CANCER RESEARCH SYMPOSIUM

JANUARY 30, 2015

Friday, January 30, 2015

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 2015 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 14 Highlights

With support from the Oklahoma TSET Cancer Research Program the Stephenson Cancer Center accomplished the following in FY 14:

- Increased cancer center membership by 21% (152 to 184 members) at seven academic institutions across Oklahoma
- Recruited four new cancer researchers to Oklahoma
- Secured $31.3 million in total grant funding related to cancer and tobacco prevention and control research
- Funded 8 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 30 research seminar speakers
- Hosted its 3rd Annual statewide Cancer Research Symposium that brought together over 250 researchers from around the state
- Hosted eight undergraduate students from five different universities for a summer cancer research experience
- Opened 142 new cancer clinical trials
- Enrolled 755 patients to interventional clinical trials
- Enrolled 442 patients to cancer therapeutic trials
- Opened 24 new Phase I and Phase I/II clinical trials
- Enrolled 133 patients to Phase I clinical trials
- Received a five-year $6.1 million Lead Academic Participating Site grant from the National Cancer Institute to support the SCC's nationally-recognized clinical trials research program. The SCC was one of 30 Lead Academic Sites designated nationally, and the only non-NCI designated center selected.
- Implemented initiatives with the Oklahoma Medical Research Foundation and OU Norman to jointly recruit cancer investigators and develop joint Shared Resources to support researchers

Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Research Center (OTRC) for co-sponsoring the 2015 Stephenson Cancer Research Symposium

About the Oklahoma Tobacco Research Center:

The mission of the Oklahoma Tobacco Research Center (OTRC) is to reduce the burden of tobacco-related health problems in Oklahoma by stimulating the generation and dissemination of knowledge and the implementation and diffusion of effective practices. To achieve this mission, the OTRC engages local, state, tribal and national partners to address the following goals:

1. Facilitating research that advances the prevention and treatment of tobacco use and tobacco-related health problems.

2. Facilitating the dissemination and exchange of knowledge relevant to the reduction of tobacco use and tobacco-related health problems.

3. Fostering the implementation and diffusion of evidence-based practices relevant to the prevention and treatment of tobacco use and tobacco-related health problems.

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:	D. Robert McCaffree, MD
OTRC Co-Directors:	Laura Beebe, PhD, Steven Gillaspy, PhD, Theodore Wagener, PhD.
Program Coordinator:	Laura DeLongy

Contact Information:
Oklahoma Tobacco Research Center
Stephenson Cancer Center
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OTRC OKLAHOMA TOBACCO RESEARCH CENTER Stephenson Cancer Center

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Cancer Research Symposium Schedule at a Glance

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10:30 - 10:45 a.m.	Break
10:45 - 12:05 p.m.	**Concurrent Session III**
12:05 - 1:35 p.m.	Lunch and Poster Viewing
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3:10 - 4:30 p.m.	**Concurrent Session V**
4:30 - 4:45 p.m.	Transition
4:45 - 5:00 p.m.	**Closing Remarks and Awards**
5:00 - 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)

8:30-9:30 a.m. CONCURRENT SESSION I

B / T / C	**BASIC MECHANISMS AND THERAPEUTIC DEVELOPMENT - PART I** Moderator: Christopher West, PhD	Level Two Auditorium
8:30-8:50	HISTONE DEMETHYLASE JMJD2A: A NOVEL ONCOGENIC PLAYER IN PROSTATE CANCER Ralf Janknecht, PhD Department of Cell Biology University of Oklahoma Health Sciences Center	
8:50-9:10	FINALLY—EFFECTIVE USE OF CANCER STROMA AS A THERAPEUTIC TARGET Kenneth W. Jackson, PhD Department of Microbiology & Immunology University of Oklahoma Health Sciences Center	
9:10-9:30	CNS INVASION BY T CELL LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA J. Kimble Frazer, MD, PhD Department of Pediatrics University of Oklahoma Health Sciences Center	
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9:30-10:30 a.m. CONCURRENT SESSION II

B / T / C	**BASIC MECHANISMS AND THERAPEUTIC DEVELOPMENT – PART II** Moderator: Lawrence Rothblum, PhD	Level Two Auditorium
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9:50-10:10	MECHNISMS OF MIGRATION AND INVASION OF GLIOBLASTOMA MIGRATION James Battiste, MD, PhD Department of Neurology University of Oklahoma Health Sciences Center	
10:10-10:30	DISCUSSION	
CHD	**TRANSLATIONAL THINK TANK: PREVENTION OF HPV-ASSOCIATED CANCER IN OKLAHOMA** Moderator: Mark Doescher, MD, MSPH	Level B B3
9:30-10:30	OVERVIEW Paul Darden, MD Department of Pediatrics University of Oklahoma Health Sciences Center	
	DISCUSSION: IDENTIFYING STRATEGIES TO REDUCE THE BURDEN OF HPV IN OKLAHOMA: RESEARCH, CLINICIANS, AND COMMUNITY PARTNERS	

10:45-12:05 p.m. CONCURRENT SESSION III

B / T / C	**DISEASE SITES AND COLLABORATIVE SCIENCE – PART I** Moderator: Dave Jones, PhD	Level Two Auditorium
10:45-11:05	BMI-1 REGULATES CELLULAR BIOENERGETICS BY STABILIZING MITOCHONDRIAL TRANSCRIPTS Soumyajit Banerjee Mustafi, PhD Stephenson Cancer Center	

University of Oklahoma Health Sciences Center

11:05-11:25 RON KINASE AS A NEW TARGET FOR OSTEOLYTIC BONE METASTASIS: PRE-CLINICAL DATA AND PLANS FOR CLINICAL TRANSLATION
Alana Welm, PhD
Immunobiology and Cancer Research
Oklahoma Medical Research Foundation

11:25-11:45 EPSIN IN CANCER DEVELOPMENT AND PROGRESSION
Hong Chen, PhD
Cardiovascular Biology Research
Oklahoma Medical Research Foundation

11:45-12:05 DISCUSSION

CHD **SYSTEMS CHANGE FOR SMOKING CESSATION: OPPORTUNITIES FOR RESEARCH** Level B B3
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Stephen Gillaspy, PhD
Department of Pediatrics
University of Oklahoma Health Sciences Center

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Heather Summers, MS, RN
Chickasaw Nation

Joy Leuthard, MS, LSWA
Oklahoma Hospital Association

11:25-12:05 DISCUSSION

1:35-2:55 p.m. CONCURRENT SESSION IV

B / T / C **DISEASE SITES AND COLLABORATIVE SCIENCE – PART II** Level Two
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CV Rao, PhD
Department of Internal Medicine
University of Oklahoma Health Sciences Center
Center for Cancer Prevention and Drug Development
Stephenson Cancer Center

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Lijun Xia, MD, PhD
Cardiovascular Biology Research Program
Oklahoma Medical Research Foundation
Department of Biochemistry and Molecular Biology
University of Oklahoma Health Sciences Center

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Min Li, PhD
Department of Medicine, Department of Surgery
University of Oklahoma Health Sciences Center

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Stephenson Caner Center
University of Oklahoma Health Sciences Center

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Dorothy A. Rhoades, MD
Department of Internal Medicine
University of Oklahoma Health Sciences Center

1:55-2:15 ARE E-CIGARETTES AND OTHER MODIFIED RISK TOBACCO PRODUCTS GATEWAYS TO MORE HARMFUL TOBACCO USE?
Ted Wagener, PhD
Department of Pediatrics
University of Oklahoma Health Sciences Center

2:15-2:35 DUAL USERS CALLING A STATE QUITLINE: WHAT DO THEY DO AND WHAT DO THEY WANT?
Ted Wagener, PhD
Department of Pediatrics
University of Oklahoma Health Sciences Center

2:35-2:55 THE VIEW FROM THE OTHER SIDE OF THE COUNTER: INTERVIEWS WITH VAPOR STORE OWNERS
Marshall Cheney, PhD
Department of Health & Exercise Science
University of Oklahoma

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Session Chair: Scott McMeekin

3:10 – 3:30 OPPORTUNITIES AND RESOURCES FOR CLINICAL TRANSLATIONAL RESEARCH
Scott McMeekin, MD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center

3:30 – 3:50 TSET PHASE I PROGRAM: WHAT HAVE WE LEARNED IN OUR FIRST 5 YEARS
Kathleen Moore, MD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center

3:50 – 4:10 LUNG CANCER: PROGRAM DEVELOPMENTS AND OPPORTUNITIES
Mohamad Razaq, MD
Department of Internal Medicine
University of Oklahoma Health Sciences Center

4:10 - 4:30 PRECISION MEDICINE: IMPROVING OUR AIM
Scott McMeekin, MD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center

CHD	**Research Presentations: Hot Topics in Cancer Health Disparities** Session Chair: Mark Doescher, MD, MSPH	Level B B3
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3:30-3:50	PROMOTING REGULAR SCREENING MAMMOGRAPHY IN AN AMERICAN INDIAN COMMUNITY IN OKLAHOMA: AN UPDATE Eleni Tolma, PhD, MPH Department of Health Promotion Sciences University of Oklahoma Health Sciences Center	
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Cancer Health Disparities Keynote Speaker Biography

Charles Wiggins, PhD

Director, New Mexico Tumor Registry

Dr. Wiggins joined the faculty in the Department of Internal Medicine - Division of Epidemiology and Biostatistics - in August, 2003. He is an Alumnus of the University of New Mexico (B.S., Health Education, 1978), and received graduate degrees in Epidemiology from the University of Alabama-Birmingham (M.S.P.H., 1983) and the University of Washington (Ph.D., 1999). Dr. Wiggins is Director and Principal Investigator for the New Mexico Tumor Registry. He has over 35 years of experience in cancer surveillance and epidemiology and has a strong interest in cancer among underserved populations. He has examined issues that impact cancer surveillance among American Indian communities in the United States, including misclassification of American Indians as non-Indian in central cancer registries. He has been a member of the Spirit of Eagles (formerly the National Network for Cancer Control Research for American Indian and Alaska Native Populations) since 1994. Dr. Wiggins has coordinated instruction in epidemiology and biostatistics for medical students at the University of New Mexico School of Medicine since 2006. He is married and has three sons.

