trimmed the list to 51 genes with little or no characterized function. To test our prediction, we did RNAi on a model system consisting of 4 immortalized human cell lines from breast epithelial tissue, two each with a high and low frequency of stem cell markers, one of each transfected with an activated hRAS oncogene. Our 4 cell lines, BPLER, BPLE, HMLER and HMLE correspond to cancer stem cell like, stem cell like, cancer like and normal cells respectively. Of the 51 genes tested we found 8 that had significantly more inhibition in BPLER than the other three cell lines.

Supported by a grant from the Oklahoma Center for Adult Stem Cell Research (OCASCR).

INTRUSION OF ELECTRICAL CIGARETTE AEROSOL IN NEIGHBORING SHOPS – AN OCCUPATIONAL FOCUS

PRESENTER: Evan Floyd

Evan L. Floyd, Micah Savin, Theodore Wagener, David Johnson

Occupational use of electronic cigarettes (EC) is concerning due to the potential negative effects on indoor air quality, chemical exposure of non-vapers, contamination of surfaces and intrusion of EC aerosol into neighboring venues. Vapor shops (VS) are one workplace where indoor EC use is not only inevitable but explicitly encouraged. Most VS encourage customers to socialize and participate in special events such as cloud blowing and vapor trick competitions. Additionally, most VS offer free e-juice sampling for customers and supply employees free e-juice while “on the clock”.

With such heavy vaping activity indoors, the present study sought to characterize airborne particulate levels in VS and determine if EC aerosol was intruding into neighboring shops by measuring particulate concentration using a Grimm field portable spectrometer. Fourteen randomly selected VS in the Oklahoma City area were sampled for 15-120 minutes. At these locations, 8 adjacent shops (AS) and 10 control shops (CS) across the street from the VS were also measured the same day.

Size distributions were similar in all locations with modes at 0.3 microns and nearly half particles >0.23 microns, suggesting a large presence of ultrafine particulate matter. Fine particle matter was 5-100 fold greater in both VS and AS than in CS. Nearly half of the VS sampled had total respirable particulate above the OSHA limit for particulates not otherwise regulated (5 mg/m^3) with a median of 4.72 mg/m^3 . Total particulate matter (TPM) was 20 fold greater in VS (7.37 mg/m^3) than control (0.36 mg/m^3 , $p=0.006$) but only 3 fold greater than AS (2.35 mg/m^3 , $p=0.088$), showing that adjacent shops have TPM levels greater than CS but not significantly so ($p=0.106$). Indeed, at one location, EC aerosol was observed intruding into the neighboring shop through the ventilation system and particle counts were actually higher at this NS than in the VS.

Just as indoor smoking rooms and lounges are expected to prevent intrusion of smoke to other establishments, VS should be held to the same standard. Full shift personal sampling should be conducted to determine the TPM, respirable particulate matter and formaldehyde exposures of VS employees.

RAT GENOME-WIDE CAPTURE OF GENE REGULATORY REGIONS AND BASE-RESOLUTION QUANTITATION OF DNA METHYLATION

PRESENTER: Willard Freeman

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Departments of ¹Physiology and ²Geriatric Medicine,
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We have been testing the hypothesis that retinal cellular and molecular changes during a period of poor glycemic control which persist long after establishment of good glycemic control contribute to the pathogenesis of diabetic complications such as diabetic retinopathy. This phenomenon, called metabolic memory, may be perpetuated by epigenetic mechanisms, both histone modifications and DNA methylation. Rat model systems are the preferred rodent model in a number of biomedical research areas including neuroscience, diabetes, and aging. Epigenetic analyses of these rat models have trailed that of mice, in part due to the lack of available species-specific research tools. To enable DNA methylation studies in rats we have developed a capture-probe approach that targets the promoter regions of RefSeq genes as well as CpG islands not present in repeat regions. As the accuracy of 5-mC analysis is dependent on sequencing depth, a capture oligonucleotide based approach allows for greater depth sequencing to be targeted to the regions of interest. Our approach targets 18,411 CpG islands, including their shores and shelves. Additionally 4kB upstream and 1 kB downstream of the transcription start site of 18,814 RefSeq genes is captured. The non-overlapping set comprises 22,146 regions and targets approximately 170 million bases of the rat genome. Validation testing of this capture probe set with rat whole genome methylation standards demonstrates accurate base-specific quantitation of CpG and CpH methylation in the targeted regions for both plus and minus genomic strands. Use of a targeted approach provides for genome-wide analysis while also greatly increasing accuracy of 5-mC quantitation, reducing sequencing costs, and increasing sample throughput compared to whole genome bisulfite sequencing methods. The construction and validation of this epigenetic tool for the rat genome will allow for discovery of differentially methylated regions in one of the most commonly used rodent models and will enable the identification and quantification of epigenetic modifications in specific retinal cell populations with diabetes.

A UNIQUE HIGH SENSITIVITY ASSAY TO PREDICT SUSCEPTIBILITY TO TOBACCO-INDUCED DISEASE

PRESENTER: Vengatesh Ganapathy

Vengatesh Ganapathy¹, Wilbur Mills¹, Elangovan Thavathiru¹, Ilangovan Ramachandran¹, Leslie Chandler², Antonio Reis¹, Lurdes Queimado¹⁻⁵

Departments of ¹Otorhinolaryngology, ³Cell Biology and ⁴Pediatrics; ²The Oklahoma Tobacco Research Center and ⁵Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Background: Tobacco smoking is the number one preventable cause of death worldwide. Tobacco smoke contains known carcinogens and high levels of reactive oxygen species which can cause DNA damage and lead to cancer initiation. Recently, we developed a novel technique named primer-anchored DNA damage detection assay (PADDA) that allows for the quantification (q-PADDA) and fingerprinting (f-PADDA) of DNA damage in the human genome. Moreover, we have reported that q-PADDA has higher sensitivity than other available assays and can detect DNA damage induced by a single puff of tobacco smoke.

Aims: (1) To quantify and map tobacco-induced DNA damage. (2) To correlate the location of identified damage with previously described *p53* cancer mutational hotspots.

Methods: DNA damage was quantified in the transcribed (TS) and non-transcribed (NTS) strands of the *p53* gene in oral mucosa scrapings obtained from smokers and non-smokers using q-PADDA. DNA lesions were mapped using f-PADDA. The location of observed DNA lesions was compared with the location of known *p53* mutations in head and neck cancer patients. Data were analyzed by t-test, Chi-square goodness of fit and exact nonparametric tests.

Results: In smokers, we observed a significant increase in DNA damage in both *p53* strands. The increase was higher in the NTS. This is consistent with the preferential repair of the TS and the higher prevalence of tobacco-induced *p53* mutations on the NTS than on the TS. Our preliminary data also show that in the oral mucosa of smokers 12 lesions/10,000 base pairs map to *p53* nucleotides previously reported mutated in head and neck cancer, in contrast to only 0.6 lesions/10,000 base pairs in the oral mucosa of non-smokers.

Conclusions: We have shown for the first time that tobacco-induced DNA damage accumulates preferentially on the NTS of the *p53* gene. Moreover, we were able to map DNA damage with high mutagenic potential before mutation fixation. These unique and important advantages of our approach suggest that PADDA has potential to establish biomarkers of susceptibility to tobacco-induced disease, which can guide preventive and diagnostic strategies.

Funding: This work was supported by the Oklahoma Tobacco Research Center and the Oklahoma Center for the Advancement of Science & Technology. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.

**NALOXONE ADMINISTRATION AMONG CANCER PATIENTS BY EMS
IN OKLAHOMA, 2011-2014**

PRESENTER: J.L. Gilpen

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BACKGROUND & OBJECTIVE: In 2013, Cancer is the second leading cause of deaths in the United States. Cancer-related pain is described as one of the most serious health-issues cancer patients’ face. Opioid prescriptions has increased considerably among cancer patients. With the increase in opioid use there has been a directly proportional increase in opioid-related deaths. To decrease opioid-related mortality, efforts are being made to increase opioid antagonist’s availability among emergency first responders and third-party individuals (e.g., family members). The Oklahoma State Department of Health’s (OSDH) Emergency Systems (ES) has developed a base-line description of suspected opioid-related toxicity and the subsequent administration of naloxone by EMS providers. In an effort to distinguish between individuals who were prescribed narcotics and those abusing opioids, ES teamed with the Oklahoma Central Cancer Registry (OCCR) to identify cancer patients who were given naloxone by EMS. Our objective was to identify cancer patients who received naloxone – naloxone administration events (NAE’s) during an emergency service call between 2011 and 2014. Study subjects were identified by matching individuals in OCCR with emergency service calls from OSDH’s Oklahoma EMS Information System (OKEMSIS) database.

RESULTS: (See Table 1.) Among the 15,149 naloxone administration events, 690 cancer patients were associated with 820 (5.4%) NAE’s. Among these, 104 (15.1%) were individuals treated on more than one occasion. The mean age was 66 years; the proportions for gender were similar. Half of all NAE’s occurred with the 1st year after diagnosis, 20.3% between 1st and 3rd year post-diagnosis, 20.1% between 4th and 5th year, and 9.6% after the 5th year. The largest group of patients by primary site of cancer was in the prostate but they only comprised 11.9% of the 690 individuals. Almost a quarter of the patients had adenocarcinoma followed by squamous cell carcinoma.

Table 1: Cancer Patients Descriptive Statistics

# of Repeated NAE’s	Age Distribution (%) (22-97 y/o)	Gender (%)	Time Since Diagnosis (%)	Cancer Histology (%)
586 – 1x	11.4 (55-59 y/o)	50.7 (M)	50.0 (≤ 1 yr)	24.3 (Adenocarcinoma)
88 – 2x	14.0 (60-64 y/o)	49.1 (F)	20.3 (1-3 yrs)	8.0 (Squamous cell)
9 – 3x	13.3 (65-69 y/o)		20.1 (4-5 yrs)	
1 – 7x	11.8 (70-79 y/o)		9.6 (6-10 yrs)	
	10.3 (≥ 90 y/o)			

CONCLUSION: Additional studies are needed to identify risk-factors associated with opioid toxicity in cancer patients. In the interim, the data presented here supports the need for the development of an education program for cancer patients, family members, and associated healthcare team regarding the risks associated with taking opioid-based pain medications.

METABOLIC REPROGRAMMING IN OVARIAN CANCER

PRESENTER: Ji Hee Ha

Ji Hee Ha, Rangasudhagar Radhakrishnan, Jeremy D. Ward, Muralidharan Jayaraman, and Danny N. Dhanasekaran

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Ovarian cancer is currently the most lethal gynecologic malignancy, with no new significant changes in treatment options for these patients in the last 30 years. Importantly, ovarian cancer patients have increased levels of lysophosphatidic acid (LPA), a bioactive phospholipid in ascites and serum that has been linked to driving oncogenesis and progression of ovarian cancer. Accumulating evidence has implicated Hypoxia-inducible factor-1 α (HIF-1 α) as a critical mediator of the glycolytic shift observed in cancer cells. However, the precise biological role of LPA in regulating HIF-1 α -mediated glycolytic shift is largely unknown. Therefore, we were interested in examining the potential role of LPA in promoting metabolic reprogramming in ovarian cancer via HIF-1 α signaling. In this study, we identified a novel mechanism by which LPA upregulates HIF-1 α expression via $G\alpha_{i2}$ (the *gip2* oncogene) in human ovarian cancer cells. This study demonstrates that LPA induces a glycolytic shift via LPA-mediated activation of $G\alpha_{i2}$, which causes a subsequent upregulation of HIF-1 α in ovarian cancer cells. Additionally, we show that LPA-signaling via $G\alpha_{i2}$ induces an increase in the expression of Hexokinase-2 (HK2) and Glucose transporter 1 (GLUT1), which are known targets of HIF-1 α . We also demonstrate that LPA induces an increase in extracellular acidification rate (ECAR) in a dose dependent manner in both ovarian cancer cell lines and in patient-derived cells taken from the ascites fluid of ovarian cancer patients using an XFe96 analyzer. Furthermore, we found that inhibition of Rac signaling caused a reduction in LPA-induced ECAR, identifying Rac as a critical downstream component of $G\alpha_{i2}$ -mediated increase of ECAR. Moreover, using NAC, an inhibitor of redox signaling, we found that this caused a decrease in LPA-induced ECAR in SKOV3-ip cells, indicating that inhibition of redox signaling abolishes LPA-induced ECAR in ovarian cancer cells. Similarly, the use of EUK-134, a scavenger of superoxide and H₂O₂, also decreased LPA-induced increase in ECAR. Altogether, these results indicate that LPA regulates glycolysis through redox signaling via a $G\alpha_{i2}$ -Rac-HIF1 α -dependent signaling pathway. Most importantly, the $G\alpha_{i2}$ -Rac-dependent pathway identified in this study more than likely serves as a potential driver of HIF-1 α -mediated metabolic changes in ovarian cancer cells and represents a potential target for therapy in these patients.

EXOSOME-ASSOCIATED microRNAs AS PLASMA BIOMARKERS FOR BREAST CANCER

PRESENTER: Bethany Hannafon

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Introduction: microRNAs are promising candidate biomarkers due to their cancer-specific expression profiles. However, efforts to develop circulating breast cancer biomarkers are challenged by the heterogeneity of microRNAs in the blood. To overcome this challenge, we aimed to develop a molecular profile of microRNAs specifically secreted from breast cancer cells. The key to identifying breast cancer-derived microRNAs relies on capturing and analyzing the contents of exosomes, which are small secretory vesicles that selectively encapsulate microRNAs indicative of their cell of origin.

Methods: Exosomes were collected from the conditioned media of breast cancer cell lines, breast ductal fluids, mouse plasma from patient-derived orthotopic xenograft models (PDX), and from human plasma samples. Exosomes were verified by electron microscopy, nanoparticle tracking, and western blot analysis. Cellular and exosome microRNAs from breast cancer cell lines were profiled by next-generation small RNA sequencing. Plasma exosome populations were selected by immunoaffinity isolation. Exosome microRNA expression was measured by qRT-PCR.

Results: Small RNA sequencing and qRT-PCR analysis showed that several microRNAs are selectively secreted in breast cancer exosomes. Importantly, human breast cancer specific microRNAs were detectable in PDX mouse plasma. The microRNA expression patterns in the plasma exosomes differed between breast cancer patients and control subjects.

Conclusions: Several microRNAs are selectively enriched in breast cancer exosomes, which can be detected in the plasma of PDX mice and breast cancer patients. These results provide a potential new strategy to selectively analyze plasma breast cancer microRNAs that may be indicative of the presence of breast cancer and a promising new strategy for breast cancer biomarker development.

CD82 REGULATES CELL MEMBRANE DOMAIN ORGANIZATION TO GENERATE ENDOCYTOTIC VESICLE ASSEMBLY

PRESENTER: Chao Huang

Chao Huang, Xin A Zhang*

Membrane protein CD82 inhibits metastasis formation in a variety of cancers, and expression of CD82 is frequently down regulated or lost in aggressive or late stage cancers. Though it has been shown that CD82 inhibits cell movement in vitro, the mechanism how CD82 inhibits cell movement is not clear.

Our study demonstrated that CD82 regulates cell membrane domains organization: CD82 promotes tetraspanin enriched microdomains (TEM) components such as tetraspanins, integrins and growth factor receptors localization to lipid raft in a cholesterol binding dependent manner. And this enhanced localization to lipid raft is corrected with increased endocytosis of proteins in the TEM. By site directed mutagenesis of the cholesterol binding motif, we made a cholesterol binding deficient mutant that can no longer enhance lipid raft localization of TEM proteins, and this mutant failed to inhibit cell movement in vitro, also this mutant does not promote endocytosis of TEM proteins. Though a variety of TEM proteins are down-regulated on the cell surface of CD82 over-expressing cells, it remains a question whether CD82 inhibits TEM components such as integrin and growth factor receptor activity on the cell surface in a cholesterol binding dependent manner. We will determine the activity of integrins and growth factor receptors on the cell surface later.