Concurrent Sessions:
Information
&
Abstracts

Concurrent Session I – Basic / Translational / Clinical

8:30 a.m. – 9:30 a.m. Level Two, Auditorium

BASIC MECHANISMS AND THERAPEUTIC DEVELOPMENT – PART I

Moderator: Christopher West, PhD

8:30 a.m. – 8:50 a.m.	HISTONE DEMETHYLASE JMJD2A: A NOVEL ONCOGENIC PLAYER IN PROSTATE CANCER Ralf Janknecht, PhD Department of Cell Biology University of Oklahoma Health Sciences Center
8:50 a.m. – 9:10 a.m.	FINALLY—EFFECTIVE USE OF CANCER STROMA AS A THERAPEUTIC TARGET Kenneth W. Jackson, PhD Department of Microbiology & Immunology University of Oklahoma Health Sciences Center
9:10 a.m. – 9:30 a.m.	CNS INVASION BY T CELL LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA J. Kimble Frazer, MD, PhD Department of Pediatrics University of Oklahoma Health Sciences Center

HISTONE DEMETHYLASE JMJD2A: A NOVEL ONCOGENIC PLAYER IN PROSTATE CANCER
Presenter: Ralf Janknecht, PhD

JMJD2A, also called KDM4A, is a histone demethylase. Here, we show that it is overexpressed in human prostate tumors and correlates with aggressive disease. A transgenic mouse model demonstrates that JMJD2A overexpression leads to the initiation of prostate cancer. Further, JMJD2A interacts with ETS transcription factors that are prominently overexpressed in prostate tumors. Jointly, they can upregulate YAP1, a downstream effector in the Hippo signaling pathway. YAP1 itself is overexpressed in human prostate tumors and partially rescues the effect of JMJD2A downregulation in LNCaP prostate cancer cells. These data strongly suggest that JMJD2A and YAP1 are valid drug targets in the ~70% of prostate tumors displaying ETS factor overexpression.

FINALLY—EFFECTIVE USE OF CANCER STROMA AS A THERAPEUTIC TARGET
Presenter: Kenneth W. Jackson, PhD

Kenneth W. Jackson[a], Victoria J. Christiansen[a], Vivek R. Yadav[b], Robert Silasi-Mansat[d], Florea Lupu[d], Vibhudutta Awasthi[b], Roy R. Zhang[c] and Patrick A. McKee[a]

[a]William K. Warren Medical Research Center, Department of Medicine; [b]College of Pharmacy; [c]Department of Pathology, University of Oklahoma Health Sciences Center and [d]Cardiovascular Biology Program, Oklahoma Medical Research Foundation

Tumor microenvironments (TME) 1-2 mm^3 contain parenchymal-derived cancer cells within stroma consisting of activated fibroblasts, developing microvasculature, and extracellular matrix (ECM); stroma may account for ~90% of tumor weight. Fibroblast activation protein (FAP), a type II integral membrane protein and prolyl-specific serine proteinase, is over-expressed on cell membranes of stromal fibroblasts in > 90% of epithelial cell-derived malignancies, i.e., lung, breast, colon, etc. FAP is rarely found on adult normal tissues or benign tumors, thereby making it an attractive diagnostic and therapeutic target. It is believed that (i) FAP engages in proteolysis of ECM during tissue invasion; (ii) FAP-expressing cells may foster immune tolerance within TME; and (iii) FAP supports angiogenesis. Efforts to limit FAP activities that enhance tumor growth have focused on inhibiting its proteolytic properties with non-specific inhibitors or blocking putative FAP^+ cell-induced immunotolerance of growing cancer.

Commanding less attention has been prolyl oligopeptidase, POP, normally found in many tissues and commonly over-expressed along with the ubiquitous protein thymosin β4 in most malignancies. After partial cleavage of Tβ4 by an unknown enzyme, its derivative form is cleaved by POP to yield the potent angiogenic peptide, Ac-SDKP. POP proteinase activity clearly has a role in angiogenesis, but unlike FAP, it resides on cells throughout the tumor and not just on stroma. The therapeutic potential for targeted POP inhibition to diminish angiogenesis and reduce tumor growth has not been explored.

To examine these issues, we designed and synthesized stable, specific and soluble inhibitors of FAP and POP termed M83 and J94. The primary structure around the scissile bond of the physiologic substrate for FAP, namely $alpha_2$-antiplasmin, was a template for designing M83, and the scissile bond region of POP substrates was used to design J94. Both inhibitors possessed excellent solubility at neutral pH and retained inhibitory function after prolonged exposure to human plasma. Both M83 and J94 have low nanomolar K_i's for inhibiting FAP or POP, or only POP, respectively, and neither significantly inhibits DPPIV. When on live cells characteristic of TME, the membrane-associated form of either enzyme is rapidly and completely inhibited, suggesting easy accessibility to the active-site. We found substantial growth suppression of human colon cancer xenografts occurred in response to M83 or J94 in immune deficient mice without apparent adverse effects. Both inhibitors suppressed human colon cancer xenograft growth >90% in mice. By immunohistochemical stains, M83- and J94-treated tumors had fewer microvessels and contained large apoptotic areas; M83 also caused

disordered ECM collagen accumulations. Diminished angiogenesis and the accompanying profound reduction in cancer growth with inhibition of FAP or POP suggest new therapeutic approaches that target tumor microenvironments directly.

CNS INVASION BY T CELL LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA

Presenter: J. Kimble Frazer, MD, PhD

Chiara Borga[1,2], Lance Batchelor[2], Silvia Bresolin[1], Ilaria Bronzini[1], Giuseppe Basso[1], Geertruy te Kronnie[1], J. Kimble Frazer[2]

[1]Department of Women's and Children's Health, University of Padua, Italy
[2]Jimmy Everest Section of Pediatric Hematology-Oncology, OUHSC

Central nervous system (CNS) involvement in T cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LBL) is a significant clinical problem. Patients with CNS+ disease receive more intense therapy, yet despite this, they still have inferior prognoses. Little is known about the molecular mechanisms that mediate CNS lymphoblast invasion, and such insights are difficult to obtain from clinical samples. Studying the mechanisms that lymphoblasts use to infiltrate the CNS requires animal models. We investigated two zebrafish genetic models: an ENU mutant, hlk, and an hMYC transgenic line that expresses human MYC in lymphoblasts; both are prone to T lymphoblast cancers. We histologically analysed fish with localized thymic lymphomas (i.e., T-LBL) and disseminated disease (T-ALL), and found that CNS invasion occurs in both hlk and hMYC animals at high frequency and is often present at an early stage. Patterns of CNS involvement in zebrafish closely resemble those which occur in human patients. These morphologic studies were complemented by microarray gene expression profiling which revealed induction of distinct gene networks that regulate cell motility in hlk and hMYC cancers, implying that multiple mechanisms can drive lymphoblast homing to and invasion of the CNS. Specifically, expression of cxcr4 pathway genes correlates with the high rates of CNS invasion in hMYC fish, suggesting this genetic program may confer an advantage to T-lymphoblasts in the CNS. Further, our data also implicate Yy1, a transcriptional regulator whose human homologue, YY1, is highly conserved and known to bind MYC and regulate mammalian CXCR4 expression.

Concurrent Session I – Cancer Health Disparities

8:30 a.m. – 9:30 a.m. Level B, Room B3

KEYNOTE ADDRESS

TURNING DATA INTO ACTION: USING PUBLIC HEALTH SURVEILLANCE TO GUIDE CANCER CONTROL IN INDIAN COUNTRY

Charles Wiggins, PhD

Director and Principal Investigator, New Mexico Tumor Registry
Associate Professor, Division of Epidemiology and Biostatistics
Department of Internal Medicine, UNM School of Medicine

Dr. Wiggins will describe how the burden of cancer among American Indians and Alaska Natives varies across geographic regions of the United States. He will discuss the implications of such observations in targeting cancer control programs for Native communities.

As a result of participating in this session, you will be able to:

1. Compare and contrast the burden of cancer for American Indians in your region with the cancer burden in another region of the country;
2. Describe the importance of utilizing local and/or regional data for planning cancer control programs in your community;
3. Identify resources for obtaining local cancer surveillance data that are most relevant to your community.

Concurrent Session II – Basic / Translational / Clinical

9:30 a.m. – 10:30 a.m. Level Two, Auditorium

BASIC MECHANISMS AND THERAPEUTIC DEVELOPMENT – PART II

Moderator: Lawrence Rothblum, PhD

9:30 a.m. – 9:50 a.m.	INTEGRATING PATIENT-DERIVED TISSUE AND FORWARD-CHEMICAL GENETICS TO IDENTIFY TARGETABLE VULNERABILITIES IN BREAST CANCER Bryan Welm, PhD Immunobiology and Cancer Research Program Oklahoma Medical Research Foundation
9:50 a.m. – 10:10 a.m.	MECHNISMS OF MIGRATION AND INVASION OF GLIOBLASTOMA MIGRATION James Battiste, MD, PhD Department of Neurology University of Oklahoma Health Sciences Center
10:10 a.m. – 10:30 a.m.	DISCUSSION

INTEGRATING PATIENT-DERIVED TISSUE AND FORWARD-CHEMICAL GENETICS TO IDENTIFY TARGETABLE VULNERABILITIES IN BREAST CANCER

Presenter: Bryan Welm, PhD

Immunobiology and Cancer Research Program, Oklahoma Medical Research Foundation

A long-standing, formidable challenge in cancer research is the development of experimental models that replicate human cancer. Established cell lines and their derived xenografts are commonly used as research models; however, they only partially recapitulate the heterogeneity and complexity of bona fide human tumors. In contrast tumor grafts can be established from patients by implanting intact fragments of a tumor into cleared mammary fat pads of immune deficient mice. These tumor grafts accurately reflect the disease pathologies observed in patients and provide a renewable source of human cancer cells that are applicable to a variety of assays and screens. We use small molecules and forward-chemical genetics to discover vulnerabilities in cancer cells derived from patients with intractable, chemoresistant tumors. To identify cancer-selective small molecules, compounds are screened against cancer cells and, in parallel, against normal primary human or mouse mammary tissue. Using this screen we identified and validated several novel small molecules that selectively kill cancer cells, have limited general toxicity, and demonstrate anti-tumor efficacy in *in vivo* breast cancer models. Our studies validate the utility of patient-derived breast tumor grafts as a valuable model for screening and pre-clinical evaluation of small molecules.

MECHNISMS OF MIGRATION AND INVASION OF GLIOBLASTOMA MIGRATION

Presenter: James Battiste, MD, PhD

Department of Neurology, University of Oklahoma Health Sciences Center

Diffuse single cell infiltration into surrounding normal brain is a pathological hallmark of glioblastoma (GBM). The mechanisms by which glioblastoma cells gain traction and generate sufficient contractile forces to overcome the mechanical challenge of migrating through the tightly confined spaces of the brain parenchyma are unclear. To investigate the role of extracellular matrix topography in glioblastoma migration, we use an *in vitro* microfluidic platform in which a defined, 3D extracellular matrix forms channels of varying diameters (20, 15, 10, 8 & 5 μm) approximating the confinement of cells in the brain. GBM cell culture lines derived from human glioblastomas were monitored in live cell imaging and after fixation to characterize the influence of confinement on the cells. Channels were initially coated with laminin, but in subsequent experiments other substrates were used including poly-D-lysine. Cytoskeleton proteins were visualized by immunofluorescence. The migration velocities of various lines was measured and correlated with their *in vivo* aggressiveness. The ability of the cells to migrate was challenged by either antibodies targeting the cell surface or chemicals aimed at disrupting cell migration. The more aggressive cell lines produced faster migration velocities in the microfluidic chambers. The tubulin cytoskeleton changes in response to confinement allowing the cell to become more flexible while migrating through confined spaces. This data suggests that glioblastoma cells are able to migrate using mechanisms previously unappreciated on traditional migration platforms. The three dimensional environment appears to provide unique mechanisms to generate motile force. It challenges the dogma that glioblastoma migration involves primarily proteolytic degradation of the extracellular matrix followed by a mesenchymal pattern of migration with classic lamellipodia attaching to the extracellular matrix. New discoveries are now emerging that can help elucidate cancer cell migration in native tissue. Microfluidic chambers can now serve as platforms for further characterization of migration mechanisms of glioma cells and as a platform to develop new therapies to stop cell migration.

Concurrent Session II – Cancer Health Disparities

9:30 a.m. – 10:30 a.m. Level B, Room B3

TRANSLATIONAL THINK TANK: PREVENTION OF HPV-ASSOCIATED CANCER IN OKLAHOMA

Moderator: Mark Doescher, MD, MSPH

Paul Darden, MD
Department of Pediatrics
University of Oklahoma Health Sciences Center

Discussion: IDENTIFYING STRATEGIES TO REDUCE THE BURDEN OF HPV IN OKLAHOMA: RESEARCH, CLINICIANS, AND COMMUNITY PARTNERS

The goal for this session is to provide a forum for the exchange of experiences and ideas related to the prevention of HPV-associated cancer in Oklahoma.

Concurrent Session III – Basic / Translational / Clinical

10:45 a.m. – 12:05 p.m. Level Two, Auditorium

DISEASE SITES AND COLLABORATIVE SCIENCE – PART I

Moderator: Dave Jones, PhD

10:45 a.m. – 11:05 a.m.	BMI-1 REGULATES CELLULAR BIOENERGETICS BY STABILIZING MITOCHONDRIAL TRANSCRIPTS Soumyajit Banerjee Mustafi, PhD Stephenson Cancer Center University of Oklahoma Health Sciences Center
11:05 a.m. – 11:25 a.m.	RON KINASE AS A NEW TARGET FOR OSTEOLYTIC BONE METASTASIS: PRE-CLINICAL DATA AND PLANS FOR CLINICAL TRANSLATION Alana Welm, PhD Immunobiology and Cancer Research Oklahoma Medical Research Foundation
11:25 a.m. – 11:45 a.m.	EPSIN IN CANCER DEVELOPMENT AND PROGRESSION Hong Chen, PhD Cardiovascular Biology Research Oklahoma Medical Research Foundation
11:45 a.m. – 12:05 p.m.	DISCUSSION

BMI-1 REGULATES CELLULAR BIOENERGETICS BY STABILIZING MITOCHONDRIAL TRANSCRIPTS
Presenter: Soumyajit Banerjee Mustafi, PhD

Soumyajit Banerjee Mustafi[1], Shailendra Kumar Dhar Dwivedi[1], Prabir Kumar Chakraborty[2], Rumki Basak[1], Michael T Kinter[3], Priyabrata Mukherjee[2] and Resham Bhattacharya[1#]

[1]Department of Obstetrics and Gynecology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, United States of America
[2]Department of Pathology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, United States of America
[3]Department of Geriatric Medicine, Reynolds Oklahoma Center on Aging, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States of America

The pre-dominantly nuclear protein Bmi-1 has been mainly studied as a chromatin modifier and through regulation of INK4A/ARF can partially rescue phenotypes in cancer cells, stem cells and knockout mice. An INK4A/ARF independent role of Bmi-1 in regulating mitochondrial function and ROS production has been described but the mechanism remains elusive. Here, we provide evidence for a direct role of Bmi-1 in regulating mitochondrial RNA metabolism orchestrating mitochondrial bioenergetics. Subcellular fractionation and confocal imaging revealed a previously unidentified presence of Bmi-1 in the mitochondria in addition to the nucleus. Silencing Bmi-1 in cancer cells significantly inhibited mitochondrial oxidative phosphorylation, cytochrome C oxidase activity and ATP production while mitochondrial mass and integrity remained unaltered. Importantly all of these phenotypes could be reverted by the expression of extra-nuclear Bmi-1. Bmi-1 positively regulated the steady state level of the mitochondrial mRNA transcripts. Bmi-1 interacted with the stabilizing complex LRPPRC/SLIRP and the degradation complex PNPase/SUV3A respectively and prevented mitochondrial mRNA degradation. Loss of Bmi-1 enhanced the nuclease activity of PNPase towards specific mitochondrial transcripts thereby altering their steady state that was reflected at the protein level. Together these data explain why Bmi-1 is indispensable in the normal and cancer stem cells that are reportedly quiescent and dependent on mitochondrial OxPhos for survival and suggest that silencing Bmi-1 will restrict expansion of stem cells and increase glucose dependence that can be exploited for therapeutic purposes. Collectively these results establish a new and fundamental role of Bmi-1 in regulating mitochondrial bioenergetics and purport possible applications in restricting stem cell expansion, premature brain aging and mitochondrial respiratory chain linked metabolic diseases.

RON KINASE AS A NEW TARGET FOR OSTEOLYTIC BONE METASTASIS: PRE-CLINICAL DATA AND PLANS FOR CLINICAL TRANSLATION

Presenter: Alana Welm, PhD

Immunobiology and Cancer Research, Oklahoma Medical Research Foundation

We report a new pathway responsible for two types of bone loss: osteoporosis and cancer-mediated bone destruction. We found that macrophage-stimulating protein (MSP) facilitates bone loss by activating osteoclasts through its receptor, the Ron receptor tyrosine kinase. MSP/Ron-driven osteoclast activation is notable in that it does not require RANKL or TGFβ signaling, but functions directly through activation of Src kinase. Loss of Ron activity (genetic or pharmacologic) blocks bone resorption by osteoclasts, but can be rescued by expression of a constitutively active Src mutant. Importantly, pharmacological inhibition of Ron kinase can prevent both the onset and progression of bone loss, in animals and in humans. These findings not only elucidate an important new role for the MSP/Ron pathway in osteoclast activity but also provide rationale for the use of Ron inhibitors for treatment of bone destruction. Our plans for an exploratory Phase 2a trial to test ASLAN002, a new Ron inhibitor, in patients with breast or lung cancers that have spread to the bone will be discussed.