Conclusion: CD82 regulates cell membrane domain organization in a cholesterol binding dependent manner, and proper membrane domain organization is required for CD82 promoted endocytosis of TEM proteins.

CXCR4 CHEMOKINE RECEPTOR ANTAGONIST SJAS: ANTI-TUMOR ACTIVITY AND TUMOR IMAGING STUDIES

PRESENTER: Tim Hubin

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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 tetraazamacrocyclic 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-tetraazamacrocyclic has been selected for further development.

As a copper complex, SJA5 can seamlessly incorporate ⁶⁴Cu Positron Emission Tomography (PET) imaging capability by simply using positron emitter ⁶⁴Cu in place of “cold” copper during synthesis. Initial imaging studies in healthy mice show no loss of ⁶⁴Cu from its chelator, a biodistribution consistent with CXCR4 binding, and facile renal excretion of intact ⁶⁴CuSJA5. 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 ⁶⁴CuSJA5 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.

TREATMENT OF HUMAN BLADDER CANCER CELLS WITH DIAMOND NANOPARTICLES CHANGES CD55 EXPRESSION

PRESENTER: Janaki Iyer

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Complement regulatory proteins (CRPs), such as CD55 play an important role in protecting host cells from complement-mediated lysis. CD55 mediates this protective action by accelerating the decay of the C3/C5-convertases that are part of the classical, as well as, alternative pathway of the complement cascade. However, CD55 levels are upregulated in many cancers like bladder, prostate and blood malignancies to enable tumor cells evade immune surveillance and complement-mediated lysis. Thus, upregulation of CD55 in cancer cells also interferes with the therapeutic activity of immunotherapy drugs in treating cancers. Therefore, it is desirable that therapeutic agents have an adjuvant action on cells resulting in downregulation of CD55, which makes cancer cells more susceptible to complement-mediated lysis.

Diamond nanoparticles (DNPs) are becoming popular in therapeutics as they are biocompatible and can be differentially functionalized to facilitate loading of various therapeutic agents. They have been designed for targeted drug delivery of anti-cancer drugs to treat tumors effectively by using lower doses of drugs. In the present study we tested the hypothesis that DNPs can be effective drug delivery agents and also display adjuvant properties of immunomodulation by affecting the expression of CD55 in cancer cells.

Bladder cancer is the 4th most common cancer in males and 6th most common in females and if diagnosed and treated early, the rate of survival is good. Therefore, in the current study, we used T24 human bladder cancer cell line as an *in vitro* model system to study the immunomodulatory effects of DNPs on bladder carcinoma. Our experiments indicated that the concentrations of DNPs used in the study were non-toxic to the T24 cells. The DNPs were internalized into the T24 bladder cancer cells by an actin-dependent mechanism as visualized by confocal microscopy. Finally, treatment of T24 bladder cancer cells with DNPs resulted in a dose dependent decrease in CD55 expression. Thus, DNPs can serve in targeted therapeutics for treating bladder cancer as DNPs can perform the dual action of targeted delivery of anti-cancer drugs and reducing the expression of CD55, which sensitizes these cancer cells to complement-mediated lysis. This study was supported by funds from OCAST HR14-065 and Cancer Sucks Inc., Bixby.

RACIAL, ETHNIC, AND AGE DIFFERENCES IN THE INCIDENCE AND SURVIVAL OF CHILDHOOD CANCER IN OKLAHOMA, 1997-2012

PRESENTER: Amanda Janitz

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Introduction: While cancer is relatively rare in children under 20 years, it is the leading cause of disease-related death among children aged 5 to 14 years. Risk factors vary by cancer type and many of the proposed risk factors have limited or insufficient evidence to evaluate causality. We aimed to describe the incidence and survival of childhood cancer in Oklahoma from 1997-2012.

Methods: Data for both incidence and survival in Oklahoma was collected from the Oklahoma Central Cancer Registry, which has collected data on cancers diagnosed in Oklahoma residents since January 1, 1997. We calculated overall age-adjusted, age-specific, and age-adjusted race-specific incidence rates for acute lymphocytic leukemia (ALL), astrocytoma, and Hodgkin lymphoma in Oklahoma. We compared these results with the Surveillance, Epidemiology, and End Results (SEER) estimates for childhood cancers from 1997-2012. To estimate survival, we calculated five-year observed survival proportions for Oklahoma children diagnosed between 1997 and 2008 and compared to five-year observed survival from the SEER registry for the same timeframe.

Results: The average annual age-adjusted incidence rate (AAIR) of childhood cancer was 168.9 per million for the US and 171.7 per million for Oklahoma. The three most common types of cancer in Oklahoma and the US during this time were ALL (OK AAIR: 32.5 per million; SEER AAIR: 34.7 per million), astrocytoma (OK AAIR: 13.0 per million; SEER AAIR: 14.0 per million), and Hodgkin lymphoma (OK AAIR: 10.8 per million; SEER AAIR: 12.0 per million). Overall, Oklahoma had lower survival from childhood cancer compared to the US (77.0% v. 80.6%). Patterns of survival by age differed for each cancer type, although the trends were similar between Oklahoma and the US with the exception of astrocytoma among children aged 15-19 years (OK five-year survival: 49%, SEER five-year survival: 76%).

Conclusions: Overall, trends for incidence and survival were similar between the US and Oklahoma, with increases in some tumor types and decreases in others. Further study is needed to determine whether survival from astrocytoma is lower in Oklahoma or if there is a difference in tumor classification compared to SEER. While there are many obstacles to studying such a rare disease, it is important to understand the burden of childhood cancer in Oklahoma in order to better understand risk factors, etiology, and the overall health of the state, which may lead to future prevention strategies.

DOCOSAHEXAENOIC ACID AND DISULFIRAM ACT IN CONCERT TO ENHANCE THEIR ANTICANCER ACTIVITY

PRESENTER: Yang Jiao

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Introduction: We have recently demonstrated the synergistic anticancer action of clioquinol, a metal binding compound and antibiotic, and docosahexaenoic acid (DHA, 22:6, n-3), a long chain n-3 polyunsaturated fatty acid. DHA has been extensively and safely used in humans, however clioquinol has been banned clinically in many countries because of its observed neurological toxicity. The present study tested whether disulfiram (DSF), a metal binding compound and an inhibitor of aldehyde dehydrogenase (a marker of stem cells) that has been safely used to combat alcoholism in human for many years, could be an effective alternative compound to clioquinol that will act in concert with DHA to more effectively suppress cancer progression.

Methods: A human ovarian cancer cell line A2780 and human breast cancer cell lines MDA-MB-231, MCF7 and BT-20 were utilized in this study. Cell viability was analyzed by MTS assay. MDA-MB-231 xenograft nude mice were utilized for an *in vivo* study. Gene expression was analyzed by reporter gene assay and western blot. The mammosphere formation and extreme-limiting-dilution assay were performed to evaluate cancer cell “stemness” after drug treatment.

Results: DSF was more toxic to cancer cells when combined with zinc and copper, thus confirming its metal binding activity. Treatment with DSF plus DHA induced a greater suppression of tumor growth both *in vitro* and *in vivo*, as compared to DSF and DHA used alone. Mechanistic studies demonstrated that the combination of DSF and DHA induced heme oxygenase 1 (HO-1) expression to a greater extent, indicating that DHA-induced cellular oxidative stress is augmented by DSF. This enhancement of HO-1 expression was mediated at the transcription level through the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathway. On the other hand, DHA was found to enhance DSF-induced suppression of mammosphere formation and stem cell frequency in selected breast cancer model systems, indicating that alterations of cancer cell “stemness” is involved in the combinatory anticancer action of DSF and DHA.

Conclusions: DHA and DSF act in concert to more effectively suppress cancer cell viability and tumor progression. This anticancer action is mediated, at least in part, by an enhancement of cellular oxidative stress and the suppression of cancer cell “stemness”.

OVEREXPRESSION AND PURIFICATION OF HUMAN JMJD4 FOR STRUCTURAL STUDIES

PRESENTER: Cheidza Kanyumbu

Chiedza Kanyumbu, Irene Chen, Kyle Cahill, Molly Denny, Jugmen Sherpa, Karissa Hughes, and Blaine Mooers

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Jumonji domain-containing protein 4 (JMJD4) belongs to the Jumonji C (JmjC) family of oxygenases. 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. This side chain makes direct contact with the stop codon. The improper termination of translation is linked to colorectal, breast and ovarian cancers. It is also linked to the inherited diseases cystic fibrosis and muscular dystrophy. So structural data from JMJD4 will be valuable for structure-based drug design and development.

Structural data about JMJD4 are absent, so our first aim is to purify enough JMJD4 for structural studies. We have made dozens of MBP-JMD4 fusions with different N- and C-terminal truncation sites. Our selection of these truncation sites was guided by a homology model. We made this model using crystal structures of other members of the JmjC family. Some constructs gave high yields of protein that were free of aggregates. These constructs 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 also carry out small angle X-ray scattering studies to determine the shape of the JMJD4 protein in solution. We will compare this shape to that of the crystal structure to assess the relevance of the crystal structure to the structure in solution. We also plan to use some constructs in biophysical experiments to measure the interaction between JMJD4 and eRF1.

GALECTIN-3 AND-4 AS SIGNATURE MARKERS OF LUNG, COLON, PANCREATIC AND BLADDER TUMOR PROGRESSION AND CHEMOPREVENTIVE INTERVENTIONS

PRESENTER: Gaurav Kumar

Gaurav Kumar¹, Venkateshwar Madka¹, Altaf Mohammed¹, Jagan Mohan R. Patolla¹, Naveena B. Janakiram¹, Qian Li¹, Yuting Zhang¹, Laura Biddick¹, ²Allison Gillaspay, Stanley Lightfoot¹, Chinthalapally V. Rao¹.

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Galectins, a family of glycan-binding proteins, interact with cell-surface glycoconjugates and influence tumor progression by triggering a cascade of transmembrane signaling events which influence pathogenesis of cancer or tumor outcome. Despite considerable progress in identifying the involvement of individual galectins in tumor biology, an integrated portrait of the galectin network in different organ-site tumors or its microenvironments is not fully established. To understand the role of each galectin in lung, colon, pancreas and urinary bladder tumors and their relevance as markers of tumor progression; chemoprevention intervention trials was evaluated. Lung adenoma and adenocarcinomas were induced by tobacco specific carcinogen, NNK and colon adenomas and adenocarcinomas by azoxymethane (AOM). Whereas, pancreatic ductal tumors were induced by Kras^{G12D} activation in p48^{Cre}.Kras^{G12D} mice and bladder tumors were induced by SV40 activation in UPII-SV40T mice. Expression profiling of galectins was obtained by whole genome-transcriptome analysis with SOLiD methodology from RNAs of tumors and normally appearing tissues from each organ-site. Further profiling and characterization of each galectin (Gal) was carried by RT-PCR, western blotting, and immunohistochemical analysis. Data from transcriptome suggest that Gal-1, Gal-3, Gal-4, and Gal-12 are significantly associated with tumor progression. Particularly, Gal-1, Gal-3, and Gal-4 expressions were positively correlated with tumor progression in all the above cancers compared to their respective normal tissues and early lesions. Gal-12 was significantly increased in pancreatic and bladder tumor tissues but not in lung and colonic tumors. To understand prognostic value of galectins for chemoprevention interventions, we tested well-established and highly efficacious agents, difluoromethyl ornithine (DFMO), an inhibitor of ODC, and Licofelone, a dual COX-LOX inhibitor in above organ site cancers. DFMO (up to 2,000 ppm) and Licofelone (up to 500 ppm) was administered in the diet to mice after initiation of preneoplastic lesions or adenomas and continued until malignant tumor formations. As anticipated, both agents significantly inhibited malignant tumor formation. Importantly, intervention of tumor growth with mice fed with chemopreventive agents (DFMO and licofelone) showed a significant decrease in expression of Gal-3 and Gal-4 in tumor tissues and correlated with progression of tumor growth inhibition. Overall, these data provide impetus for further studies to delineate the role of Gal-3 and Gal-4 in various cancers and their usefulness as prognostic markers of chemoprevention interventions.

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PANCREATIC CYSTIC NEOPLASMS: A SINGLE INSTITUTION EXPERIENCE

PRESENTER: Alessandra Landmann

A Landmann MD, T Garwe PhD, Z Shakir BS, MM Bonds MD; N Bhandari MPH, JL Calisto MD, RG Postier MD

Background

Cystic lesions of the pancreas, once an uncommon pathology, are increasing in frequency; many are diagnosed incidentally after abdominal imaging, with a cited prevalence in the literature of 2.5%-13.5%. These neoplasms present a diagnostic and management challenge to the general surgeon, as the treatment is constantly evolving. This study describes demographic and clinical characteristics of patients diagnosed with cystic neoplasms.

Methods

A retrospective chart review of 866 patients who underwent pancreatic resection at a single institution from January 2002-December 2013 was conducted. Patients were included in the study if they had pathology confirmed cystic neoplasms. Means and proportions were used to summarize the data. Univariate analysis comparing the different cystic neoplasm pathologies was performed using analysis of variance (ANOVA) for continuous variables and chi-square/Fisher's Exact tests for categorical variables.

Results

The prevalence of CNPs in our patient cohort was 14.6% (127/866). Of the 127 patients included in our study, intraductal papillary mucinous neoplasm (IPMN) was present in 71 patients (56%, national average 27-48%), 25 patients had mucinous cystic neoplasm (MCN) (20%, national average 11-23%), and 31 patients had serous cystic adenoma (SCA) (24%, national average 12-23%). These lesions were identified based on CT imaging in the majority of patients (50%, 43%, 69% respectively). Ductal dilation and chronic pancreatitis were more common in IPMN than other neoplasms ($p < 0.05$). There was a male and older patient predominance for IPMN ($p < 0.05$). Of the IPMNs, 18% were malignant and 48% were borderline malignant. MCN demonstrated 11% malignancy, 37% borderline malignancy, while the majority of SCNS are benign (87%). The most common postoperative complications were intra abdominal abscess (11%) and delayed gastric emptying (3%). Non-infectious complications were more common in the IPMN cohort, and infectious complications were more common in the remainder.

Conclusion

Pancreatic cystic neoplasms represent an increasing cohort of patients presenting for pancreatic resection. While many lesions are diagnosed based on imaging characteristics, we demonstrate that a large cohort of patients harbor lesions with malignant potential.

TAX RECIPROCITY AGREEMENTS AS A STRATEGY TO REDUCE TRIBAL TOBACCO SALES IN OKLAHOMA

PRESENTER: Fritz Laux

Laux, Fritz
University of Oklahoma Health Sciences Center

The U.S. Supreme Court addressed the issue of discount tobacco retailing on tribal lands in three landmark decisions, *Moe* (425 US 463, 1976), *Colville* (447 US 134, 1980), and *Potawatomi* (498 US 505, 1991). In essence, these decisions established that, while sales to own-tribe members should be free from state tax liability, sales to non-members of a tribe were subject to state tax.

In his dissent to the *Colville* opinion, Justice Brennan argued that these rulings biased the law against tribal governments in that they permit “the State to enact a tax without risking any attendant loss of business for its retailers while the Tribes must court economic harms when they enact taxes of their own.”

This paper suggests that the logical extension of Brennan’s point is that state-tribal tobacco tax sharing arrangements should be based on reciprocity. Thus, if nontribal sales within tribal jurisdictions are subject to state taxes, sales to tribal members within state jurisdictions should be subject to tribal taxes.

Since the tracking of which sales go to own-tribe members is administratively impractical, the asymmetry of current law has led to arrangements whereby tribal sales pay state tax at discounted rates, to allow for the fact that some tribal sales will be to own-tribe members. Using Oklahoma data we present calculations to demonstrate that, via these arrangements, the tribes tend to benefit from using price discounting to increase market share.