EPSIN IN CANCER DEVELOPMENT AND PROGRESSION

Presenter: Hong Chen, PhD

Cardiovascular Biology Research, Oklahoma Medical Research Foundation

Epsins are ubiquitin-binding endocytic adaptor proteins, implicated in clathrin-mediated endocytosis. Recently, we have uncovered a positive correlation between cancer severity and elevated epsins expression within tumor samples from human cancer patients. Importantly, elevated epsin expression is specific to the tumor cells thus implicating a tumor intrinsic role for epsins in the development and/or progression of cancer. We have embarked on studies to identify and characterize the mechanistic roles of tumor cell-specific epsins in regulating cancer development and progression through the creation of epsin-depleted genetically manipulated mouse cancer models and human xenograft models. Methodical *in vivo* and *in vitro* analyses of these epsin deficient models allowed us to clearly identify oncogenic roles for epsins in cancer development and progression. Furthermore, we have successfully identified a novel regulatory role for epsins that is completely independent of its classically defined endocytic adaptor function. The details of these novel and unique intrinsic regulatory roles for epsin in cancer cells are the topic of this presentation.

Concurrent Session III – Cancer Health Disparities

10:45 a.m. – 12:05 p.m. Level B, Room B3

SYSTEM CHANGE FOR SMOKING CESSATION: OPPORTUNITIES FOR RESEARCH

Moderator: D. Robert McCaffree, MD

10:45 a.m. – 11:05 a.m.	TOBACCO INTERVENTIONS WITH PATIENTS AND PARENTS: ASSESSING THE TRAINING AND CONFIDENCE OF INCOMING PEDIATRIC AND FAMILY MEDICINE INTERNS Stephen Gillaspy, PhD Department of Pediatrics University of Oklahoma Health Sciences Center
11:05 a.m. – 11:25 a.m.	CHICKASAW NATION ADVANCES PATIENT TOBACCO TREATMENT THROUGH TRIBAL HEALTH SYSTEM CHANGES AND ELECTRONIC HELPLINE REFERRALS Heather Summers, MS, RN Undersecretary of Operations Hospital and Clinics for the Chickasaw Nation & Joy Leuthard, MS, LSWA Manager of Health Improvement Initiatives at the Oklahoma Hospital Association
11:25 a.m. – 12:05 p.m.	DISCUSSION

TOBACCO INTERVENTIONS WITH PATIENTS AND PARENTS: ASSESSING THE TRAINING AND CONFIDENCE OF INCOMING PEDIATRIC AND FAMILY MEDICINE INTERNS

Presenter: Stephen R. Gillaspy, PhD

Stephen R. Gillaspy, Ph.D.[1,2]; Kristina I. Suorsa, M.S.[1,3]; Leslie M. Driskill, M.S.[1,2]; Theodore L. Wagener, Ph.D.[1,2]; Diane Jarrett, Ed.D.[4]; Laura Sisterhen, MD[4]; Michael Gomez, MD[2]; Kevin Nelson, MD[5]; Lisa Gren, PhD, MSPH[5]; and Jennifer Leiser, MD[5]

[1]Oklahoma Tobacco Research Center (OTRC), [2]University of Oklahoma Health Sciences Center, [3]Oklahoma State University, [4]University of Arkansas for Medical Sciences 5. University of Utah School of Medicine

Limited information is available assessing physician training and confidence about discussing smoking cessation and second hand smoke exposure (SHSe) with children and families. The purpose of this study was to compare incoming family medicine (FMIs) and pediatric (PIs) interns' training and confidence in these areas. PIs and FMIs from University of Oklahoma Health Sciences Center–Oklahoma City, University of Oklahoma Health Sciences Center–Tulsa, University of Arkansas for Medical Sciences, and University of Utah School of Medicine participated in this project. Data collection from 3 of 4 sites has been completed. Participants were surveyed about previous training in tobacco prevention or control and SHSe, levels of confidence in their ability to provide education, and assistance about smoking cessation. Confidence was assessed using a 6-item, Likert scale, with item scores ranging from 1 (Not confident at all) to 7 (Very confident). Confidence total scores were calculated by adding all items resulting in a range of scores between 6 and 42. Sixty-one participants completed the survey. Of these participants, 57.4% were PIs and 42.6% were FMIs. Participants had a mean age of 28.5 years (SD=2.44) and 67.2% were female. An one-way analysis of variance (ANOVA) indicated a significant difference between the previous training of PIs and FMIs, $F(1,59)=8.32, p=.005$, such that 85.7% of PIs reported previous training in tobacco prevention or control and SHSe compared to 53.8% of FMIs. An ANOVA revealed a significant difference in confidence in addressing smoking cessation and SHSe between PIs and FMIs ($F(1,59)=5.12, p<.05$), with PIs (M=30.1, SD=6.6) reporting lower confidence ratings than FMIs (M=33.8, SD=5.8). This study highlights reported differences in prior training between PIs and FMIs, as well as PIs having less confidence in intervening with parents regarding smoking cessation and SHSe. This finding suggests PIs could benefit from additional experiences addressing smoking cessation in order to improve their level of confidence in their ability to provide education and assistance.

CHICKASAW NATION AND THE OKLAHOMA HOSPITAL ASSOCIATION PARTNER TO ADVANCE PATIENT TOBACCO TREATMENT THROUGH TRIBAL HEALTH SYSTEM CHANGES AND OKLAHOMA'S FIRST ELECTRONIC HELPLINE REFERRALS

Presenters: Joy Leuthard, MS, LSWA and Heather Summers, MS, RN

Joy Leuthard, MS, LSWA, Oklahoma Hospital Association; Heather Summers, MS, RN, Chickasaw Nation Medical Center

Oklahoma hospitals admit approximately 120,000 tobacco users each year, many for diseases resulting from tobacco use. Traditionally, many of these patients' tobacco use has not been addressed. To reach more Oklahomans through their health care providers and assist them to successfully quit tobacco use, the Oklahoma Hospital Association (OHA) works with hospitals and their clinics statewide to implement sustainable health system changes by integrating an evidence-based tobacco treatment protocol for all tobacco-using patients. This model, based upon the nationally endorsed U.S. Public Health Service clinical guidelines, *Treating Tobacco Use and Dependence: 2008 Update,* is also known as the 5 A's – Ask, Advise, Assess, Assist and Arrange.

Through a grant from the Tobacco Settlement Endowment Trust, the OHA provides free guidance and technical assistance to member hospitals to embed and sustain the following processes within both paper and electronic medical systems: (1) identify all tobacco-using patients; (2) assess addiction level and readiness to quit; (3) prescribe FDA approved medications to manage nicotine withdrawal while in hospital and for outpatients; and (4) proactively send a referral to the Oklahoma Tobacco Helpline (OTH) for all patients ready to quit.

With five years of experience working with a wide variety of hospitals and health systems, the OHA most recently partnered for the past 18 months with the Chickasaw Nation Medical Center, based in Ada, Oklahoma, to implement this treatment system which successfully launched in November 2014. Unique to the design of this system, all components of the treatment processes were embedded into the electronic medical record, Resource and Patient Management System (RPMS), including a bi-directional electronic referral directly to the OTH. This process allows the hospital and clinics to send an encrypted patient "e-referral" to the OTH and receive back an electronic report from the OTH detailing patient services and patient outcome. This outcome information is directed to the electronic patient chart as permanent documentation, thereby keeping all health providers within that system, inpatient and outpatient, updated on the patient's progress and outcome. This enhances the continuity and quality of patient care receives regarding all health issues including ongoing tobacco use status.

The Chickasaw Nation Medical Center is the first hospital in Oklahoma to successfully build this technology within the RPMS electronic medical record. RPMS is the standard electronic medical record used by all Indian Health Service facilities, nationally and the adaptations built into the Chickasaw Nation systems have the potential to be expanded throughout all IHS faculties.

Concurrent Session IV – Basic / Translational / Clinical

1:35 p.m. – 2:55 p.m. Level Two, Auditorium

DISEASE SITES AND COLLABORATIVE SCIENCE – PART II

Moderator: Adam Asch, MD

1:35 p.m. – 1:55 p.m.	CENTER FOR CANCER PREVENTION AND DRUG DEVELOPMENT: ORGAN SITE RESEARCH AND COLLABORATIONS CV Rao, PhD Department of Internal Medicine University of Oklahoma Health Sciences Center
1:55 p.m. – 2:15 p.m.	IMPAIRED COLONIC MUCUS BARRIER CAUSED BY DEFECTIVE MUCIN-TYPE O-GLYCOSYLATION LEADS TO COLITIS-ASSOCIATED CANCER IN MICE Lijun Xia, MD, PhD Cardiovascular Biology Research Program Oklahoma Medical Research Foundation Department of Biochemistry and Molecular Biology University of Oklahoma Health Sciences Center
2:15 p.m. – 2:35 p.m.	ZIP4 SILENCING COMBINED WITH SURGICAL RESECTION SIGNIFICANTLY IMPROVES SURVIVAL OF PANCREATIC CANCER THROUGH INHIBITING P38 MAPK-MEDIATED CACHEXIA Min Li, PhD Department of Medicine, Department of Surgery University of Oklahoma Health Sciences Center
2:35 p.m. – 2:55 p.m.	GOLD NANOPARTICLES SENSITIZE OVARIAN CANCER CELLS TO CISPLATIN BY INHIBITING CANCER STEM CELL POOLS Xunhao Xiong, PhD Stephenson Cancer Center University of Oklahoma Health Sciences Center

CENTER FOR CANCER PREVENTION AND DRUG DEVELOPMENT: ORGAN SITE RESEARCH AND COLLABORATIONS

Presenter: CV Rao, PhD

Department of Internal Medicine, University of Oklahoma Health Sciences Center
Center for Cancer Prevention and Drug Development, Stephenson Cancer Center

Environmental Risk Factors and Pre-Cancerous Biology: Research emphasizes cancer risks incited by lifestyle factors and environmental agents such as tobacco smoke. Studies are conducted to gain an integrated understanding of how nutrition, genetics, and environmental carcinogens participate in cancer causation and progression. The entire tumor microenvironment is interrogated to identify risk factors and potential molecular targets as well as to understand how modulation of immune responses may improve the selection of target(s) for high-risk cohorts. The findings from these studies serve as the basis for the development of cancer prevention intervention strategies in preclinical models and then in clinical trials. In addition to an individual's inherited genetic risk factors, life-style habits (physical activity, smoking, diet), concurrent diseases (obesity, diabetes), and etiological agents (environmental carcinogens and tumor promoters, microbes) may influence cancer risks. Thus, CCPDD research focuses on genetic as well as on environmental risk factors of relevance to Oklahomans in the development of precancerous tumors and their progression to malignant invasive cancers.