Revisions to current law or negotiated state-tribe agreements that brought symmetry into this relationship would encourage either sales quota systems or, more simply, tax revenue apportionment agreements. Using Oklahoma data, we demonstrate that (1) all Oklahoma tribes currently selling cigarettes would almost certainly do financially better under quota or revenue apportionment regimes and (2) that under these arrangements, there would be little incentive to price discount.

We conclude that more reciprocity in state-tribal tobacco tax treatment would lead to reduced tobacco consumption, higher market share for nontribal retailers, and increased tribal revenue. The application of this result to other states is also discussed.

STRATEGY OPTIMIZATION FOR NIR-ACTIVATED PACLITAXEL PRODRUG USING A QUANTITATIVE INTRACELLULAR PK/PD MODEL

PRESENTER: Mengjie Li

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Purpose: We developed a unique prodrug concept which combines photodynamic therapy (photosensitizer) and chemotherapeutic drug (Paclitaxel) with a singlet oxygen-cleavable linker. Near IR light can activate photosensitizer (PS) to produce singlet oxygen (SO), which in turn activates paclitaxel release from the prodrug. Our NIR-activated prodrug can greatly improve the spatial- and temporal-limited antitumor efficacy of photodynamic therapy and reduce doses of cytotoxic drugs. In this study, we aimed to optimize the paclitaxel prodrug strategy in vitro using a quantitative computational model.

Methods: We synthesized paclitaxel prodrugs using either SO-cleavable linker (PS-(L-PTX)₂) or SO-noncleavable linker (PS-(NCL-PTX)₂). A mechanism based, pharmacokinetic/pharmacodynamics (PK/PD) model was developed in order to characterize the intracellular concentration-time profiles and anti-tumor efficacy in response to prodrugs. Key features of our model included light activation of SO generation, kinetics of extracellular and intracellular drug binding and accumulation, time and concentration dependent PTX and tubulin binding process, tumor cell growth with antitumor responses. The model was further validated by comparing the kinetic and dynamic profiles of drugs that were obtained from both literature and experimental data.

Results: Our model successfully predicted the time- and concentration- dependent tumor cell growth changes and inhibition responses of prodrugs under different circumstances from a concentration range of 0.1 to 1000 nM. According to the predictions, PS-(L-PTX)₂ demonstrated a more thoroughly ablation of tumor cells than PS-(NCL-PTX)₂ at high concentrations. Dose-dependent changes in cell numbers showed distinct growth patterns between PS-(L-PTX)₂ and PS-(NCL-PTX)₂ groups, indicating a wider concentration range can be achieved after PS-(L-PTX)₂ treatment in vitro.

Conclusions: Our model provides quantitative insights into the advantages of PDT combined anti-cancer agent therapy. Our findings suggest that PS-(L-PTX)₂ can demonstrate its antitumor effect on a wide concentration range. The model can be further applied to in vivo dose optimization of the NIR-activated prodrug system.

**MODULATION OF MTOR AND P53 SIGNALING USING RAPAMYCIN PLUS
CP-31398 INHIBITS GROWTH AND PROGRESSION OF UROTHELIAL CARCINOMA *IN-VIVO***

PRESENTER: Venkateshwar Madka

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Bladder cancer is the second most common genitourinary cancer worldwide. Despite multidisciplinary treatment advances, muscle-invasive bladder cancer continues to have high mortality. Since dysregulation of p53 and mTOR signaling in urothelium is associated with tumor initiation, growth and invasiveness, we investigated whether up-regulation of TP53 plus inhibition of mTOR additively or synergistically inhibits tumor growth and progression *in vivo*. Transgenic UPII-SV40T male mice (n=15/group) were generated, genotyped and fed control or experimental diets containing the mTOR inhibitor rapamycin (8 or 16 ppm) and/or the p53 stabilizing agent CP31398 (150 ppm) starting at 6 weeks of age. After 34 weeks, control diet fed transgenic mice developed urothelium-specific high-grade, invasive transitional cell carcinoma (TCC) with significant increase in bladder weights (140.2 ± 9.8 mg; $p < 0.0001$) compared with wild type (27.3 ± 0.8 mg). Rapamycin (8 or 16 ppm) reduced tumor weight by ~ 67% or 77% and CP31398 decreased it by >70%. The combination of CP31398 with 8 ppm rapamycin decreased tumor weight by ~83% (16.47 ± 5.4 mg; $p < 0.0001$). Rapamycin (8 or 16 ppm) suppressed tumor invasion by 53% ($p < 0.005$) or 66% ($p < 0.0005$). CP-31398 alone failed to inhibit tumor invasion; however its combination with low-dose rapamycin inhibited tumor invasion >71% ($p < 0.0001$). Molecular analysis of tumors via real-time PCR, IHC and western blotting showed synergistic inhibition by the drug combination of tumor growth and invasion with suppression of mTOR signaling (mTOR, pmTOR, raptor, rictor, Akt, pAkt); induction of p53 expression; and decreased expression of proliferation (PCNA), cell cycle regulators (cyclin D1, cyclin A), pro-survival molecules (Hif1a, Vegf) and androgen receptor. The combination of CP-31398 and rapamycin appears to be a promising approach for preventing urothelial TCC invasion. (Supported in part by NCI-CN53300)

FORMULATION OF SHetA2 IN A VAGINAL SUPPOSITORY FOR CHEMOPREVENTION AGAINST CERVICAL DYSPLASIA

PRESENTER: Sanjida Mahjabeen

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Purpose: Cervical dysplasia induced by high risk human papilloma virus is likely to progress to cervical cancer. Standard therapeutic options include chemotherapy and cryogenic or surgical removal of dysplastic lesion. SHetA2 is a novel compound with demonstrated therapeutic and preventive efficacy against tumors induced by the Human Papilloma Virus in mice and humans. In order to maximize drug concentrations at the site of action, our aim was to develop a vaginal suppository formulation to deliver SHetA2 directly to the cervix.

Methods: The following formulation factors were optimized using Design of Experiments (DoE, statistical software): (1) Suppository base; (2) Percentage of Kolliphor; and (3) Optimum Drug-Base-surfactant ratio to retain the solid state of the suppository at room temperature. Cocoa Butter (CB) and Poly Ethylene Glycol (PEG) of various molecular weights were used as the suppository base. Vaginal suppositories were manufactured by the Fusion-Molding method as follows: The base is melted and the surfactant and SHetA2 (particle size of 45-63 μm) are subsequently dispersing the in melted base. This dispersion is then poured into bullet-shaped plastic molds custom-made in our laboratory to fit the vagina of Friend Leukemia Virus B (FVB). Vaginal suppository formulations were optimized as specified in United States Pharmacopoeia to achieve content uniformity (85% -115%), weight variation (Std.Dev. < 20%), solid at room temperature, melting time (for CB)/ softening time (for PEG) [within 30 minutes]. Maximum drug solubility was evaluated in water (pH=6.9) and simulated vaginal fluid (pH=4.2).

Results: The first DoE (16 experiments) revealed that combinations of evaluated PEGs (PEG 3350, PEG 1000, PEG 400) and kolliphor at 5-30%, all were stable and solid at room temperature. The second DoE (8 experiments) revealed that two CB suppository formulations and one PEG suppository formulation [PEG1000 and PEG3350 (3:1) combination] having 5% kolliphor were solid at room temperature and met USP specifications. The content uniformity of these three optimized formulations was 105.44 ± 0.42 % for CB suppositories and 107.54 ± 0.07 % for PEG suppositories. The melting time for CB suppositories was 3.86 ± 0.64 minutes and softening time for PEG suppositories was 5.02 ± 0.58 minutes. The length and width of custom made vaginal suppositories for FVB mice were 0.4 cm and 0.3 cm, and were inserted in their vaginal cavity easily. Maximum solubility of SHetA2 in water and simulated vaginal fluid was similar.

Conclusion: We developed two optimized vaginal suppository formulations meeting USP requirements for quality control and suitable for easy vaginal insertion in FVB mice.

ACTIVE AND PASSIVE SMOKING INCREASE EPITHELIAL NORMAL AND CANCER STEMNESS AND INDUCE DRUG RESISTANCE

PRESENTER: Jimmy Manyanga

Jimmy Manyanga^{1,2}, Célia Bouharati¹, Vengatesh Ganapathy¹ and Lurdes Queimado¹⁻⁵

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Background and Aims: Cigarette smoking remains one of the major leading causes of preventable cancers. Continued smoking after cancer diagnosis has been associated with increased drug resistance, toxicity and recurrence, but the mechanisms underlying these effects are poorly understood. When a cigarette is smoked, it results in a mixture of two types of smoke: mainstream (MS) smoke, the main smoke directly drawn and inhaled by an active smoker, and sidestream (SS) smoke, the material released into the air from the burning cigarette tip which constitutes more than 90% of secondhand smoke. MS and SS smoke differ in their chemical composition. 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 active smoking on CSCs remain poorly studied. Currently no studies have reported the effects of secondhand smoke on CSCs or drug resistance. Here, we examined the individual effects of MS and SS smoke on the stemness of head and neck epithelial cells, and the concomitant effects on drug efficacy.

Methods: Normal and cancer epithelial cell lines were exposed every other day for 2 weeks to smoke extracts and their self-renewal and pluripotency properties were evaluated using ALDEFLOUR assay and spheroid formation. For drug testing, cancer cells were simultaneously exposed to cisplatin (0.1-100 M) and MS or SS extracts. Cell viability and gene expression were assessed by the MTT and quantitative PCR assays, respectively.

Results: Exposure to MS and SS smoke extracts caused a significant increase in the number of head and neck normal epithelial and cancer stem cells. Cells treated with MS and SS smoke extracts formed an increased number of spheres. Interestingly, the spheroids formed in the presence of SS smoke extracts were morphologically different from those formed in the MS-exposed cells, suggesting that MS and SS smoke may affect human cells via different molecular mechanisms. Importantly, both MS and SS smoke extracts caused a significant increase in the expression of *OCT4*, the gatekeeper of stem cell pluripotency, and of *WNT3A*, a major activator of the canonical Wnt pathway with key roles in stem cell self-renewal and tumor progression. Exposure to MS or SS smoke also resulted in a significant increase in resistance to cisplatin treatment.

Conclusion: These data provide novel mechanisms by which active and passive smoking, distinctively, might contribute to tumor initiation, progression, and therapy resistance. Of major clinical importance, our data suggests for the first time that exposure to secondhand smoke might worsen the overall cancer prognosis of nonsmokers.

Funding: This work was supported by the Oklahoma Tobacco Research Center. Dr. Queimado holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.

A TARGETED AGENT FOR PHOTOTHERMAL ABLATION OF CUTANEOUS MALIGNANT MELANOMA

PRESENTER: Patrick McKernan

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Introduction: Despite its infrequent appearance in dermatology, cutaneous malignant melanoma (CCM) represents the most frequent source of skin cancer related deaths. Employing a recombinant protein-nanotube conjugate, we target the tumor vasculature for photothermal ablation. Phosphatidylserine (PS) is a unique marker of tumor angiogenesis. Employing a PS ligand, annexin V (AV), we selectively 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.

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 tumor studies 1×10^6 B16F10-luc cells are subcutaneously injected to create primary tumors. Primary tumors are treated with NIR irradiation 2 hours after SWNT-AV injection at an energy and power level of 175 J/cm^2 and 1 W/cm^2 , respectively (time of 175 s; Diodevet-50 NIR laser at 980 nm). Pulmonary metastases are generated via intravenous injection of 1×10^6 B16F10-luc cells. Pulmonary tumor burden is monitored via bioluminescent live animal imaging and lung histology.

Results and Discussion: To determine the minimal dosage necessary to treat B16F10 tumors, mice are shaved and inoculated with a subcutaneous injection of B16F10 cells and the tumors are allowed to grow to 4 mm in diameter. The following day mice receive an intravenous dose of 0.0, 0.1, 0.2, and 0.8 mg/kg SWNT-AV ($n = 7$ per group), and the primary tumor is then irradiated. A dose of 0.8 mg/kg SWNT-AV resulted in near complete tumor eradication in all animals. Doses of 0.1, and 0.2 mg/kg SWNT-AV resulted in visible charring of the primary tumor, but tumors were again palpable within 4 days post irradiation in all mice. A dose of 0.0 mg/kg SWNT-AV yielded no visible effect.

Conclusions: The photothermal ablation of tumors is limited by tissue attenuation. The tumor specific agent SWNT-AV overcomes this problem by serving as a radiation target, optimizing the delivery of energy to cutaneous melanoma. This reduces the radiation necessary for tumor eradication, minimizing the damage of healthy tissue surrounding the tumor. Future work will seek to harness the abundant antigenic material at the site of ablation in conjunction with immunostimulation to create an in situ vaccine.

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TARGETING INFLAMMATION BLOCKS TUMOR INITIATING STEM CELLS AND PANCREATIC CANCER PROGRESSION

PRESENTER: Altaf Mohammed

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Pancreatic cancer (PC) is a deadly disease with the lowest survival of all cancers. Recent development of genetically engineered mouse models (GEMs) for PC that recapitulate human disease progression has enabled development of new strategies to delay or inhibit pancreatic cancer and testing of experimental interventions in preclinical trials. Pancreatic tumor-initiating or cancer stem cell (CSC) populations contribute to tumor growth, metastasis, and resistance to therapy. We first found that expression of the CSC marker DclK1 occurs at an early stage of PC in both early and late pancreatic intraepithelial neoplasia (PanINs) and increases as the disease progresses. Genome-wide next generation sequencing of pancreatic ductal adenocarcinoma (PDAC) from GEMs revealed significantly increased DclK1 along with inflammatory genes compared to normal pancreas. Genetic ablation of cyclo-oxygenase (COX)-2 decreased the DclK1 in GEMs. Induction of inflammation with cerulein induced pancreatitis in GEMs increased DclK1, and DclK1 was reduced by the novel anti-inflammatory dual COX/5-lipoxygenase (5-LOX) inhibitor licofelone. We investigated the long term pharmacologic inhibitory efficacy of licofelone on PDAC in vivo using a GEM model. GEM (n=86) and wild type mice (n=24) were fed a diet containing different doses of licofelone for 300 days and evaluated for formation of PanINs and for their progression to PDAC. Dietary licofelone at tested doses significantly inhibited the incidence of PDAC (60-90%; p<0.0001) with a profound suppression of carcinoma in situ (35-60%; p<0.001) in male and female GEMs. Licofelone caused a dose-dependent suppression of pancreatic tumor COX-2 and 5-LOX activities and modulated miRNAs for inflammation markers and CSCs, including DclK1, CD133, CD44, and Lgr5 (p<0.001) in correlation with the PDAC inhibition. Licofelone also inhibited inflammation-induced CSCs in vitro. These studies provide the first evidence that modulation of inflammation with a dual COX-LOX inhibitor effectively blocks CSCs and inhibits pancreatic tumorigenesis. In summary, our preclinical data indicate that licofelone has potential for chemoprevention of PC and should be evaluated in other PDAC models in anticipation of future clinical trials. {Supported by NCI-CN-53300}

UNCOVERING THE ROLE OF XRN2 IN GENOMIC INSTABILITY AND THE DNA DAMAGE RESPONSE

PRESENTER: Julio Morales

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University of Oklahoma Health Sciences Center, Department of Neurosurgery

The role of transcriptional by-products as a source of genomic instability and initiating the DNA damage response is becoming more apparent. Several studies have found that factors classically viewed in context of RNA metabolism are also intimately involved in the DNA damage response (DDR), with the best examples being factors involved in transcription termination. Transcription termination is a process that involves a number of different proteins. Several transcription termination factors have been shown to have direct roles in regulating double strand break (DSB) repair or the DDR response to transcriptional by-products. In this study we examine the role of the transcription termination factor XRN2 in the DDR. XRN2 is a 5'-3' ribo-exonuclease involved in several RNA degradation pathways. We find that XRN2 responds to multiple forms of DNA damage by undergoing nuclear transcription dependent relocalization and co-localizes with transcriptional by-products, in particular RNA:DNA hybrids (R-loops). The loss of XRN2 also leads to increased sensitivity to several forms of DNA damaging lesions, increased genomic instability, increased amounts of replication stress, and R-loop formation. Interestingly, loss of XRN2 leads to the initiating of the DDR signaling and an accumulation of factors involved in repairing DSBs at the 3' end of genes that undergo poly-A mediated transcription termination. Loss of XRN2 also leads to delayed DNA damage repair kinetics in response to ionizing radiation. Importantly, we find that the difference in DNA repair kinetics in cells that have lost XRN2 is due to active transcription and formation of R-loops. This suggest that XRN2 is involved in regulating transcription after DNA damage and that this regulation is important for repairing DSBs in a timely manner.

TUMOR-TARGETED HuRsiRNA-NANOPARTICLE TREATMENT INHIBITS LUNG TUMOR GROWTH *IN VIRTO AND IN VIVO*

PRESENTER: Ranganayaki Muralidharan

Ranganayaki Muralidharan^{1,4}, Narsireddy Amreddy^{1,4}, Anish Babu^{1,4}, Yan D. Zhao^{3,4}, Anupama Munshi,^{2,4} Rajagopal Ramesh^{1,4,5}.

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HuR, an mRNA binding protein regulates the stability of many oncoproteins associated with cell survival, proliferation, migration and angiogenesis. Overexpression of HuR has been demonstrated to be a marker for poor prognosis in patients diagnosed with cancer of lung, ovary, breast and colon. We hypothesized that the silencing of HuR using small interfering RNA (siRNA) could be a promising approach for lung cancer therapy. To test our hypothesis, we developed a tumor-targeted nanoparticle (NP) system that is targeted to transferrin receptor (TfR) for delivering HuRsiRNA (HuR-TfNP) in human lung cancer cells.

Human lung cancer cells (A549, HCC827) and normal lung fibroblast (MRC-9) cell lines expressing varying levels of TfR were used in the present study. TfR expression was highest in A549, moderate in HCC827, and low to undetectable in MRC9 cells. Transferrin (Tf) -NP were prepared by conjugating Tf into DSPE-PEG 2000 which was post inserted into the liposomes (DOTAP:chol). *In vitro* studies demonstrated enhanced uptake of Tf-NP (51%) in TfR overexpressing A549 cells, compared to the non-targeted NP. Specificity studies using desferrioxamine (DFO; 100 μ M), a stimulator of TfR, showed increased uptake of Tf-NP whereas blocking TfR with exogenous transferrin (1 μ g/well) reduced the uptake by 3 fold in A549 cells. Further, HuR-TfNP targeting increased HuR knockdown by 2 fold and decreased cell viability in A549 cells when compared to the non-targeted NP. Additionally, HuR-TfNP suppressed cell proliferation at 24 and 48h compared to control siRNA C-Tf-NP in all three cell lines tested. Greatest inhibition was observed in A549 cells (23 and 30% at 24 and 48 h respectively) compared to 15 and 25% in HCC827 and 4 and 4% MRC-9 cells. Inhibition of cell proliferation in these cell lines correlated well with G1 phase cell cycle arrest in HuR-TfNP treated cells. Decrease in Bcl2, Cyclin D1 and Cyclin E protein expression was observed as a consequence of HuR knockdown. Silencing HuR significantly inhibited cell migration and invasion ($p < 0.001$) in HuR-TfNP treated tumor cells compared to C-TfNP treatment.

In-vivo Tf-NP bio-distribution studies using indocyanine green (ICG) showed accumulation of the NP in tumor tissues over time with maximum accumulation at 24 h post NP injection. Efficacy studies demonstrated systemic administration of HuR-TfNP significantly inhibited A549 tumor growth compared to C-TfNP treatment ($P < 0.05$). Further, tumor growth delay was sustained over 70 days when compared to control groups. Molecular studies examining the tumor tissues revealed marked reduction in HuR expression and in the expression of HuR-regulated oncoproteins.

Our study results demonstrate tumor-targeted HuR-TfNP therapy suppressed lung tumor growth both *in vitro* and *in vivo* and could be developed for clinical testing against lung cancer.

Acknowledgements. This study was funded by a grant (R01CA167516) from the National Cancer Institute.

**PRIMARY CARE PHYSICIAN DENSITY AND INSURANCE STATUS ON STAGE OF DIAGNOSIS FOR
UROLOGIC MALIGNANCIES**

PRESENTER: Kristy Nguyen

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Cancer stage at diagnosis is an important indicator of outcome. Previous studies have shown an inverse relationship to primary care physician (PCP) density and stage of cancer diagnosis. Insurance status has also been previously shown to affect the stage of diagnosis. This study evaluated PCP density and insurance status for urologic malignancies in Oklahoma to test the hypothesis that increased PCP density and being insured would be associated with lower stage disease even in a state with a generally low PCP density.

OK2Share, the Oklahoma State Department of Health database, was accessed for Bladder, Kidney, and Prostate cancer diagnoses from 2000-2010. Each was stratified by county, insurance type, and stage at diagnosis. Advanced stage was defined as the presence of regional or distant disease; in-situ results were not included. Age was restricted to 20 years old and beyond. The number of PCPs was determined by using the Oklahoma State Licensing Board for active internal medicine and family medicine physicians by counties. Population data was obtained through the 2010 national census. High PCP density was defined as anything greater than or equal to the mean value: 3.17 PCP/10,000. Statistical program "R" was utilized to produce odds ratios (OR) and logarithmic regressions. VA, Military, Indian Health Service, and Medicaid insurance were excluded from analysis due to insufficient data.

27,134 patients were identified across 77 counties of which 36 were considered high PCP density. Logarithmic regression showed that as the PCP density increases by 1 PCP/10,000, the odds ratios of having an advanced stage at diagnosis were 0.383, 0.468, 0.543 for bladder, kidney, and prostate cancer respectively. In high PCP density areas, Medicare coverage reduced the likelihood of having advanced bladder or prostate cancer (OR: 0.67 and 0.68 respectively) but increased the likelihood of advanced kidney cancer (OR: 1.46) compared to private insurance. Being uninsured had a higher likelihood of advanced kidney and prostate cancers (OR: 1.61 and 2.45 respectively) compared to having private insurance.

This study confirms previous studies finding increases in PCP density reduced the odds of advanced cancer stage at diagnosis. Insured patients also had reduced odds of advanced stage at diagnosis. Implementation of policies to improve access to healthcare, through increasing PCP density and insuring patients may result in improved cancer-related outcomes through diagnosis at earlier cancer stage.

Table 1. Odds Ratios with Confidence Intervals of Advanced Diagnosis

	Bladder (n=2,942)	Kidney (n=3,749)	Prostate (n=20,443)
Log Regression			
With each addition of 1 PCP/10,000	0.38 (0.30 – 0.49)	0.47 (0.40 – 0.55)	0.54 (0.49 – 0.57)
High PCP Density			
Private insurance	Ref	Ref	Ref
Uninsured	0.18 (0.02 – 1.36)	1.61 (1.08 – 2.52)	2.45 (1.72 – 3.49)
Medicare	0.67 (0.52 – 0.87)	1.46 (1.24 – 1.72)	0.69 (0.62 – 0.77)

Values in bold with P<0.05

A NOVEL APPROACH IN LEUKEMIA THERAPEUTICS: SELECTIVE INHIBITOR TARGETING OF OSBP-RELATED PROTEIN 4 (ORP4)

PRESENTER: Juan Nunez

Juan Nunez, Anh Le, Rama Kothapalli, Anthony Burgett

Department of Chemistry and Biochemistry, University of Oklahoma

Oxysterol binding protein (OSBP) and OSBP-related proteins (ORPs) are a family of conserved proteins thought to function as lipid transports and/or lipid sensor proteins. Recently, the OSBP/ORP family were determined to be the cellular targets of a class of novel and potent anti-proliferative small molecules. These compounds, named the ORPphilins (Figure 1, compounds 1-5), indicates that the OSBP/ORP proteins could be a new class of druggable targets for anti-cancer therapeutic development. Published research, in 2014, revealed ORP4 is a driver of cellular proliferation, and this protein is established to have high and selective expression in myeloid leukemias, making this protein a promising target for personalized drug development. Our goal is to synthesize, identify and develop specific ORP4 small molecule inhibitors for exploration as potential anti-leukemia agents. We are currently focused on the development of ORP4-selective analogs based on the natural product compound OSW-1 (1) (NCI-60 GI₅₀ average = 0.78 nM). OSW-1 has been shown to be a high affinity inhibitor of ORP4, ($K_i = 54$ nM), but the compound shows little selectivity for ORP4 over OSBP, which is ubiquitously expressed in tissues. We will synthesize a library of OSW-1 analogs, and test the analogs for ORP4-specific binding using a high-throughput OSBP/ORP ligand binding assay. We are currently employing our OSBP/ORP binding assay to systematically characterize the ligand binding of the entire OSBP/ORP family through screening a wide array of endogenous lipids, synthetic lipids, and ORPphilin compounds. The characterization of OSBP/ORP ligand binding will help direct the synthesis of new ORP4-specific OSW-1 analogs for further potential drug development.

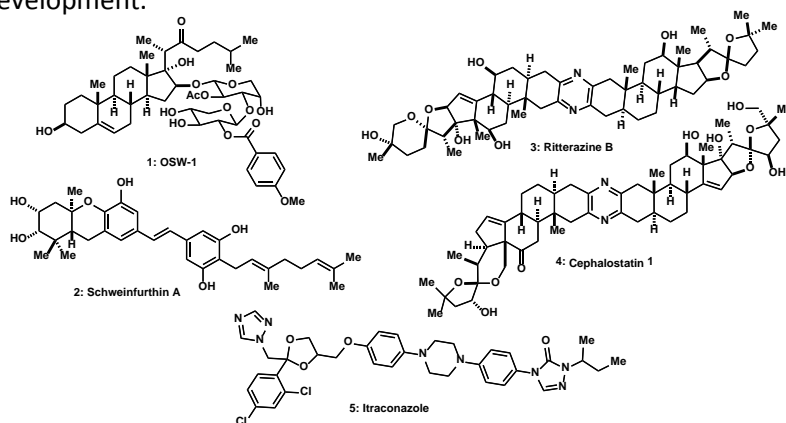


Figure 1. Natural product compounds: OSW-1 (1), Schweinfurthin A (2), Ritterazine B (3), Cephalostatin 1 (4), and synthetic antifungal Itraconazole (5)

IL-24 MODULATES THE HIGH MOBILITY GROUP (HMG) A1/MIR222 /AKT SIGNALING IN LUNG CANCER CELLS

PRESENTER: Janani Panneerselvam

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Background: High mobility group A1 (HMGA1), a member of the non-histone chromosomal proteins and commonly referred to as architectural transcription factor, regulates transcription of various genes involved in cell growth and survival. Overexpression of HMGA1 has been shown to be associated with tumor progression and metastasis in several cancers, including human lung cancer. A recent study demonstrated that HMGA1 activates AKT function by reducing the activity of the protein phosphatase, phosphatase 2A subunit B (PPP2R2A) *via* the oncogenic micro (mi) RNA-222. We demonstrated that interleukin (IL)-24, a novel tumor suppressor/cytokine, inhibited AKT in lung cancer cells. However, the molecular mechanism of AKT inhibition by IL-24 remains elusive.

Aim: To determine the molecular mechanism of IL-24-mediated AKT inhibition involved the HMGA1/miR-222 axis.

Methods: Human H1299 lung tumor cell line was stably transfected with a tetracycline-inducible plasmid vector carrying the IL-24. After the induced expression of IL-24 protein, expression levels of HMGA1 and its downstream molecular mechanisms were analyzed at the RNA and protein levels in lung cancer cell lines. The inhibitory effect of IL-24 on HMG A1/miR222 /AKT axis in the lung cancer cells is determined by RT-qPCR, western blot, reporter assay, and immunocytochemistry. Mechanistic approaches on overexpression and knockdown of HMGA1 and or miR-222 were utilized and the consequences of its inhibition/overexpression were analyzed on HMGA1/miR222 /AKT signaling axis and *in vitro* migration and invasion.

Results: Upon induction of IL-24 expression in the H1299 lung tumor cells, we observed a marked reduction in HMGA1 protein and mRNA levels. Using a mechanistic approach, we found that IL-24 reduced miR-222-3p and -5p levels, as determined by qRT-PCR. Associated with HMGA1 and miR-222 inhibition was a marked increase in PPP2R2A, with a concomitant decrease in phosphorylated AKT^{T308/S473} expression. siRNA-mediated knockdown of HMGA1 in combination with IL-24 significantly reduced AKT^{T308/S473} protein expression and greatly reduced cell migration and invasion compared with individual treatments. Further combination of IL-24 and a miR-222-3p inhibitor significantly increased PPP2R2A expression.

Conclusion: Our results demonstrate for the first time that IL-24 inhibits AKT *via* regulating the HMGA1/miR-222 signaling node in human lung cancer cells and acts as an effective tumor suppressor. HMGA1 should present a novel target for the effective treatment of lung cancer.

DISCOVERY OF NOVEL BREAST TUMOR-HOMING PEPTIDES THAT ENABLE TARGETED PHOTOTHERMAL ABLATION OF BREAST TUMORS

PRESENTER: Xuewei Qu

Xuewei Qu, Penhe Qiu, Chuanbin Mao

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Phage display is a convenient approach to identify polypeptides that have strong affinity toward the target materials, which can be inorganic and organic matters, biological proteins, cells and tissues¹. Specifically, for cancer treatment, polypeptides of many different sequences that can bind preferentially to different tumor types have been reported. By conjugating the targeting motifs, which can be peptides, phage fusion coat proteins or even phage particles, with drug molecules or drug-carrying nanoparticles, significantly enhanced accumulation of drugs at the tumor sites has been achieved, which further lead to the improved cancer-killing efficiency.² In addition, when the selected peptides are linked with imaging probes, i.e. fluorescent dyes and magnetic nanoparticles, they can also be used in the detection of cancers. Phage display can be carried out both in vitro and in vivo. Of these two approaches, peptides selection is conducted against cancer cells in the former while in the latter the tumor-bearing animals. In principle, in vivo selection against tumors should be more specific and more effective for clinic applications, as the peptides were selected under conditions similar to the physiological environment. In the literature, peptides selected by both the methods have been employed for enhanced drug delivery to cancer cells and tumor tissues.^{2c-e, 3} Particularly, for MCF-7 cancer, such study was reported exclusively based on peptides selected through in vitro phage display.⁴ Although a 7-residue peptide EGEVGLG was discovered by in vivo selection against MCF-7 tumors, this peptide can only show enhanced accumulation if the tumor is responsive to sunitinib, a chemotherapy agent. For MCF-7 tumors having no response to sunitinib, no enhanced accumulation of peptides can be observed.⁵ In this sense, this peptide can only be used as an indicator for the effectiveness of chemotherapy, rather than an active targeting motif that can initiate the enhanced accumulation of drugs. In the current work, we discovered several 15-residue peptides that home to MCF-7 breast cancer tumors through in vivo phage display. Our in vivo imaging results showed that the as-selected peptides can actively target untreated MCF-7 tumors. We then incorporated the peptides with a well-known photothermal reagent, gold nanorods, to study in vivo the effectiveness of the selected peptide in enhanced delivery. The enhanced accumulation of gold nanorods in the tumor sites was confirmed both by the ICP-MS measurement and the improved efficiency of photothermal treatment. To the best of our knowledge, this is the first example of using in vivo selected peptides for active targeting of MCF-7 tumors to achieve enhanced photothermal efficiency.