Cancer Preventive Drug Development: This area includes development and testing of drugs, vaccines, and natural products individually and/or in combination for primary and secondary cancer prevention. Drug development is an arduous and multistep process. CCPDD research focuses on developing chemopreventive agents and/or biologics to target the precursor lesions of major epithelial cancers and their progression to metastatic invasive cancers. Thus, CCPDD research involves identifying potential drug targets, developing small molecule inhibitors and biologics using high through-put screening assays, establishing the optimal drug doses & preventive efficacy towards major organ site cancers, and assessing their pharmacokinetics (PK), pharmacodynamics (PD), and toxicities in preclinical models before considering them for Phase 0, I, or II clinical trials. Testing chemopreventive and/or immunopreventive agents (vaccines) or other biologics in pre-clinical studies will determine whether or not the candidate agents are safe and effective enough to be advanced to clinical trials in high-risk individuals. A comprehensive team of expertise and state-of-the-art research facilities exist at the CCPDD and SCC to undertake these cancer drug developmental activities.

Early Detection – Diagnosis / Biomarkers: The positive impact of early detection on cancer mortality is one victory in the war on cancer; yet, there is enormous room for improving early detection / diagnosis of pancreatic, lung, and ovarian cancers. Those cancers typically are diagnosed in an advanced stage when chances of a cure are remote because there are no effective screening tests. The focus of our early detection research is to develop improved early detection technologies and diagnostic biomarkers that can detect tumors at early stages. Thus, as an essential part of the CCPDD ongoing strategy, investigators are establishing early detection technologies by applying novel imaging biomarkers. The OUHSC / OMRF imaging

centers led by Drs. Awasthi and Towner provide comprehensive advance imaging technologies, including a Gamma Medica-Ideas Flex X-O-CT/X-PET, a Bioscan NanoSPECT system, a Biomarker Generator (aka Cyclotron), an Optical IVIS-Xenogen, and magnetic resonance imaging (MRI) systems: a 7.0 T 30 cm horizontal-bore imaging system and a 11.7 T 89 mm vertical-bore microimaging systems.

IMPAIRED COLONIC MUCUS BARRIER CAUSED BY DEFECTIVE MUCIN-TYPE O-GLYCOSYLATION LEADS TO COLITIS-ASSOCIATED CANCER IN MICE

Presenter: Lijun Xia, MD, PhD

Kirk Bergstrom[1], Jianxin Fu[1,2], Lijun Xia[1,2]

[1]Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, [2]Department of Biochemistry and Molecular Biology, Oklahoma Center for Medical Glycobiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

Mucin-type-*O*-linked oligosaccharides (*O*-glycans) are major components of the protective colonic mucus layer. Defective forms of colonic *O*-glycans such as Tn antigen are frequently observed in ulcerative colitis (UC) and colorectal cancer with unknown etiological role. *O*-glycans mainly consist of core 1-derived structures, which are ubiquitous, and core 3-derived structures, which are mainly restricted to gastrointestinal epithelia. Our previous study shows that mice whose intestinal epithelial cells lack core 1 *O*-glycans (IEC *C1galt1*$^{-/-}$) develop spontaneous colitis. In this study, we found that mice lacking both core 1- and core 3-derived *O*-glycans (DKO) expressed Tn antigen but not sialyl-Tn, and exhibited more severe intestinal mucus barrier defects and spontaneous colitis than IEC *C1galt1*$^{-/-}$ mice. Furthermore, both IEC *C1galt1*$^{-/-}$ and DKO mice developed spontaneous colon tumors at older ages with the disease in DKO mice occurring earlier and with more severity than that in IEC *C1galt1*$^{-/-}$ mice. The colitis and cancer were dependent upon inflammation, as microbial depletion reduced colitis and tumors but not Tn expression in DKO mice. Moreover, microbiota-mediated activation of epithelial caspase 1-dependent inflammasomes was required for colitis-associated colorectal cancer in DKO mice. These findings reveal an important role of mucin-type *O*-glycans for intestinal mucus barrier function and implicate their loss, rather than the appearance of Tn antigen per se, as contributing to the pathogenesis of colitis-associated colon cancer.

ZIP4 SILENCING COMBINED WITH SURGICAL RESECTION SIGNIFICANTLY IMPROVES SURVIVAL OF PANCREATIC CANCER THROUGH INHIBITING P38 MAPK-MEDIATED CACHEXIA

Presenter: Min Li, PhD

Department of Medicine, Department of Surgery, University of Oklahoma Health Sciences Center

Cachexia and muscle wasting are hallmarks of pancreatic cancer, it is associated with early death, debility, chemotherapy-refractory disease, and heightened chemotherapy toxicity. Current therapies provide little benefit in reducing cachexia and improving patient survival, highlighting the importance of understanding the mechanism of cachexia and developing new therapy targeting cachexia pathway in pancreatic cancer. Here, we describe a novel role for the zinc transporter ZIP4 and a new signaling pathway through which ZIP4 activates pancreatic cancer cachexia and muscle wasting. Our data 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 atrogin1/MAFbx upregulation. Together these findings define a novel pathway on pancreatic cancer-induced weight loss through enhanced activation of the p38 MAPK/atrogin1/MAFbx in muscle cells by ZIP4. This knowledge may also help the development of adjuvant therapies in combination with surgery to treat pancreatic cancer.

GOLD NANOPARTICLES SENSITIZE OVARIAN CANCER CELLS TO CISPLATIN BY INHIBITING CANCER STEM CELL POOLS

Presenter: Xunhao Xiong, PhD

Xunhao Xiong, Rochelle R. Arvizo, Sounik Saha, David J. Robertson, Scott McMeekin, Resham Bhattacharya and Priyabrata Mukherjee

Epithelial ovarian cancer (EOC) is the leading cause of gynecologic cancer death. Most patients respond initially to platinum-based chemotherapy after surgical debulking, however relapse is very common and ultimately platinum resistance emerges. The mechanism of recurrence and evolution of drug-resistance is poorly understood. Understanding the mechanism of tumor growth, metastasis and drug resistant relapse will profoundly impact therapeutic management of ovarian cancer. In this report we demonstrate that gold nanoparticle (AuNP) sensitizes ovarian cancer cells to cisplatin by inhibiting cisplatin-induced epithelial to mesenchymal transition (EMT), enrichment of stem cell pool, upregulation of multi-drug resistance genes and activation of NF-□b signaling. Specifically, cisplatin treatment upregulated the expression of stem cell markers such as ALDH1, CD24, CD44, CD133, EpCAM, Nannog, Oct-4 and Sox2, enhanced multi-drug resistance gene MDR1 expression and increased the side population cells in ovarian cancer cell lines that were depleted/dowregulated upon AuNP treatment. Mechanistically, AuNPs prevent cisplatin-induced activation of Akt and NF-□B signaling axis in ovarian cancer cells that are critical for EMT, stem cell maintenance and drug resistance. *In vivo*, AuNPs sensitize orthotopically implanted ovarian tumor to a low dose of cisplatin and significantly inhibit tumor growth via facilitated delivery of both AuNP and cisplatin. These findings suggest that by depleting stem cell pools and inhibiting key molecular pathways gold nanoparticles sensitize ovarian cancer cells to cisplatin and may be used in combination to inhibit tumor growth and metastasis in ovarian cancer.