LIGHT-ACTIVATABLE PRODRUGS FOR LOCAL RELEASE OF ANTICANCER DRUG AND OVERCOME LIMITATIONS IN PHOTODYNAMIC THERAPY

PRESENTER: Pallavi Rajaputra

Pallavi Rajaputra,¹ Moses Bio,¹ Gregory Nkepan,¹ Pritam Thapa,¹ Sukyung Woo,¹ Youngjae You

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A unique prodrug strategy for treating localized cancers, in which NIR light-illuminated prodrug effectively ablates tumors through the combined effects of photodynamic therapy (i.e., singlet oxygen [SO]) and locally released anticancer drugs has been proposed. Due to short distance of action ($< 0.04 \mu\text{s}$) and short lifetime ($< 0.02 \mu\text{m}$) of SO, direct damage of PDT is both areally and temporally limited. We hypothesized that the locally released anticancer drugs would overcome the areal and temporal limits of SO. Near IR-activatable prodrug of combretastatin A-4 (CA4), Pc-(L-CA4)₂, and its pseudo-prodrug, Pc-(NCL-CA4)₂, were evaluated *in vitro* and *in vivo*. After partial illumination of a 24 well, all the cells in the prodrug-treated well were killed by the released CA4. Limited areal damage was observed in the pseudo-prodrug-treated wells. A time-dependent cell survival study revealed more extensive cell death in the prodrug-treated cells, due to the sustained damage from the released CA4. Cell cycle analysis and microscopic imaging data demonstrated the typical damage patterns of CA4 in the prodrug-treated cells. A time-dependent histological study showed that prodrug-treated tumors lacked mitotic bodies. The prodrug caused broader and more long-lasting tumor size reduction than did the pseudo-prodrug. These data consistently support that the released CA4 overcomes the areal and temporal limits of SO, providing far superior antitumor effects.

TARGETING MORTALIN-P53 INTERACTION IN DIFFERENTIAL INDUCTION OF APOPTOSIS IN CANCER OVER NORMAL CELLS

PRESENTER: Satish Kumar Ramraj

Satish Kumar Ramraj, Elangovan Thavathiru, Coralee Toal, Katie Smith, Elisa Crouse, Doris M. Benbrook

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Mortalin is a chaperone protein located throughout the cell, except for the nucleus. It plays a major role in protecting cancer cells from apoptosis, by binding to the tumor suppressor protein p53 and preventing it from entering the nucleus where it transactivates apoptosis-inducing genes. This mortalin-p53 interaction only occurs in stressed or cancer cells and not in healthy cells. SHetA2 is an anti-cancer drug that binds mortalin and induces apoptosis in cancer, but not in normal cells. We hypothesized that this differential induction of apoptosis is due to the differential status of mortalin and its interactome in cancer compared to healthy cells. To test this, we compared the interactions of SHetA2, mortalin and p53 in human ovarian cancer cell lines and human fallopian tube secretory epithelial cells (hFTSECs), which are believed to be the origin of the most common type of ovarian cancer, high grade serous. We optimized specimen collection and culturing conditions of hFTSECs from fallopian tube fimbria donated by consented patients under an IRB-approved protocol. In support of the hypothesis, SHetA2 caused dose-responsive nuclear accumulation of p53 in A2780 ovarian cancer cell line, but not in hFTSECs. Western blots comparing protein extracts from untreated solvent control and SHetA2-treated cultures, identified that SHetA2 caused appearance of a lower mobility mortalin band in hFTSECs, but not in ovarian cancer cell lines. Using an antibody that we had made to the mortalin mitochondrial localization sequence, we demonstrated that this lower mobility band is the precursor form of mortalin that has not had the mitochondrial localization sequence removed to form the fully-processed form of mortalin. In conclusion, our hypothesis that the different status of mortalin and its interactome is responsible for the differential effect of SHetA2 in cancer compared to normal cells is supported by the findings that SHetA2 causes nuclear accumulation of p53 in ovarian cancer cells, but not in hFTSECs, and prevents mortalin processing in hFTSECs and not in ovarian cancer cells. Currently we are optimizing immortalization conditions for hFTSECs to study how mortalin, its interactome and sensitivity to SHetA2 are changed by immortalization. Also, we are performing mortalin and p53 immunohistochemistry on tissue microarrays of human ovarian specimens to study how these proteins and their interactions differ in benign, borderline and various stages of cancer specimens.

Supported by [1R01CA196200-01A1](#), acknowledge SCC Core.

NEXT GENERATION IMAGE GUIDED DRUG DELIVERY USING ULTRASOUND IMAGEABLE LIPOSOMES AND HIGH INTENSITY FOCUSED ULTRASOUND FOR ENHANCED CHEMOTHERAPY PENETRATION IN SOLID TUMORS

PRESENTER: Ashish Ranjan

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Cancer chemotherapy typically employs systemic delivery of antitumor drugs having limited specificity, causing toxic side effects in normal tissues, and also inefficient and insufficient drug delivery to tumors. To overcome these barriers, we have developed a ultrasound imageable heat-activated liposome (E-LTSL)-based drug delivery system that provides 2 major advantages: 1) an echogenic tracking agent (Perfluoropentane, PFP) to permit in vivo tracking of liposome distribution and improve/fine-tune real-time control of drug delivery, and 2) locally-inducible drug release, using heat-activated liposomes (low temperature-sensitive liposomes; LTSL) that are sensitive to mild, non-destructive temperature elevations above normal body temperature, achieved by precise external warming of the tumor-containing region using ultrasound (US)-guided High-Intensity Focused Ultrasound (HIFU).

Data suggest that E-LTSLs can be efficiently co-loaded with PFP and doxorubicin. Phantom and transmission electron microscopy study clearly showed that E-LTSLs are echogenic. Temperature vs. size increase and drug release kinetics of E-LTSL demonstrated no difference with control (LTSL alone). Doxorubicin release in physiological buffer was <5% in 1 hr at baseline (25°C) and body temperatures (37°C), vs. >99% release with hyperthermia (~41°C). In vivo studies in mouse model of colon cancer showed that E-LTSL enhanced tumor imaging (~15-20 min.). Additionally, a combination of E-LTSL with hyperthermia delivered by US-guided HIFU resulted in significantly greater Dox delivery (~2-4fold) to tumors and heated muscle compared to E-LTSL, free Dox, and non-thermosensitive echogenic liposomes (E-NTSL) in mouse model of colon cancer.

In conclusion, an US imageable heat sensitive liposome formulation co-loaded with doxorubicin and an US contrast agent was developed for clinical translation. Stability, imageability, and US monitoring of contrast agent and doxorubicin release suggest that US-guided HIFU and E-LTSL may assist physicians in enhancing real-time tumor drug delivery.

A STUDY OF BIOLOGY OF THE OXYSTEROL-BINDING PROTEIN FAMILY AND THE RESPONSE TO ANTI-CANCER NATURAL PRODUCT IN CANCER CELLS

PRESENTER: Brett Roberts

Brett Roberts, Naga Rama Kothapalli, Anthony Burgett

Department of Chemistry and Biochemistry, University of Oklahoma

Oxysterol-binding protein (OSBP) and OSBP-related proteins (ORPs) are a protein family conserved among eukaryotes and involved in sterol and lipid biology. Recently, a class of potent anti-proliferative compounds were determined to exert their anti-cancer activity through targeting the OSBP/ORPs. This class of drugs was named ORPhillins, and identified the OSBP/ORPs as potential druggable targets for anti-cancer therapies. The founding member of this class, OSBP, is ubiquitously expressed in mammalian cells. ORP4 is the most closely related family member to OSBP (77% sequence identity), but is only expressed in select tissue types and various cancers. Although these proteins share high sequence similarity, OSBP and ORP4 have many differences in cellular function. OSBP is localized to ER-Golgi contact sites upon ligand binding, while ORP4 is associated with the vimentin network and ER-plasma membrane contact sites. ORP4 has recently been linked to cell survival and proliferation, suggesting this protein could be a novel and druggable target for anti-cancer drug development. The anti-cancer natural product OSW-1 is known to exert anti-proliferative activity by targeting OSBP/ORPs. OSW-1 is known to be a high affinity ligand for OSBP and ORP4, and therefore is a powerful chemical probe to study these proteins' biological functions. Our goal is to better understand the biology of OSBP and ORPs and by doing so, determine the mechanism of action of OSW-1. We are currently focused on the differences of ORP4 and OSBP protein levels in various cancerous cell lines. We have determined that OSW-1 treatment alters the expression of OSBP but does not change ORP4 expression levels. This result suggests that OSBP could have a significantly different biological role than ORP4. We are currently using RT-PCR methods to determine if the compound induces changes of OSBP on either transcriptional or translational level. The characterization of OSBP/ORPs cellular function in cancer cells, especially ORP4, will help solidify these proteins as anti-cancer targets. Additionally, these biological findings highlight key differences in cancer cell biology and provide insight into the mechanism of OSW-1.

SIGN CHI DO AND EXPRESSIVE WRITING FOR SLEEP AND FATIGUE OUTCOMES IN BREAST CANCER SURVIVORS

PRESENTER: Carol Rogers

Carol Rogers, PhD RN, Melissa Craft PhD APRN-CNS AOCN

Fran and Earl Ziegler College of Nursing, University of Oklahoma Health Sciences Center

Background: Many breast cancer survivors experience decreased quality of life (QOL) due to symptoms of fatigue and disturbed sleep that continue long after treatment. Exercise, meditation, and expressive writing (EW) have been effective in reducing fatigue in this population. Sign Chi Do (SCD), a gentle exercise incorporates diaphragmatic breathing, meditation, choreographed to a group of sign gestures, has shown improved function, endurance, and physical activity among sedentary older adults. EW is postulated to enhance meaning of the sign gestures in SCD, increase adherence to weekly practice, improve sleep, mood, QOL, and fatigue in breast cancer patients during treatment.

Aims: To evaluate acceptability, feasibility, and effects of Sign Chi Do combined with Expressive Writing (SCD/EW) on sleep and fatigue outcomes in breast cancer patients receiving treatment.

Methods: This descriptive, pre-post study explored the effect of a 12 week SCD/EW intervention on sleep and fatigue outcomes in 4 women with breast cancer receiving treatment. The intervention was delivered via IP video to reach participants living outside the metropolitan area of Oklahoma City. Outcomes included: Sleep quality [Pittsburgh Sleep Quality Index] and daytime function [Functional Outcomes of Sleep Questionnaire]); fatigue (self-report [Patient Reported Outcomes Measurement System Fatigue scores] and performance [6-minute walk])

Results: All outcomes improved following 12 weeks of SCD/EW. One participant decreased use of sleep medications. Participants reported the intervention was easy to perform and data collection was not taxing. By the end of 12 weeks, there was one participant at the site of the live class and one at the remote class. While both enjoyed the class, a larger class size is preferred.

Discussion and Conclusions: This specifically-adapted SCD, with meditation enhanced by EW, was both feasible and acceptable to breast cancer survivors during treatment. It also improved sleep and fatigue outcomes. This SCD/EW intervention holds potential to impact the long term QOL of breast cancer patients in a variety of urban and rural settings. Future research to include other cancer patients to increase class participation and explore effects.

**MEASURING PHYSICAL ACTIVITY ENVIRONMENTS, BEHAVIOR AND HEALTH IN TRIBAL NATIONS:
RESULTS FROM COMMUNITY-BASED PARTICIPATORY RESEARCH IN OKLAHOMA**

PRESENTER: Alicia Salvatore

Alicia L. Salvatore¹, Joy Standridge², Jill Fox², Jennifer Spiegel², AnDina Wiley², Michael Peercy², Bobby Saunkeah², Tammie Cannady³, Mandy Grammar³, Natia Anderson³, Dannielle Branam³, Jordan Hearod¹, Tvli Jacob¹, Marianna Wetherill¹, Valarie Blue Bird Jernigan¹

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Achieving 150 minutes of moderate physical activity per week is an important and well-recognized strategy for cancer prevention. Recent decades have brought major advances in measuring built and policy environments and their multiple influences on physical activity behavior. Relatively little, however, is known about the built and policy environments of sovereign tribal nations and how these environments shape physical activity behavior and health outcomes among American Indians (AIs). In this presentation, we will share results from a cross-sectional survey of perceived built and policy environments, physical activity behavior, and health status, conducted in partnership with two tribal nations in Oklahoma.

Our tribal-university Community-based Participatory Research (CBPR) partnership created a culturally tailored questionnaire that was administered to AI adults living within the tribal jurisdictional areas of the two tribal nations. Overall response to the survey was very positive (91.4% response rate) and a total of 513 adults completed the survey. Although a large portion of participants (73.6%) reported their towns had indoor exercise areas, few (26.1%) reported using these facilities. Fewer participants reported that their towns had outdoor exercise areas (66.3%), but a larger percentage reported using outdoor exercise areas (47.7%). Participants' overall perceptions of school activity environments were positive, although less than a third reported their schools had joint use agreements (26.5%). Over a third of participants (36.0%) reported that their town had bike lanes and the majority of participants living in towns with town centers reported that there were sidewalks in/near their town center (82.2%). Participants noted multiple condition issues with this infrastructure with implications for physical activity behavior. Participants reported engaging in at least 30 minutes of physical activity an average of 3.2 days per week (SD=2.1 days), which is approximately an hour less than recommended (i.e., 150 minutes of moderate physical activity per week). Participants most often exercised alone (38.0%) or with family members (37.1%) and indicated that stronger social support for physical activity would encourage them to be more active.

These findings, coupled with results showing that the majority of participants had been told by their doctor that they were pre-hypertensive or had high blood pressure (71.4%), were diabetic or pre-diabetic (19.0%) and were overweight (58.3%) or obese (27.0%), underscore the need for additional policy, environmental, and other interventions that benefit tribal members and lead to increased physical activity and other important cancer prevention behaviors.

INFLUENCE OF TEMPERATURE RISE ON NANOSCALE

PRESENTER: Pratik Samant

Pratik Samant, Jian Chen, Liangzhong Xiang

Department of Biomedical Engineering , University of Oklahoma

We are developing a label free nanoscale photoacoustic tomography (nPAT) for imaging a single living cell. nPAT uses a laser induced acoustic pulse to generate a nanometer-scale 3D image. The primary motivation behind this imaging technique is the imaging of biological cells in the context of diagnosis without fluorescent tagging. A 532 nm laser will be used for imaging red blood cells (RBCs). During this procedure, temperature damage due to the laser pulse is a potential risk that may damage the cells. A physics model is built to estimate the temperature rise and thermal relaxation during the imaging procedure. Through simulations using finite element method (FEM) analysis, we demonstrate that a 1kW peak power laser with a single 5ps pulse duration will generate a temperature rise about xxxk on the surface of the RBCs. And the temperature rise with a laser pulse repetition rate up to 400Hz is about xxxk. All the simulation results show that there is no significant temperature rise in a red blood cell (RBC). Therefore, the thermal safety of our nPAT imaging system can be guaranteed according to our simulation results. We believe that the nPAT will open a new avenue for disease diagnosis and cell biology in nanometer-scale level.

DEVELOPING ALLO- AND XENO-TRANSPLANTED ZEBRAFISH AS AN ONCOGENIC MODEL

PRESENTER: Rikin Shah

Rikin Shah MD, Talha Ahmed MD, Kimble Frazer MD, PhD

Jimmy Everest Section of Pediatric Hematology/Oncology, University of Oklahoma Health Science Center

Cancer is the most lethal disease of U.S. pediatric patients, with leukemia the most frequent cancer in children 0-14, and lymphoma most common in adolescents 15-19 years. Current multi-agent chemotherapy regimens achieve survival in many of these patients, but the drugs used carry considerable short- and long-term toxicities. To improve therapeutic 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. Zebrafish endogenous cancers have already proven to be feasible for drug testing, but relatively few of these models exist. In addition, just as in mice, endogenous zebrafish cancers do not model the unique genetic makeup of each clinical case. Transplants of *D. rerio* tumor cells into wild-type (WT) zebrafish (allo-transplants) or human cancers into WT zebrafish embryos (xeno-transplants) have also been used to assay oncogenicity, metastasis, and drug efficacy. However, both strategies are limited by transient immunosuppression in WT hosts, resulting from either sub-lethal irradiation of adult fish or the immaturity of the embryonic immune system.

To alleviate these problems, 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 are suitable for allo- and xeno-grafting. To establish a *D. rerio rag2*-mutant transplant model, we have transplanted cells from zebrafish with endogenous green fluorescent protein-positive (GFP⁺) T-cell acute lymphoblastic leukemia (T-ALL). GFP⁺ cancer cells were isolated from donor fish by Fluorescence-Activated Cell Sorting (FACS), and intra-peritoneally injected in varying amounts into recipient *rag2*-mutant fish. Once injected, recipient *rag2*-mutant fish were screened by serial fluorescent microscopy. Engraftment of GFP⁺ tumor cells has been detected as early as 9 days post injection (DPI), and sustained until 35 DPI. After developing this technique using allo-transplants, we next plan to establish xeno-transplants in *rag2*-mutants of human T-ALL and Burkitt lymphoma (BL) cell lines. Stably-xenografted human cell lines would demonstrate that human cancers can engraft in *rag2* fish, opening the door to xenografts with patient-derived samples. The greater feasibility and lower cost of *in vivo* drug trials in zebrafish position *rag2*-mutant xenografts as an attractive alternative for personalized testing, which will ultimately maximize treatment efficacy and minimize toxicity in pediatric oncology patients.

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS FOR SHETA2 IN ORTHOTOPIC MURINE MODEL OF OVARIAN CANCER

PRESENTER: Ankur Sharma

Ankur Sharma¹, Elangovan Thavathiru², Satish K Ramraj², Doris M Benbrook^{2,3}, Sukyung Woo^{1,3}

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Purpose:

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 vivo* chemoprevention activity. The objective in this study is to assess the tissue distribution characteristics of SHetA2 in tumor bearing mice by developing a physiologically-based pharmacokinetic (PBPK) model, thereby providing an insight into SHetA2 tissue exposure and tumor uptake in humans.

Methods:

An orthotopic model of ovarian cancer was chosen to most accurately mimic the ovarian cancer tumor biology and micro-environment in peritoneal cavity. This model involves intraperitoneal injection of SKOV3-luc human ovarian cancer cell lines. Blood and tissue kinetics of SHetA2 were determined in various tissues up to 36 hr following a single oral dose of 60 mg/kg. Plasma and tissue concentrations of SHetA2 were analyzed by a validated HPLC/UV method.

Results:

Following oral administration SHetA2 was absorbed relatively rapidly, reaching a peak plasma concentration of 628 ng/mL at 2 hr, while the tumor concentration achieved during 0.25-4 hr was greater than IC₅₀ values (3 μM or 1,200 ng/mL) for growth inhibition in ovarian cancer cell lines. Oral bioavailability at 60 mg/kg was 12% and plasma terminal half-life was 4.5 hr. SHetA2 distribution in tumor and other tissues was described as perfusion rate-limited compartments. SHetA2 was detected in all tissues up to 36 hr and was partitioned in tissues more as compared to blood. The tissue-to-blood partition coefficient ranged from 1.9 (brain) to 14 (lung) with moderate distribution (1.90-3.82) in brain, tumor, spleen, heart and muscle, and extensive distribution (6.05-14.11) in fallopian tubes/ovaries, kidneys, liver, uterus, skin and lung.

Conclusion:

This PBPK model can be used to predict tissue distribution of SHetA2 in different species, selection of proper time points for tissue collection and can be scaled up to predict the drug exposure at tumor sites or local sites of action in humans. This will facilitate understanding of a relationship between efficacy and PK profile.

**ROLE OF JAK2 AS A DETERMINANT OF RESPONSE TO CANCER IMMUNOTHERAPY IN LUNG
ADENOCARCINOMA**

PRESENTER: Tao Shen

Tao Shen and Jie Wu

Translational Cancer Biology Program, Stephenson Cancer Center, and Department of Pathology,
University of Oklahoma Health Sciences Center

The novel anti-PD-1/PD-L1 immune checkpoint inhibitors are promising new therapies for several types of cancers, including non-small cell lung cancer (NSCLC). The PD-1/PD-L1 blockage therapy allows CD8+ cytotoxic T lymphocytes (CTLs) to destroy tumor cells. However, $\geq 80\%$ of NSCLC patients are not responsive to anti-PD-1 (Nivolumab) or anti-PD-L1 (Pembrolizumab) immunotherapies. A pre-condition for the tumor-specific CTLs to destroy tumor cells is the presentation of MHC class I tumor antigens on the tumor cell surface for CTLs to recognize these tumor cells. Recognition of MHC class I antigens on tumor cells by T cell receptor on CTLs is dominant over the feedback PD-L1/PD-1 immune check point. MHC class I antigen presentation on tumor cells is regulated by the interferon- γ (IFN- γ)-IFNGR1-JAK1/JAK2-STAT1-IRF1 signaling pathway. We found loss of JAK2 occurs most often among components of the IFN- γ -regulated antigen presentation pathway in lung adenocarcinoma. In JAK2 deficient (JAK2^{SS07*}) H1573 NSCLC cells, IFN- γ failed to induce STAT1-mediated LMP2/TAP1 antigen processing machinery (APM) and surface expression of HLA-ABC. Expression of exogenous wildtype JAK2 in H1573 cells restored the MHC class I antigen presentation capability. In contrast, knocking out JAK2 with CRISPER/Cas9 or inhibition of JAK2 with roxolitinib in the JAK2 wildtype A549 and H661 NSCLC cells impaired IFN- γ -induced APM and surface expression of HLA-ABC. These data indicate that JAK2 loss renders lung cancer cells defective in presentation of MHC class I antigen in response to IFN- γ , suggesting that JAK2 deficiency is a mechanism of resistance to anti-PD-1/PD-L1 cancer immunotherapies. Our data also suggest that care must be taken when considering combination of JAK inhibition with T-cell-mediated immunotherapy.

PROFILING DNA REPLICATION TIMING IN ZEBRAFISH EMBRYOS REVEALS DYNAMIC REGULATION DURING DEVELOPMENT AND RELATIONSHIPS WITH COPY NUMBER MUTATIONS

PRESENTER: Joseph Siefert

Joseph Siefert

Oklahoma Medical Research Foundation

DNA replication timing is a remarkably stable trait of any given cell type, yet the mechanisms and determinants of replication timing have remained largely elusive. Changes in the stable patterns of replication timing are observed when embryonic stem cells are differentiated in culture, as well as in multiple types of cancer, but the role replication timing plays in development and disease is not known. Therefore, understanding how replication timing is regulated has implications in both development and human disease. We have generated genome-wide replication timing maps from zebrafish embryos at key stages of development, as well as from primary zebrafish tailfin fibroblasts. We profiled the changes in replication timing that occur throughout vertebrate development and show a gradual shift from a rudimentary unstructured timing program, to a structured mature timing program. Furthermore, a number of acute changes are observed to occur within 1-2 cell cycles that demonstrate developmentally regulated changes in replication timing occur in vivo coincident with differentiation and G1-lengthening. Replication timing correlates with human mutation rates and contributes to mutational heterogeneity in cancer, and here we show the replication timing program in zebrafish highly correlates with copy-number variations, revealing evolutionary conservation of this relationship with mutational frequencies. Ongoing analysis will examine the role replication timing plays in cancer by profiling replication timing changes that occur in a zebrafish model of T-ALL, and will determine if this is a gradual and dynamic process or if it is acutely regulated. This will be done by investigating the replication timing program in non-cancerous T-cells (prior to oncogene activation), pre-cancerous T-cells (after oncogene activation but before tumors develop), and cancerous T-cells, (after tumors develop), and will aid in understanding if replication timing plays a role in transformation. Finally, we have a number of zebrafish mutants that are deficient for proteins we believe to be responsible for replication timing control, and we will investigate the changes in replication timing that occur in these mutants and what effect this has on development and disease.

**HDAC INHIBITION WITH JNJ-26481585 ENDORSE RD3-DEPENDENT CANCER STEM CELL
DIFFERENTIATION**

PRESENTER: Dinesh Babu Somasundaram

Dinesh Babu Somasundaram and Natarajan Aravindan

Department of Radiation Oncology, University of Oklahoma Health Science Center

Recently, we characterized the adaptive stemness and extreme plasticity of neuroblastoma (NB) cancer stem cells (CSCs). Further, new to science, we defined the loss of retinal degeneration protein 3 (RD3) in high-risk NB and identified its novel tumor evolution stabilization function. Moreover our studies identified definitive contribution of HDACs in the evolution of progressive NB. Herein, we investigated the potential of pyrimidyl-hydroxamic acid HDAC inhibitor, Quisinostat in restoring RD3 and NB-CSCs differentiation. Well characterized CD133⁺-CD34⁺ human NB CSCs exposed to increasing concentrations (2.5, 5, 10, 100, 200nM, 1, 2, 4, 8 μ M) of quisinostat were examined for inhibition of HDACs (HDACs 1-11, QPCR analysis), transcriptional (QPCR) and translational (immunoblotting) restoration of RD3, CSCs cell viability (automated trypan exclusion assay) differentiation (real-time live cell imaging) and formation of organized tumorspheres (tumorsphere formation assay). Quisinostat inflicted complete inhibition of NB-CSCs cell viability at 100nM concentration and beyond. QPCR analysis revealed a dose-dependent inhibition of HDACs in NB CSCs with quisinostat. We observed a significant transcriptional/translational restoration of RD3 selectively at 100nM and above of quisinostat treatment. Live-cell imaging demonstrated a dose-dependent -loss of stemness behavior and –increased differentiation of NB CSCs with quisinostat treatment. Tumorsphere formation assay demonstrated complete inhibition of organized tumorspheres at/after 100nM treatment. These results imply that Quisinostat restores RD3 and promotes NB-CSCs differentiation. More importantly, selective dose-dependent specificity of HDAC inhibition by Quisinostat and, restoration of RD3 and regulation of stemness physiognomies at/above 100nM concentrations identifies that HDAC 7 could serve as a critical player in this setting. Taken together, these results for the first time identify the potential of quisinostat in the regulation of NB evolution and with further studies may serve as a potential drug deliverable in the treatment and cure of high-risk NB.

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GOLD NANOPARTICLE FUNCTIONALIZED EXOSOMES A NOVEL ANTI-CANCER THERAPEUTIC DELIVERY SYSTEM FOR CANCER THERAPY

PRESENTER: Akhil Srivastava

Akhil Srivastava^{1,7}, Narsireddy Amreddy^{1,7}, Hogyoun Kim⁵, Rachel Ruskin^{2,7}, Katherine M. Moxley^{2,7}, Danny Dhanasekaran^{3,7}, Shaorong Liu^{6,7}, Si Wu⁶, Yan D. Zhao^{4,7}, Asim B. Abdel-Mageed⁵, Rajagopal Ramesh^{1,7}

Departments of ¹Pathology, ²Gynecologic Oncology, ³Cell Biology and ⁴Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; ⁵Department of Urology, Tulane Cancer Center, Tulane University School of Medicine; ⁶Department of Chemistry and Biochemistry, University of Oklahoma; ⁷Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Chemotherapy is an effective strategy for management of metastatic cancers like lung cancer but is limited in its use due to off-target cytotoxicity. Gold nanoparticles (GNPs) due to their ability to incorporate a variety of targeting and therapeutic molecules are attractive tools that can be exploited for therapeutic purposes. However, current GNP-based treatment like chemotherapy has limitations. Thus, a good cargo delivery system that can circumvent these limitations is critically needed to improve the prognosis for lung cancer patients. Exosomes are submicron sized cellular vesicles shed by all cells and are known to participate in ferrying biomolecules across the biological membranes without eliciting any immune responses. In this study, we developed a novel anti-cancer therapeutic delivery vehicle system (Exo-GNP-Dox), by loading exosomes (Exo) with doxorubicin (Dox) conjugated GNPs (GNP-Dox) by a pH-sensitive hydrazone bond. The average size of exosomes (diameter) used for complexation was 84 nm, as measured by IZON qNano particle analyzer system. The successful formation of vehicle system was confirmed by transmission electron microscopy (TEM). The encapsulation efficiency of Dox in the complex was estimated to be ~80% and drug release kinetics showed 25% release of drug in 24 hrs under acidic condition (pH 5.5). Further to study the uptake of Exo-GNP-Dox, green fluorescence protein (GFP) tagged exosomes loaded with GNP-Dox were added to H1299 lung cancer cells. Fluorescence microscopy imaging and fluorescence intensity measurements were carried out to study their successful cellular uptake. To evaluate the therapeutic efficacy of the Exo-GNP-Dox, H1299 and MRC9 (lung fibroblast) were treated with 5µg equivalent Dox containing Exo-GNP-Dox for 24hrs and 55% and 40% cell death were observed respectively. Interestingly, an increase in cell proliferation was noted in both cell lines, when only exosomes derived from H1299 cells were added, probably because the exosomes originating from cancer cells carry various pro-oncogenesis molecules in their lumen. Hence, exosome derived from normal MRC9 fibroblast cells was used for preparing Exo_(MRC9)-GNP-Dox and its treatment with H1299 cells resulted in 40% cell death. The increase in cell proliferation observed when MRC9 exosomes were added in H1299 cells was negligible. In addition, we observed that Dox toxicity was reduced in Dox-sensitive Human coronary artery smooth muscle cells when it was delivered as Exo-GNP-Dox (30% cell death) compared to toxicities induced by GNP-Dox (63%) and free Dox (77%). This result suggests the limited effect of exosomes based vehicle on non-cancerous cells. Results of the cell viability experiments were confirmed by western blots, which showed Dox induced apoptotic cleavage of caspase 9. Our study results demonstrate the use of exosomes as an amenable drug delivery vehicle for cancer therapy.

4D XACT SCANNER: CONCEPT AND DESIGN

PRESENTER: Shanshan Tang

Shanshan Tang¹, Jian Chen¹, Pratik Samant¹, Yong Chen², Hong Liu¹, Liangzhong Xiang^{1*}

¹Center for Bioengineering and School of Electrical and Computer Engineering, University of Oklahoma,

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We present the concept and design of a new imaging paradigm, X-ray induced acoustic computed tomography (XACT). The X-ray-induced acoustic effect process is intrinsically three-dimensional (3D), as the X-ray induced acoustic waves are spherical in nature and propagate in all directions from their point of generation. A 3D ultrasonic transducer array can then detect the signals and create volumetric images for the object. The advantageous is obvious: a single projection X-ray exposure is sufficient to generate acoustic signals in 3D space. It offers the capability of reducing the radiation dose and improving the imaging speed. The ultimate imaging speed is only limited by the X-ray pulse repetition rate. A theoretical model is developed to analyze the sensitivity of XACT as compared with conventional CT. An XACT imaging system with nanoseconds X-ray pulse is designed to evaluate the X-ray induced acoustic signal generation. Theoretical analysis shows that the X-ray induced acoustic signal is only sensitive to the X-ray absorption. The X-ray induced acoustic pressure variation is proportional to the variation of density and atomic compositions, showing that XACT has the potential capability to quantitatively measure the change of tissue density and tissue composition. This new imaging modality has the potential to revolutionize medical diagnosis and treatment monitoring.