Concurrent Session IV – Cancer Health Disparities

1:35 p.m. – 2:55 p.m. Level B, Room B3

EMERGING RESEARCH IN THE USE OF ELECTRONIC CIGERETTES

Moderator: Laura Beebe, PhD

1:35 p.m. – 1:55 p.m.	ELECTRONIC CIGARETTES AMONG AMERICAN INDIAN YOUTH Dorothy A. Rhoades, MD Department of Medicine University of Oklahoma Health Sciences Center
1:55 p.m. – 2:15 p.m.	ARE E-CIGARETTES AND OTHER MODIFIED RISK TOBACCO PRODUCTS GATEWAYS TO MORE HARMFUL TOBACCO USE? Theodore Wagener, PhD Department of Pediatrics University of Oklahoma Health Sciences Center
2:15 p.m. – 2:35 p.m.	DUAL USERS CALLING A STATE QUITLINE: WHAT DO THEY DO AND WHAT DO THEY WANT? Theodore Wagener, PhD Department of Pediatrics University of Oklahoma Health Sciences Center
2:35 p.m. – 2:55 p.m.	THE VIEW FROM THE OTHER SIDE OF THE COUNTER: INTERVIEWS WITH VAPOR STORE OWNERS Marshall Cheney, PhD Department of Health and Exercise Science University of Oklahoma

ELECTRONIC CIGARETTES AMONG AMERICAN INDIAN YOUTH

Presenter: Dorothy A. Rhoades, MD

Dorothy A. Rhoades[1,2], Mark P. Doescher[3,2], Theodore Wagener[4,6], Kai Ding[5], Justin Dvorak[5], Michelle Hopkins[6], Gloria Tallbull[7], Laura Beebe[5,6]

[1]Department of Medicine, University of Oklahoma Health Sciences Center; [2]Cancer Health Disparities, Stephenson Cancer Center, University of Oklahoma Health Sciences Center; [3]Department of Family Medicine, University of Oklahoma Health Sciences Center; [4]Department of Pediatrics, University of Oklahoma Health Sciences Center; [5]Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center; [6]Oklahoma Tobacco Research Center, Stephenson Cancer Center, University of Oklahoma Health Sciences Center; [7]University of Oklahoma

Purpose The uptake of electronic cigarettes (e-cigs) is growing very rapidly among youth, potentially leading to long term nicotine addiction. The use of e-cigs by American Indian (AI) youth has never been reported despite a high prevalence of smoking in AI youth. We report preliminary findings regarding the use of e-cigs and its correlates among a sample of AI youth.

Procedures To date, 161 AI youth ages 11-17 years were recruited at 3 Indian Health Service (IHS) clinics and events in Oklahoma during the summer and fall of 2014. For this study, we adapted the National Youth Tobacco Survey and an e-cig survey of college students to assess youth experiences with e-cigs and tobacco products. The final 79-item questionnaire included multiple domains, including socio-demographic factors, attitudes, behaviors, exposure to advertising, flavor preference, smoking and other tobacco use, and perception of harm. Surveys were self-administered for nearly all participants. Approvals were obtained from a local intertribal health board, the IHS facilities, and IHS and OUHSC Institutional Review Boards.

Potential correlates of ever use of e-cigs were assessed with logistic regression. Variables associated with a *P*-value <0.10 were entered into models in blocks and adjusted for age and sex. Interactions between age and sex, and age and other variables were not statistically significant. Variables with a *P* value <.05 in these models were then entered into a final model. Sex was included in all models regardless of *P* value.

Summary of Data Overall, 54% of the youth were aged 13 years or less, 42% were in high school (grades 9-12), and 56% were female. Although 18% of the participants ever used e-cigs, 38% of the high school students in the sample had ever tried e-cigs. In comparison, the prevalence of e-cig use in the US all-races high school population in 2013 was only 12%. The 3% prevalence of ever use of e-cigs among middle school students in our sample was the same as the 3% estimate for the US all-races middle school population. While several variables were significantly associated with e-cig use in unadjusted analyses, those that remained significant in multivariate analyses included: age (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.2-2.5); living with someone who smokes cigarettes (OR 5.8, CI 1.3-25.9); ever having tried cigarettes (OR 27.2, CI 6.1-120.6); and perception that e-cigs are not dangerous (OR 51.8, CI 4.1-629.3).

Conclusion Our preliminary research reveals a striking prevalence of ever having tried e-cigs among AI in high school that is much higher than reported for the general US high school population. These initial findings also suggest that perceived l
ck of harm of e-cigs may be an important factor in ever using them. Longitudinal study of the uptake of e-cigs and their correlates, including perceptions of harm, is urgently needed among AI youth to further illuminate the role of these products in nicotine addiction.

ARE E-CIGARETTES AND OTHER MODIFIED RISK TOBACCO PRODUCTS GATEWAYS TO MORE HARMFUL TOBACCO USE?

Presenter: Theodore Wagener, PhD

Theodore Wagener, PhD and Ellen Meier, PhD

Debate continues as to whether modified risk tobacco products (MRTPs) like e-cigarettes (EC) will serve as gateways to more harmful tobacco use (i.e., cigarettes). Previous research from our lab suggests that very few students who first tried ECs transitioned to daily tobacco use (1.7%), compared to 10% and 21% of those who first tried cigarettes and traditional smokeless tobacco (SLT), respectively. The present study examines the gateway hypothesis with a second wave of college students. Undergraduate students (N = 792; M_{age} = 19.6; 75.5% = Caucasian) completed an online survey of past/current use of cigarettes, SLT, hookah, dissolvables, snus, ECs, and nicotine replacement therapy (NRT), between October 2013 and May 2014. Descriptive statistics and multinomial regressions were used to determine whether first tobacco product tried predicted current use. Given the small number of participants who first tried dissolvables, snus, and ECs, these three tobacco products were summed into a MRTP category for inferential analyses. Overall, 51.5% of participants reported trying a tobacco product with an average age of first use of 16.6 years (SD = 8.23). Hookah was the most frequently tried tobacco product (39.4%), but cigarettes were most often the first product tried (21.2%), followed by Hookah (13.9%), SLT (10.0%), ECs (3.9%), Snus (1.6%) and dissolvables (0.1%). Participants who first tried cigarettes or SLT were significantly more likely to be a current single (cigarettes: OR = 3.46, p = .012; SLT: OR = 3.29, p = .026) and/or poly user (cigarettes only: OR = 2.49; p = .051) compared to those who first tried a MRTP. Of those who first tried cigarettes, 7.1% (12 of 168) became daily smokers and 23.2% (39 of 168) non-daily smokers; no student who first tried ECs reported being a daily smoker, but 6.5% (2 of 31) did report non-daily smoking. MTRP experimentation continues to increase, but the likelihood of these products serving as a gateway product continues to appear minimal. However, continued surveillance, especially in longitudinal designs, is warranted in light of the rapid technological advancements with these products.

DUAL USERS CALLING A STATE QUITLINE: WHAT DO THEY DO AND WHAT DO THEY WANT?
Presenter: Theodore Wagener, PhD

Theodore L. Wagener, Ph.D., Laura A. Beebe, Ph.D., Lindsay Boeckman, M.S., Stephen R. Gillaspy, Ph.D.

Oklahoma Tobacco Research Center & University of Oklahoma Health Sciences Center

Dual use of e-cigarettes (ECs) and combustible cigarettes is becoming more common among callers to state tobacco quitlines. How to treat these dual users is unclear, as little is known about the prevalence of dual use among callers, as well as their reasons for dual use, frequency and quantity of use, level of nicotine dependence, and intention to quit both or just one product. Moreover, it is unclear how dual use with e-cigarettes will impact callers' treatment completion and outcomes. To begin to address these questions, we analyzed data from 16,959 callers to the Oklahoma Tobacco Helpline who registered for intervention between October 2013 and June 2014. Seven-month follow-up data collection is ongoing and was not analyzed. Approximately 13% (n=2,135) of callers were dual users. Among dual users, 58% were non-daily users of ECs and 42% were daily users; 32% vaped <1mL of e-liquid per day and 25% vaped between 1 to 5mL. The most common EC type used was a tank system (69%). The majority of dual users reported that they began using ECs to quit other tobacco (50%) or cut down on other tobacco (38%). The overwhelming majority of dual users (92%) were also thinking about quitting ECs. Compared to cigarette-only users, dual users had similar levels of nicotine dependence (p=.48), but they were more likely to be female (p<.0001), White (p=<.0001), and smoke fewer cigarettes per day (p<.05). In terms of treatment adherence, dual users and cigarette-only users completed a similar number of quitline intervention calls (p=.17). The prevalence of dual use of ECs among quitline callers was significant; however, compared to cigarette-only users, dual users did not report higher levels of dependence nor did their dual use appear to undermine the number of intervention calls they completed. Interestingly, the majority dual users were interested in quitting both combustible cigarettes and ECs. As 7-month follow-up data collection is ongoing, it is still not yet clear how dual use affected smoking cessation outcomes.

THE VIEW FROM THE OTHER SIDE OF THE COUNTER: INTERVIEWS WITH VAPOR STORE OWNERS

Presenter: Marshall Cheney, PhD

Department of Health and Exercise Science, University of Oklahoma

Purpose Electronic cigarette use is becoming increasingly popular but little is known about the role of the vapor store in promoting vaping behaviors and user beliefs about vaping. Customers consider vapor store staff experts and rely on their information in making decisions about vaping.

Methods Thirty-three vapor store owners and managers were interviewed about their beliefs and knowledge about e-cigarettes, marketing practices, motivations for selling e-cigarettes, how they explained the safety of vaping to customers, views about teen vapers, and types of customers who come to their store. Interviews were conducted in the vapor store and digitally recorded. The recordings were transcribed and analyzed for themes using NVivo software.

Results Most owners interviewed felt that they were performing an important health service to their customers by helping them stop smoking but regrettably the majority were often misinformed about their products and passed that misinformation along to customers. Owners described how they explained the safety of nicotine and vaping products to customers, such as equating nicotine and caffeine, as well as their beliefs about the health impacts of vaping. Owners shared their "dosing" practices for deciding how much nicotine customers should get in their e-liquid. The majority of owners reported getting most of their knowledge about e-cigarettes from Google and YouTube, including how to mix juices and the safety of their products. Owners described how they marketed their product to different user segments, and discussed their conflicting views about teen vaping and their beliefs about whether vaping promoted smoking. Owners also discussed reactions from the community and local businesses to their store and their involvement with advocacy groups. Finally, most store owners discussed their support of some types of regulation within the industry to protect customers.

Conclusions Vapor stores are the focal point of vaping culture and increasingly are seen as a resource for quitting smoking. Almost all store owners had a sincere interest in helping customers quit smoking but had little access to accurate information or training.

Concurrent Session V – Basic / Translational / Clinical

3:10 p.m. – 4:30 p.m. Level Two, Auditorium

CLINICAL RESEARCH

Moderator: Scott McMeekin, MD

3:10 p.m. – 3:30 p.m.	OPPORTUNITIES AND RESOURCES FOR CLINICAL TRANSLATIONAL RESEARCH Scott McMeekin, MD Department of Obstetrics and Gynecology University of Oklahoma Health Sciences Center
3:30 p.m. – 3:50 p.m.	TSET PHASE I PROGRAM: WHAT HAVE WE LEARNED IN OUR FIRST 5 YEARS Kathleen Moore, MD Department of Obstetrics and Gynecology University of Oklahoma Health Sciences Center
3:50 p.m. – 4:10 p.m.	LUNG CANCER: PROGRAM DEVELOPMENTS AND OPPORTUNITIES Mohamad Razaq, MD Department of Internal Medicine University of Oklahoma Health Sciences Center
4:10 p.m. – 4:30 p.m.	PRECISION MEDICINE: IMPROVING OUR AIM Scott McMeekin, MD Department of Obstetrics and Gynecology University of Oklahoma Health Sciences Center

Concurrent Session V – Cancer Health Disparities

3:10 p.m. – 4:30 p.m. Level B, Room B3

RESEARCH PRESENTATIONS: HOT TOPICS IN CANCER HEALTH DISPARITIES

Moderator: Mark Doescher, MD, MSPH

3:10 p.m. – 3:30 p.m.	THE EXPERIENCE OF CANCER IN AMERICAN INDIANS LIVING IN OKLAHOMA Kathleen Dwyer, PhD, RN Department of Nursing University of Oklahoma Health Sciences Center
3:30 p.m. – 3:50 p.m.	PROMOTING REGULAR SCREENING MAMMOGRAPHY IN AN AMERICAN INDIAN COMMUNITY IN OKLAHOMA: AN UPDATE Eleni Tolma, PhD, MPH Department of Health Promotion Sciences University of Oklahoma Health Sciences Center
3:50 p.m. – 4:10 p.m.	INFLUENCE OF CHILD CARE CENTER ENVIRONMENT ON OBESOGENIC BEHAVIORS IN PRESCHOOLERS Susan Sisson, PhD, RDN, CHES, FACSM Department of Nutritional Sciences University of Oklahoma Health Sciences Center
4:10 p.m. – 4:30 p.m.	DEATH OR DEBT? THE FINANCIAL TOXICITY OF CANCER AMONG THE NEWLY-DIAGNOSED Grant Skrepnek, PhD, RPH Department of Pharmacy: Clinical and Administration Sciences University of Oklahoma Health Sciences Center

THE EXPERIENCE OF CANCER IN AMERICAN INDIANS LIVING IN OKLAHOMA

Presenter: Kathleen Dwyer, PhD, RN

Kathleen Dwyer PhD RN[1], Melissa Craft PhD APRN-CNS AOCN[1], Beverly Patchell PhD APRN-CNS[2], Jack Friedman PhD[3], Lancer Stephens PhD[1]

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Introduction: Studies show a higher incidence rate of cancers in the American Indian (AI) tribes in the Southern Plains; Oklahoma's region. The CDC indicates that many cancers in AIs are not diagnosed at local stages leading to more morbidity associated with treatment and decreased quality of life (QOL). Several regional centers such as the Cherokee Nation in Eastern Oklahoma have been funded to provide comprehensive cancer care to AIs. Most of these programs address reducing the burden of cancer in AIs. However, scant research in the area of quality of life of the AI cancer patient/survivor was found in the literature. The purpose of this study was to describe the experience of living with cancer in AIs in Oklahoma in order to gain a greater understanding of QOL issues affecting AIs with cancer to provide the basis for future interventional studies.

Method(s): This descriptive pilot study utilized a mixed methods approach to data collection and analysis. The primary focus was an ethnographic exploration of the experience of having cancer in AI cancer patients. Twenty-one participants were recruited from AIs diagnosed with cancer and receiving care in Oklahoma. Qualitative data were analyzed using thematic analysis. Descriptive statistics were used to analyze the quantitative data.

Results: Qualitative data analysis identified eight key themes in the stories of AIs in Oklahoma diagnosed with cancer. These themes included: circles of support, finding meaning in the experience, facing personal challenges like uncertainty, physical sequelae, and emotional symptoms. Challenges described also included healthcare related issues such as having their mental health needs addressed and fragmentation of care. Other themes that are preliminarily being identified are those of strength and resilience related to culture and family, tension in balancing western medicine with traditional healing and importance of spirituality in one's cancer journey. Examining the mean FACT-G scores in comparison to published norms for ambulatory cancer patients in the U.S., more than half of the participants in our sample fell below the mean on each subscale and for the total score.

Discussion & Conclusions: The findings from this pilot study provide insights into the cancer experience for a small group of AIs in Oklahoma. The results suggest that social support along with physical sequelae and emotional needs are important aspects to address in future intervention development.

This work was supported by a grant from the Stephenson Cancer Center-Cancer Health Disparities Program

PROMOTING REGULAR SCREENING MAMMOGRAPHY IN AN AMERICAN INDIAN COMMUNITY IN OKLAHOMA: AN UPDATE

Presenter: Eleni Tolma, PhD, MPH

Introduction: Breast cancer is an important public health issue among American Indian/Alaska Native (AI/AN) women. A sustained multi-component (clinical and community) intervention based on a sound theoretical model, the Theory of Planned Behavior, and community member input has a high propensity to yield improved rates of mammography uptake and clinical outcomes among AI women in Oklahoma.

Methods: The priority population consists of women who have not had a mammogram during the last 2 years or more, ages 52-74 years old. The study has four aims: 1) conduct a needs and resource assessment of the priority population; 2) utilize the needs and resource assessment data to refine the overarching intervention Logic Model and develop a community-driven intervention program; 3) pilot-test the intervention; and 4) fully implement and evaluate the effectiveness of the intervention.

Results: Community members indicated that the proposed intervention should center on promoting the concepts of social modeling and physician recommendation while addressing the issues of breast cancer fatalism and lack of knowledge about mammography screening (Aim 1). The Logic Model has been finalized, education materials developed, and alliances built with other grassroots initiatives in the region (Aim 2). The intervention includes four main strategies: a) Structured communication between medical practitioner and patient; b) Receipt of a breast cancer brochure and subsequent follow-up letter from the medical provider; c) Participation in a discussion group modeled after the Freire methodology; and d) Congratulatory bracelet upon receipt of a mammogram. The intervention pilot testing is completed (Aim 3). Project implementation and evaluation is underway (Aim 4). We have recruited 29 women to date. Preliminary results based on the analysis of 22 available surveys indicate that only 25% ever had a Professional Breast Examination, and only 57% intend to get a mammogram within the next 3-5 months. Finally, only 20% identified screening mammography and Professional Breast Examination as the recommended modalities for early detection of breast cancer. Six discussions groups have taken place and 26 women have participated. Highlights from the discussion groups include: a) uncomfortable/painful experience from past mammograms ; b) strong cultural/life-related beliefs; c) a good social support system (including husband's support) can encourage AI women to get mammograms; and d) small group discussions with younger women and family members.

Conclusion*:* Creating a theory-based culturally-sensitive multi-component intervention within a Native American community and translating research results into practical applications is an exciting, yet challenging process. The direct involvement of the community was instrumental for developing an intervention that was culturally-sensitive, responsive to community needs, and sustainable.

INFLUENCE OF CHILD CARE CENTER ENVIRONMENT ON OBESOGENIC BEHAVIORS IN PRESCHOOLERS

Presenter: Susan Sisson, PhD, RDN, CHES, FACSM

Susan B. Sisson[1,2], Lancer Stephens[2,3,4], Janis E. Campbell[5], Karina R. Lora[1], Sandra H. Arnold[6], Diane Horm[7], Ji Li[5], Julie Stoner[5], Beth DeGrace[6]

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Child care centers (CCC) are an integral part of life for most American families with young children. Understanding relationships between CCC and children's obesogenic behaviors will move obesity prevention efforts forward, especially in groups at high risk for obesity.