APC CONTROL OF RETINOIC ACID SUPPRESSES IMMUNE CELL MEDIATED INTESTINAL PROLIFERATIVE RESPONSE

PRESENTER: Amanda Templeton

Amanda K. Templeton^{1,2,3,*}, SS Hammoud^{4,*}, Brad Cairns⁵, and David Jones^{1,2,3}

¹Functional and Chemical Genomics Program, Oklahoma Medical Research Foundation, ²Department of Pathology, University of Oklahoma Health Sciences Center, ³Stephenson Cancer Center, University of Oklahoma ⁴Department of Human Genetics, University of Michigan Medical School ⁵Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, *Co-first authors

The prevailing model for adenomatous polyposis coli (APC) tumor suppressor function is centered on its role in antagonizing Wnt/B-catenin mediated colonic proliferation. Our previous studies, however, established a model wherein *APC* mutations in zebrafish embryos results in a failure of intestinal epithelial cell differentiation due to loss of retinoic acid. Surprisingly, the loss of *APC* or retinoic acid (RA) alone in zebrafish embryos was not sufficient to drive nuclear accumulation of B-catenin or intestinal cell proliferation. However, combining *APC* or RA deficiency with a *KRAS* mutation was sufficient to induce nuclear localization of B-catenin and the proliferative response. In contrast, the loss of RA alone in adult zebrafish results in both intestinal differentiation defects and proliferation. We were therefore interested in investigating these seemingly contradictory results. Using adult zebrafish, we show for the first time that following loss of retinoic acid adaptive immune cells (but not innate immune cells) are indirectly required to elicit the proliferative response independent of *Kras* activation. We demonstrate that IL-17 secretion from adaptive immune cells in response to loss of RA predisposes colonic epithelium to inflammation resulting in compromised barrier function, loss of cell polarity, reactivation of a progenitor intestinal program, and proliferation. Importantly, we find in both mouse and human intestinal organoid cultures an evolutionarily shared response with zebrafish of T cell dependent intestinal inflammation and proliferation following loss of RA. Our model demonstrates that loss of retinoic acid causes an increase in inflammatory mediators (Cox2 and Prostaglandins) that induces infiltration of IL-17 secreting T cells. In a feed-forward loop, the IL-17 acts on the primed epithelium to up-regulate proliferative signaling mediators such as Raf and Rac1. Together, these studies provide an important new perspective on the ordering of molecular events that may underlie colon tumor progression.

LIGHT ACTIVATABLE PRODRUG FOR THE COMBINATIONAL TREATMENT OF PDT AND SITE-SPECIFIC CHEMOTHERAPY: PACLITAXEL PRODRUGS

PRESENTER: Pritam Thapa

Pritam Thapa, Mengjie Li, Moses Bio, Pallavi Rajaputra, Yajing Sun, Sukyung Woo, Youngjae You

College of Pharmacy, University of Oklahoma Health Sciences Center

We developed the photoactivatable prodrug of Paclitaxel (PTX) for the combinational treatment of chemo and photodynamic therapy (PDT). PTX causes dose-limiting side effects as other anticancer drugs when administered systemically. On the other hand, PDT suffers from incomplete ablation and subsequent recurrence in part due to the short half-life and poor diffusion rate of singlet oxygen. We prepared a conjugate of PTX with phthalocyanine via a singlet oxygen cleavable linker, as a unique prodrug of PTX, to overcome the problems of PDT and systemic chemotherapy. The PTX prodrug was evaluated for tubulin polymerization, the release rate of PTX from prodrug upon illumination at 690 nm, stability in complete media, and the combination effect in killing ovarian cancer cells *in vitro* (SKOV-3). The PTX prodrug did not enhance the tubulin polymerization unlike PTX. While it was stable in the media under dark, it rapidly released PTX upon illumination with far-red light: > 90% release in 30 min. The prodrug showed much lower dark toxicity compared to PTX. When illuminated with 690 nm at 5.6 mW/cm², the prodrug showed very potent phototoxicity: IC₅₀ = 3.9 nM, through the combinational effect of PDT and PTX. In conclusion, we found that the PTX prodrug have desired properties as light-activatable prodrug expressing the combinational effect of PDT and local PTX chemotherapy. Animal study is underway to evaluate the antitumor effect of the PTX prodrug. All experiments were performed in the Department of Pharmaceutical Sciences, University of Oklahoma Health Sciences Center.

GTSE1 IS A NOVEL REGULATOR OF CHROMOSOME ALIGNMENT DURING MITOSIS

PRESENTER: Aaron Tipton

Aaron R. Tipton, John R. Daum and Gary J. Gorbsky

Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation

Cancer is characterized by abnormal and excessive cell division. Defects in the movement or distribution of chromosomes during meiosis and mitosis is a major cause of congenital birth defects and a contributor to increased malignancy in cancer. During prometaphase and metaphase, non-kinetochore microtubules interact with chromosome arms to generate polar ejection forces that are critical for chromosome movement. 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. Cells depleted of GTSE1 fail to properly align chromosomes, are delayed in mitotic progression, form multipolar spindles and aberrantly exit from mitosis. GTSE1 binds microtubules in at least two ways, intrinsic binding with the microtubule lattice and binding to the microtubule plus-end tracking protein EB1. EB1 binding by GTSE1 is switched off during prometaphase and metaphase but GTSE1 is retained on spindle microtubules. We have identified a 151 amino acid section of GTSE1 that does not include the EB1-binding SxIP motifs but is necessary for binding to spindle and interphase microtubules. Functionally, GTSE1 enhances Aurora B kinase activity specifically on chromosome arms but not at centromeres, as depletion of GTSE1 decreases phosphorylation of S10 on Histone H3 after nuclear envelope breakdown but only mildly increases phosphorylation of S7 on the centromeric protein, CENP-A. GTSE1-stimulated Aurora B activity likely modulates arm-microtubule interactions and polar ejection forces through regulation of chromokinesins as inhibition of Aurora B activity decreases Kif4A levels on mitotic chromosomes. Similarly, depletion of GTSE1 reduces polar ejection forces in Monastrol treated cells and reduces Kif4A levels on chromosomes. However, we cannot rule out a potential role in regulating microtubule depolymerases, microtubule stabilizers or microtubule dynamics itself. At anaphase onset, polar ejection forces are switched off facilitating chromatid movement to the poles.

SIGNIFICANT LIFE EXTENSION BY TEN PERCENT DIETARY RESTRICTION

PRESENTER: Archana Unnikrishnan

Archana Unnikrishnan¹, Steven N. Austad³, Yuji Ikeno⁴, Roger J. McCarter⁵ and Arlan Richardson^{1,2}

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Work was performed at: Department of Pathology, University of Texas Health Science Center at San Antonio.

Although it is well documented that dietary restriction (DR) increases the lifespan of rodents and other animals, this effect is observed at relatively high levels of DR, usually feeding rodents 40% less than that consumed by rodents fed *ad libitum* (AL). It is generally assumed that lower levels of DR will have a lesser impact on lifespan; however, there is very little data on the effect of low levels of DR on lifespan. In this study, we show that 10% DR increased lifespan to almost the same extent as 40% DR. While both 10% and 40% DR show similar changes in non-neoplastic lesions, 10% DR had no significant effect on the incidence of neoplasia (except for pituitary adenoma) while rats fed 40% DR showed a significant reduction (40%) in neoplasia. These data clearly demonstrate that the lifespan of F344 rats does not increase linearly with the level of DR; rather, they show that even a small level of DR can have a major impact on lifespan. Our study has important translational implications because it suggests that a modest reduction in calories might have significant health benefits for humans.

PHOTOTHERMAL ABLATION OF BLADDER CANCER USING PHOSPHATIDYLSERINE TARGETED CARBON NANOTUBES

PRESENTER: Needa Virani

Needa Virani¹, Carole Davis², Paul Hauser², Robert Hurst², Joel Slaton², Roger Harrison¹

¹Biomedical Engineering Center and School of Chemical, Biological and Materials Engineering, University of Oklahoma; ²Department of Urology, University of Oklahoma Health Sciences Center

About 70-80% of patients with bladder cancer have stage I superficial tumors that are treated with a transurethral resection; however even after surgery, the recurrence rate is about 80%. This high incidence of recurrence is believed to be due to the residual tumor left behind in at least 27-62% of patients. The increased risk of relapse is also associated with a higher chance of progression into more muscle-invasive and metastatic tumors. 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 annexin V (AV). Single-walled carbon nanotubes (SWNTs) are known to 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 focuses on treating superficial bladder cancer via AV surface-modified SWNTs for thermal ablation.

In vitro studies were conducted on mouse bladder cancer (MB49) and human bladder cancer (J82) cell lines. *In vitro* binding studies confirmed a strong binding affinity of AV to MB49 ($K_d = 4.14 \pm 1.28$ nM) and J82 ($K_d = 0.38 \pm 0.20$ nM) cells. Subtoxic levels of docetaxel increased the number of bound AVs per MB49 cell but had no effect on the J82 cells. Inducing SWNT-AV heating due to NIR confirmed significant cancer cell death as compared to untreated controls for both cell lines. The *in vitro* tests provided statistically significant 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 in the various organs. NIR power tolerance tests with a 360° radiating fiber confirmed that no healthy tissue damage occurred at 50 J/cm² as determined via H&E analysis. *In vivo* treatment of MB49 bladder cancer bearing mice with SWNT-AV and NIR combination therapy resulted in significant decrease in tumor size.

SWNT-AVs have proven to preferentially target bladder cancer cells and in conjunction with NIR 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 therapeutic option for recurrent superficial bladder cancers.

TETRASPANIN CD151 IN COLON CANCER: A FRIEND OR FOE?

PRESENTER: Ge Wang

Ge Wang, Younghwa Song, Jun Chung, Xin A. Zhang

Department of Physiology, Stephenson Cancer Center, University of Oklahoma Health Science Center

Tetraspanin CD151 is a trans-membrane protein containing two extracellular loops and two short cytoplasmic tails. It has been implicated that CD151 promotes tumor metastasis and invasion. Although the mechanism still remains unclear, it has been well documented the function of CD151 is associated with its binding integrins and tetraspanins. However, rare studies have been reported about the role and mechanism of CD151 in regulating the epithelial mesenchymal transition (EMT), which is considered as an important process before cancer cells undergo metastasis and invasion.

Here we reported CD151 contributed to cancer migration and invasion in both SW480 and HT29 colon cancer cell lines, which was in extracellular matrix dependent manner. However, cell matrix adhesion assay demonstrated that CD151 could stable cell adhesion. Interestingly, our finding revealed EMT markers and other proteins involved in the EMT process were strongly up-regulated upon CD151 silencing, which implied CD151 might suppress colon cancer progression via regulating the EMT. Although sphere formation assay and stem cell population analysis by flow cytometry showed the stemness of colon cancer cells was not significantly altered after silencing CD151, our present findings suggest CD151 may have dual function in the development of colon cancer.

The role of CD151 in colon cancer needs to be further explored by *in vivo* studies, as well as elucidated by mechanism studies.

CARCINOGENIC AIR POLLUTANTS EMITTED FROM MICRO-MANUFACTURING PROCESSES

PRESENTER: Jun Wang

Jun Wang¹, Kevin O'Neil¹, Joshua Pearce²

¹Department of Occupational and Environmental Health, College of Public Health, University of Oklahoma Health Sciences Center; ²Department of Material Sciences and Engineering, College of Engineering, Michigan Technological University

Micro-manufacturing is a process that involving downloading, printing, assembling, and finalizing the products by end users, in contrary of the traditional factory-user mode. Micro-manufacturing requires the users have access to low-cost plastic and metal printers, engravers, and cutters. All these equipment rely on the high-temperature process to remold the filaments or consumables to a pre-designed shape. Injection of melted thermoplastic polymers which are then laid down in layers to achieve a pre-designed shape. The heated process raises concerns of potential carcinogenic aerosol and volatile organic compounds (VOCs) emission and exposure, and little is known about their characteristics. The lowered cost of micro-manufacturing devices brought more applications to places where sufficient ventilation is often lacking. The objective of this study was to characterize aerosol and VOCs generated from a series of low-cost micro-manufacturing equipment. A thermoplastic-based 3-D printer, a stainless steel metal 3-D printer, and a laser engraver and cutter were used in the study. A scanning mobility particle sizer and aerodynamic particle sizer were employed to measure the particle size distribution in the fine (<0.5 μm) and coarse ranges (<0.5~20 μm). Real-time VOCs concentration was monitored by a photoionization sensor and sampled on a thermal desorption tube and analyzed by thermal desorption gas chromatography mass spectrometry. The results showed a high emission (0.1×10^8 to 1.2×10^{10} #/min) of ultrafine particles (41.4~83.0 nm mode size). Total VOC concentration followed a first-order buildup, with predominant VOC species from breakdown and reaction products of the filaments, such as styrene for the ABS-based filaments. The findings suggest that although the VOC concentrations were much lower than occupational exposure limits, ultrafine particles could still lead to health risks for low-cost micro-manufacturing users.

QUANTITATIVE CHARACTERIZATION OF THE MICROBUBBLES CONCENTRATION BY USING A HIGH-ENERGY IN-LINE PHASE CONTRAST TOMOSYNTHESIS PROTOTYPE: A PRELIMINARY PHANTOM STUDY

PRESENTER: Di Wu

¹Di Wu, ¹Muhammad U. Ghani, ¹Molly D. Wong, ¹Yuhua Li, ²Kai Yang, ³Wei R. Chen, ¹Bin Zheng, and ¹Hong Liu

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The purpose of this study is to demonstrate the feasibility of using a high-energy in-line phase contrast tomosynthesis system to quantitatively imaging microbubbles in a tissue simulating phantom under a limited radiation dose. The imaging prototype used in the investigation was an in-line phase contrast tomosynthesis system operated under 120 kVp tube voltage and 0.5 mA tube current. A prime beam filter made of 2.3 mm Cu, 0.8 mm Pb and 1.0 mm Al was employed to obtain as large as possible portion of x-ray photon energy higher than 60 keV. The tissue simulating phantom was built by three acrylic slabs and a wax slab to mimic a 40 mm thick compressed breast. There were two tiny-sized structures with 1 mm depth engraved on the two different layers. The microbubble suspensions with different concentrations were injected into those tiny structures. The in-line phase contrast angular projections acquired were used to reconstruct the in-plane slices of the tiny structures on different layers. The CNRs vs microbubble concentrations were investigated. As the result, the microbubble suspensions were clearly visible, showing higher CNR when compared with the areas with no microbubble. Furthermore, a monotonously increasing relation between CNRs and microbubble concentrations was observed after calculating the area CNR of the phase contrast tomosynthesis slices.

Key Words: High-energy in-line phase contrast tomosynthesis, Microbubble, CNR, Quantitative characterization

FORMULATION OF SHETA2 NANOPARTICLES FOR THE TREATMENT OF LUNG CANCER

PRESENTER: Hooman Yari

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INTRODUCTION

Non-small cell lung carcinoma is the leading cause of death by cancer in the U.S [1]. SHetA2 is a poorly water-soluble heteroarotinoid with a low oral bioavailability that induces apoptosis in several cancer cell lines, including A549, H157, H1792, H460, 1299 and Calu-1 [1-4].

We hypothesize that pulmonary delivery of SHetA2 NPs will result in significantly higher concentrations of the drug in lungs due to the direct deposition of the drug at the target organ and eliminating the need for the absorption of the drug from the systemic circulation and also by increasing the solubility of the drug and enhanced permeability and retention (EPR) effect. This study aims to optimize the size of nanoparticles that will be used to manufacture respirable particles (1-5 μ m) by spray drying in future studies.

METHODS

Poly (lactic-co-glycolic acid) (PLGA) was used as a model compound to optimize the preparation of NPs through the solvent evaporation method. The parameters including polymer concentration, sonication power and surfactant concentration (polyvinyl alcohol, PVA) were optimized with a 2³ factorial design (Design-Expert® software, DoE) to yield particles with a geometric diameter (d_g) of approximately 200 nm and a volume diameter (d_v) close to d_g . Morphology of the NPs was evaluated by Transmission Electron Microscopy (TEM). The d_v and lognormal GSD of particles was measured by Dynamic Light Scattering, and d_g was determined by measuring at least 100 NPs from the TEM images using Image J software. The conditions resulted in the desired size of PLGA NPs were used to prepare SHetA2 NPs. However, the d_v of SHetA2 NP was not considered equivocal due to deviation of the particles morphology from spherical shape.

RESULTS AND DISCUSSION

Process parameters and characteristics of NPs are shown in Table 1. The best set of conditions yielded NPs with $d_v=243.87$ nm, GSD= 1.36 and $d_g= 144.28$ nm. It is also notable that the size distributions of dried NPs were narrower than that of particles in solution.

Table 1. Experimental variables optimized for preparation of PLGA and SHetA2 NPs

Exp. #	Sonication Power (W)	Polymer/Drug Conc. (mg/ml)	PVA Conc. (w/v %)	PLGA			SHetA2		
				dv (nm)	Lognormal GSD	dg (nm)	GSD	dg (nm)	GSD
1	10	50	3	270.13	1.61	-	-	-	-
2	24	50	3	346.44	1.64	-	-	-	-
3	10	10	3	259.14	1.56	-	-	-	-
4	10	50	1	1023.4	1.73	180.49	4.01	283.9	2.38
5	24	10	3	243.87	1.36	144.28	2.74	261.3	2.73
6	24	10	1	325.47	1.51	-	-	-	-
7	10	10	1	275.85	1.53	-	-	-	-
8	24	50	1	571.27	1.68	-	-	-	-

TEM analysis of PLGA NPs revealed a semi-spherical morphology (data not shown), while SHetA2 NPs were long and short needle shaped crystals. These different morphologies may be due to differences in the molecular weight, the viscosity, hydrophilicity, density, and chemical structure of the drug and the polymer.

The SHetA2 NPs prepared with the best set of conditions for PLGA (experiments 4 and 5) resulted in NPs with sizes (261.34 nm and 283.92 nm) and distributions (GSD= 2.38-2.73) acceptable for further spray drying.

CONCLUSIONS

We obtained SHetA2 NPs with suitable sizes (approximately 200-300nm) and distributions (GSD <3) for further spray drying. We plan to mix these NPs in solution with a sugar or amino acid prior to spray drying to obtain powders in respirable sizes for further evaluation in an animal model of lung cancer.

**SYNERGISTIC EFFECTS OF GLYCATED CHITOSAN WITH HIGH-INTENSITY FOCUSED ULTRASOUND
ON SUPPRESSION OF METASTASES IN A SYNGENEIC BREAST TUMOR MODEL**

PRESENTER: Feifan Zhou

Feifan Zhou, Aamr Hasanjee, Wei R. Chen

Biophotonics Research Laboratory, Center for Interdisciplinary Biomedical Education and Research,
University of Central Oklahoma

Stimulation of the host immune system is crucial in cancer treatment. In particular, nonspecific immunotherapies, when combined with other traditional therapies such as radiation and chemotherapy, may induce immunity against primary and metastatic tumors. In this study, we demonstrate that a novel, non-toxic immunoadjuvant, glycated chitosan (GC), decreases the motility and invasion of mammalian breast cancer cells in vitro and in vivo. Lung metastatic ratios were reduced in 4T1 tumor bearing mice when intratumoral GC injection was combined with local high-intensity focused ultrasound (HIFU) treatment. We postulate that this treatment modality stimulates the host immune system to combat cancer cells, as macrophage accumulation in tumor lesions was detected after GC-HIFU treatment. In addition, plasma collected from GC-HIFU-treated tumor-bearing mice exhibited tumor-specific cytotoxicity. We also investigated the effect of GC on epithelial–mesenchymal transition-related markers. Our results showed that GC decreased the expression of Twist-1 and Slug, proto-oncogenes commonly implicated in metastasis. Epithelial-cadherin, which is regulated by these genes, was also upregulated. Taken together, our current data suggest that GC alone can reduce cancer cell motility and invasion, whereas GC-HIFU treatment can induce immune responses to suppress tumor metastasis in vivo.

ELTD1 AS A NOVEL ANTIBODY THERAPY AGAINST GLIOMAS

PRESENTER: Jadith Ziegler

Jadith Ziegler^{1,2}, Nataliya Smith¹, Debra Saunders¹, Blake Evans¹, James Battiste⁴, Michael Sughrue⁵, Paul Tompkins⁵, Jake Sutton¹, Megan Lerner², Patricia Coutinho de Souza⁶, Kar-Ming Fung³, Johnathan Wren¹, and Rheel Towner^{1,2,3}

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Gliomas consist of up to 80% of malignant brain tumors that are invasive and typically resistant to radiotherapy and chemotherapy. Finding biomarkers to high-grade gliomas can enable better diagnosis and therapeutic intervention for this disease. We have identified ELTD1 as a biomarker for high-grade human gliomas. Here, we report our findings *in vivo* using anti-ELTD1 (at two different concentrations), Avastin®, and IgG antibodies on human G55 xenograft glioma models. Using MRI, we investigate tumor growth, perfusion, tumor blood flow, and microvessel density changes in mice. In addition, survival rates were measured.

Mice were implanted with human G55 xenograft glioma cells and were left untreated, administered anti-ELTD1, (1 mg/kg or 2 mg/kg every 2-3 days) Avastin (2 mg/kg every 2-3 days) or IgG (1 mg/kg every 2-3 days). MRI experiments were performed to assess tumor growth and calculate tumor volumes. In order to assess angiogenesis, representative histology slides were obtained and stained for blood vessels using CD34 antibody and microvessel density (MVD) was then calculated. Finally, cerebral blood flow rates from MR perfusion imaging was obtained as well as MR angiography to determine tumor blood volume from mice in each group.

Our results show a significant decrease in tumor volumes and increase in percent survival for mice treated with 1 mg/kg and 2 mg/kg of ELTD1 antibody compared to untreated mice and IgG treated mice. Mice also had an increase in perfusion, decrease in tumor blood volume and decrease in MVD. Anti-ELTD1 antibody therapy reduced tumor volumes, prolonged life, and overall decreased angiogenesis in our mouse model. Anti-ELTD1 therapy may be an ideal anti-angiogenic treatment for high-grade gliomas.

Shared Resources

Biospecimen Acquisition Core and Bank

Services Offered

The Stephenson Biospecimen Acquisition Core and Bank provides the following services to Stephenson members and other interested investigators:

- Specimen procurement for prospective and archived materials
- Storage of human tissue, blood and other types of specimens
- Distribution of fresh, frozen and paraffin-embedded specimens to approved investigators
- Prospective and retrospective annotation of specimens with demographic, pathological staging and clinical information
- Consultation with designated pathologists and researchers for protocol development and specimen evaluation

Types and availability of samples differ by organ type. Users are encouraged to contact the Core for more information. If appropriate specimens are not available in the Biospecimen Bank, Core staff will help facilitate the procurement of specimens from the appropriate sources. The Core also supports protocol-driven specimen collection for specific research projects.

Contact Information

For more information please contact:
Biospecimen Acquisition Core and Bank
Email: SCC-Biospecimen-Core@ouhsc.edu
Phone: 405-271-1688

Biostatistics Core

About the Core

The Biostatistics Core at the Stephenson Cancer Center provides Stephenson members with statistical consultation and collaboration on protocol and grant development, manuscript preparation, and other scholarly activities that need statistical support.

Services Offered

- Consultation with a biostatistician and / or epidemiologist to discuss project aims and feasibility
- Input on research design or statistical considerations (sampling plans, sample size justification, analytic plan, etc.)
- Statistical analysis of data
- Data management, processing, or entry
- Survey development and administration

Faculty and Expertise

Sara Vesely, PhD

Role: Director, Biostatistics Core

Focus: Hematology/Oncology

Statistical Expertise: Clinical Trials Methods; Data and Safety Monitoring; Longitudinal Data Analysis; Prospective Cohort Registries

Daniel Zhao, PhD

Role: Associate Director, Biostatistics Core

Focus: Cancer Biology, Experimental Therapeutics

Statistical Expertise: Adaptive Research Designs; Bayesian Analysis; Brain Imaging; Clinical Trials in Oncology, Urology, and Neuroscience; Genomics; Longitudinal Analysis; Misclassification; Multiple Testing; Nonparametrics; Structural Equation Modeling

Kai Ding, PhD

Role: Biostatistics Faculty

Focus: GI Cancers, Women's Cancer, Cancer Health Disparities

Statistical Expertise: Time-to-event Analysis; Measurement Error (Limit of Detection) Problems in Biomarker Research; Missing Data Analysis Methods; Systematic Review and Meta-analysis; Semiparametric Modeling; High Dimensional Data

Contact Information

For more information please contact:

Biostatistics Core at SCC-Biostat@ouhsc.edu

Cancer Tissue Pathology Core

About the Core

The Cancer Tissue Pathology Core provides high-quality tissue processing, histology and staining services to Stephenson members and other investigators. The Core provides tissue processing, embedding, sectioning, histochemical staining of mounted slides, immunohistochemical (IHC) staining for paraffin embedded and frozen tissues, immunocytochemical (ICC) staining for cultured cells (as tissue sections or cytopsin slides), evaluation of new antibodies for IHC staining, enzyme histochemistry and special staining. The Core also provides defined analyses including RNA / DNA preparation, reverse transcription and cDNA synthesis from total RNA, construction, staining and analysis of tissue microarrays, and construction and analysis of reverse proteomics array from user-defined biospecimens. The Core is flexible to accommodate the development of new techniques and expanding its services based on the research requirements of Stephenson members and other investigators.

Services Offered

- [Histology and Immunohistochemistry](#)
- [Tissue and Cell lines Microarray \(TMA\)](#)
- [Digitized Slides and Image Analysis](#)
- [Photographic and Imaging Services](#)
- [Molecular Biology Services; RNAscope, TUNEL](#)

Equipment

- [Semi-enclosed Benchtop Tissue Processor Leica TP1020](#)
- [Modular Tissue Embedding Center Leica EC1150](#)
- [Veridiam Tissue Arrayer](#)
- [Rotary Microtome Leica RM2255](#)
- [Leica CM1950 Cryostat](#)
- [Leica BOND-III](#)
- [Leica ST5020 Multistainer](#)
- [Nikon NI-Upright microscope](#)

Contact Information

For more information please contact:
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Phone: (405) 271-6890

Cancer Functional Genomics Core

About the Core

The Cancer Functional Genomics Core offers cutting-edge technology that can provide extremely accurate and reliable expression data to support drug discovery research. The Agilent SureScan Microarray Scanner system provides the ability to scan genome-wide microarray profiles. Quality assessment of purified RNA and DNA are provided by the Biorad Experion™ Automated Electrophoresis Station and Agilent 2100 Bioanalyzer. The Biorad CFX96™ Touch Real-Time PCR Detection System provides highly-reliable quantitative individual gene transcription profiling. Bio-Rad QX100 Droplet Digital PCR is useful to detect the absolute copy number of genes. Functional analysis of proteins using biochemical assay can be evaluated with the Perkin Elmer EnVision® Multilabel Reader. The Operetta from Perkin Elmer can provide high-resolution images for screening drugs under live and fixed cell context. Live cell metabolic changes with respect to oxygen consumption and pH change due to respiration can be determined using the Xfe 96 extracellular flux analyzer from Seahorse.

Services Offered

- Array Scanning and Quantification
- Reverse Proteomics Array
- Real-Time PCR
- Multimodal Assay Screening
- DNA / RNA / Protein Purity Analysis on a Chip
- High-content Drug Screening
- Metabolic Analysis of Live Cells
- Absolute Allele Copy Number Determination
- Colony forming units determination

Equipment

- [Agilent SureScan Microarray Scanner System](#)
- [Biorad CFX96™ Touch Real-Time PCR Detection System](#)
- [Perkin Elmer EnVision® Multilabel Reader](#)
- [Biorad Experion™ Automated Electrophoresis Station and Agilent 2100 Bioanalyzer](#)
- [Arrayit Nanoprint™ Microarray Printing](#)
- [XFe 96 Extracellular Flux Analyzer](#)
- [Biorad QX100 Droplet Digital PCR](#)
- [Perkin Elmer Operetta](#)
- [Janus Automated Workstation](#)
- Arrayit Spotware Colormetric Microarray Scanner
- Optronix GelCount system

Contact Information

For more information please contact:

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Director of Research Core Operations

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Phone: 405-271-6890

Clinical Trials Office

About the Core

The Clinical Trials Office (CTO) provides the support necessary to successfully conduct clinical research at the Stephenson Cancer Center. The goal of the CTO is to promote, support, and manage high-quality clinical research aimed at advancing cancer therapy and quality of life for cancer patients. The CTO is dedicated to excellence in regulatory compliance, data integrity, and patient safety in all of its operations.

Services Offered

- Regulatory submission and monitoring
- Protocol development
- Budget development and contract negotiation
- Screening and enrollment of eligible patients
- Data collection and monitoring
- Adverse event reporting
- Coordination of patient treatment on research study
- Biospecimen acquisition
- Training and education of staff
- Clinical research information systems management
- Quality assurance
- Protocol review and monitoring
- Data Safety Management Plan

Protocol Submission, Review, and Monitoring Process

The Protocol Review and Monitoring Committee (PRMC) oversees the submission, review, and monitoring of all clinical trial protocols at the Stephenson Cancer Center. The PRMC is comprised of three sub-committees: the Scientific Review Committee, the Protocol Monitoring Committee, and the Data and Safety Monitoring Committee. In addition, all new protocols are reviewed by a Clinical Research Disease Site Group.

Contact Information

For more information please contact:

Administrative Office

Email: SCC-Clinical-Trials-Office@ouhsc.edu

Phone: 405-271-8777

Molecular Imaging Core

About the Core

The Molecular Imaging Core provides non-invasive optical imaging services to Stephenson members and other investigators.

Services Offered

- Training and consultation
- Preclinical tumor models
- Experimental design and data analysis

Equipment

- IVIS Spectrum Imaging System: Provides a wide range of imaging capabilities including bioluminescence, fluorescence, and near-infrared imaging with 3D anatomical overlay
- Carestream In-Vivo Xtreme Imaging System: Specifically designed for researchers seeking high-sensitivity luminescence, fluorescence, radioisotopic, and radiographic imaging
- Vevo 2100 Ultrasound Imaging Machine: Provides a high-frequency, high-resolution digital imaging platform with linear array technology and Color Doppler Mode
- Leica Fluorescence Stereo Microscope
- INVIVO 400 and 500 Hypoxia Workstations
- Molecularly Tagged Cancer Cell Lines

Contact Information

For more information please contact:

Rajagopal Ramesh, PhD

Director, Molecular Imaging Core

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OUHSC Core Facilities

About the Cores

The Laboratory for Molecular Biology and Cytometry Research is a state of the art facility offering a variety of services in the areas of DNA sequencing/genomics, mass spectrometry/ proteomics and flow cytometry and imaging. The LMBCR is a University Core Facility under the direction of Dr. Allison Gillaspay, Department of Microbiology and Immunology. The main focus of the core laboratory is to facilitate research by offering specialized technology and expertise on a fee for service basis. The LMBCR accepts samples from any researcher in need of the available technology and Dr. Gillaspay and facility personnel are available to consult with PIs, Post Docs, and Graduate students in regards to experimental design and use of the core facility technology at any time.

Services Offered

- DNA Sequencing/Genomics
- Flow Cytometry and Imaging
- Mass Spectrometry/Proteomics

Contact Information

Laboratory for Molecular Biology and Cytometry Research
975 NE 10th Street, BRC1106
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Flow Cytometry and Imaging information
Email: cytometry-support@ouhsc.edu

Mass Spectrometry and Proteomics information
Email: lmocr_help@ouhsc.edu

For additional inquiries:
Dr. Allison Gillaspay, Director
Email: allison-gillaspay@ouhsc.edu
Phone: 405-271-2337 (ext. 1)

Proposal Services

About the Core

The Proposal Services Core is a service that is available to all Stephenson Cancer Center members to provide support with grant proposal preparation and submission.

Proposal preparation services include:

- Locating application packages and forms
- Ensuring adherence to and interpreting of proposal guidelines
- Constructing proposal budgets and budget justifications
- Formatting proposal documents
- Coordinating with internal and external collaborators
- Obtaining institutional letters of support
- Completing and obtaining signatures on institutional routing forms

Proposal submission services include:

- Coordination of review and submission with institutional grant offices
- Submission of electronically submitted proposals (when access can be granted to Proposal Services staff)
- Assembly of paper submission
- Coordination of mail courier service for paper submissions

Contact Information

For more information contact:

Proposal Services

Email: SCC-PM@ouhsc.edu

Phone: 405-271-1878

Walk In: Stephenson Cancer Center
800 N.E. 10th Street, Suite 5011,
Oklahoma City, OK 73104