Purpose: Determine the relationship between the CCC physical activity (PA) and nutrition environments and obesogenic behaviors in young children attending tribally-affiliated CCCs in Oklahoma. **Methods:** This cross-sectional study included 11 tribally-affiliated CCC across Oklahoma and 82 3-5 year old children. Caregivers voluntarily consented to participate. Day-long classroom observations were conducted using the Environmental and Policy Assessment Observation (EPAO) to determine the PA and nutrition environments. Children wore an ActiGraph GT3X accelerometer to measure PA. The Dietary Observation in Child Care plate waste technique was used to determine the nutrient content of foods served and consumed. **Results:** The participants were (mean±*SD*) 3.8±0.1 years, 55% male, and 67% American Indian. Thirty-eight percent were classified as overweight or obese. Participants wore the accelerometer for an average of 5.9±1.7 hours, excluding nap; 84% of this time was sedentary. Children accumulated 4294±1883 steps/day and spent 4.3±2.2 minutes/hour in moderate-to-vigorous PA. A healthier EPAO score for PA was associated with more time wearing the accelerometer and more minutes of sedentary time. Opportunities for activity, time spent in active play, and time spent outdoors were associated with more steps/day. More opportunities for PA was also associated with more minutes of vigorous PA. On average, children were served 510±241 kilocalories and consumed 387±239 kilocalories at lunch. Lunches consisted of 47% carbohydrate, 20% protein, and 33% fat. There were no relationships between EPAO nutrition and dietary variables. **Conclusion:** The prevalence of overweight and obesity was higher than national averages for young children. This study demonstrates that opportunity for active play and access to the outdoors at CCC is associated with higher levels of PA in preschoolers. Encouraging CCC to develop practices that support PA is likely an important focus for practitioners to assist in obesity prevention efforts.

Study supported by the Stephenson Cancer Center and Gretchen Swanson Center for Nutrition

DEATH OR DEBT? THE FINANCIAL TOXICITY OF CANCER AMONG THE NEWLY-DIAGNOSED
Presenter: Grant Skrepnek, PhD, RPH

Adrienne Gilligan, PhD[1,2] and Grant H. Skrepnek, PhD, RPh[3,4*]

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Introduction: Financial toxicity refers to unintended personal financial consequence and loss associated with medical care. Previous work has indicated that fewer patients initiate treatment as out-of-pocket expenditures increase, while others often discontinue care early. It is estimated that over 2 million cancer survivors did not receive necessary medical services due to financial concerns.
Objectives: To evaluate the impact of cancer diagnoses upon a patient's depletion of net worth and incursion of debt in the U.S. from 2000-2010.
Methods: This retrospective, cross-sectional, longitudinal study utilized the nationally-representative Health and Retirement Study (HRS) sponsored by the National Institutes of Aging and Social Security Administration from 1998-2010 to include all persons ≥50 years of age with newly-diagnosed cancers or malignant tumors, excluding minor skin cancers. Generalized linear models (binomial/logistic, Gaussian) were used to assess changes in both net worth and debt (consumer, mortgage, home equity) following new diagnoses of cancer, also controlling for socio-demographic variables, cancer-specific and other clinically-related attributes, human capital characteristics, economic factors, and mortality. A pre-index, baseline period for each individual was defined as two years prior to diagnosis to serve as a historical control.
Results: Across the 6,055,110 million new diagnoses of cancer observed, individuals averaged 68.1±9.0 years at diagnosis and were predominantly male (53.8%), white (90.3%), of non-Hispanic ethnicity (95.5%), married (60.9%), retired (54.8%), and Medicare beneficiaries (63.6%). Two years following an initial cancer diagnosis, approximately half (48.2%) depleted their entire life assets, increasing to almost two-thirds (64.9%) by year four; average losses approached $100,000. Longer-term depletion of net worth was significantly associated with private insurance (versus Medicare), continued requirement of treatment beyond two years, and the 2007-2008 fiscal crisis ($p<0.05$). The proportion of persons with consumer, mortgage, and home equity debt was significantly greater at four years versus two following an initial cancer diagnosis ($p<0.05$).
Conclusion: This investigation of over 6 million newly-diagnosed persons with cancer indicates marked financial toxicity associated with the condition and its treatment. While limited research has focused on the economic attributes of cancer survivorship, a large financial burden may adversely affect a patient's access and adherence to known and effective approaches to prevent, treat, and cure cancer.

Poster Presentation Abstracts

Cancer Research Symposium Poster Session

12:05 p.m. – 1:35 p.m. **Level 1**

Poster Presentation List (listed A-Z by presenter)	Poster Location	Track
THYROID PAPILLARY MICROCARCINOMA: A 10 YEAR INSTITUTIONAL EXPERIENCE Agarwal, Shweta	27	B/T/C
IMPACT OF INSURANCE STATUS ON THE DAY OF ADMISSION AND CLINICAL OUTCOME IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS Ahmad, Bilal	97	B/T/C
INHIBITION OF ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3-MEDIATED DRUG TRANSPORT BY PROTEASOME INHIBITOR BORTEZOMIB: IMPLICATIONS IN CANCER THERAPY Alam, Khondoker	59	B/T/C
TARGETING A TUMOR STEM CELL MARKER DOUBLECORTIN-LIKE KINASE FOR THE TREATMENT OF LIVER CANCER AT EARLY STAGE Ali, Naushad	1	B/T/C
TUMOR-TARGETED DELIVERY OF DOXORUBICIN IN LUNG CANCER CELL LINE USING MULTIFUNCTIONAL GOLD NANOPARTICLES Amreddy, Narisreddy	28	B/T/C
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ABNORMAL INTEROCEPTIVE INSULA ACTIVITY ASSOCIATED WITH NICOTINE CRAVING IN LONG-TERM SMOKERS Avery, Jason A.	98	CHD
AG311 TARGETS THE MITOCHONDRIAL RESPIRATORY CHAIN TO TRIGGER CELL DEATH IN BREAST CANCER CELLS Bastian, Anja	60	B/T/C

THYROID PAPILLARY MICROCARCINOMA: A 10 YEAR INSTITUTIONAL EXPERIENCE
Presenter: Shweta Agarwal

Shweta Agarwal[1] MD, Kar-Ming Fung[1, 2] MD, PhD, Elizabeth Gillies[1, 2] MD

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Thyroid microcarcinoma is defined as thyroid cancer ≤ 10 mm in diameter and is usually papillary microcarcinoma (PMC). Despite recent increase in incidence, there is little consensus in the management of thyroid microcarcinomas. This study aims to review the frequency of multifocality, lymph node (LN) metastasis, extrathyroidal extension and the surgery performed on patients diagnosed with PMCs at the University of Oklahoma Medical center from 2004-2014. During this time, 20 PMCs were diagnosed at the Department of Pathology with tumor size ranging from 2mm to 10 mm. 9/20 PMCs were treated with total thyroidectomies, of which 4 demonstrated multifocality. For Multifocal PMCs, microcarcinoma foci were present bilaterally and tumor sizes ranged from 4 mm-10 mm. 1/11 PMCs treated with lobectomies showed multifocal PMCs in the resected lobe and the largest focus of microcarcinoma in this case measured 10 mm. 7/20 cases had accompanying LN dissection with central compartment LNs in 6 cases, central and ipsilateral cervical LN dissection in 2 cases and contralateral cervical LN dissection in 1 case. 3/7 cases showed LN metastasis to central compartment with or without lateral cervical LN involvement with only one case showing contralateral LN metastasis. Extra thyroidal extension and metastasis was identified in one case each. To summarize, multifocal PMCs were found in 5/20 (25 %) cases, LN metastasis (central and lateral cervical) was reported in 20% (4/20) cases. In addition, extrathyroidal extension and soft tissue metastasis were seen in 5% cases each. In this study, tumor size for cases showing features of adverse prognosis was recorded as ≥4mm. This data supports total thyroidectomy as the preferred treatment for PMCs with a conservative LN dissection approach limited to central compartment and/or palpable neck nodes.

Table 1: Tumor demographics and biological parameters for Thyroid Papillary microcarcinoma (PMCs), 2004-2014 (a review)

Age range	13 - 61 yrs
Sex ratio	F: M= 17:3 (5.7)
Tumor size range	2 mm-10 mm
Multifocality	5/20 (25 %), 4 total thyroidectomies, 1 lobectomy
Lymph node metastasis	4 (20%), 3 central LNs+/- Ipsilateral LNs, 1 contralateral
Extrathyroidal extension	1 (5%)
Metastasis	1 (5%)

IMPACT OF INSURANCE STATUS ON THE DAY OF ADMISSION AND CLINICAL OUTCOME IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS

Presenter: Bilal Ahmad

Bilal Ahmad MD[1], Hossein Maymani MD[2], Haseeb Saeed, MD[2], Mohamad Khawandanah, MD[1], Samer A Srour, MB ChB[1], Michael G Machiorlatti, MS[3], Adam S. Asch, MD[1] and Mohamad Cherry MD[1]

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Background:

In patients with acute myeloid leukemia (AML), insurance status has not been demonstrated to adversely impact outcomes. However, insurance status appears to be an independent factor in healthcare utilization. University of Oklahoma Health Sciences Center (OUHSC) is the main tertiary hospital in the State of Oklahoma treating patients with acute leukemia. We hypothesized that treatment patterns might be different between the insured and uninsured patients. We hereby attempt to analyze the association between insurance status, week day of admission and outcomes.

Methods:

We retrospectively analyzed patients from January 2000 to June 2012 diagnosed with AML over 18 years of age, who were treated at OUHSC with induction chemotherapy. We retrospectively analyzed patients from January 2000 to June 2012 diagnosed with AML over 18 years of age, who were treated at Oklahoma University Health Sciences Center (OUHSC) with induction chemotherapy. Patients were divided into two groups: Group 1 included patients who were admitted earlier in the week (Sun-Wed) and group 2 included patients admitted towards the weekend (Thurs-Sat). Patients were also sub-classified as having private insurance, public insurance (Medicaid and Medicare) or no insurance.Primary outcomes were overall survival at follow up (OS), complete remission (CR) and relapse. Chi-Square analysis was utilized to assess if day of admission and insurance status was related to OS, CR and relapse. Cox proportional hazards model was used to measure association of insurance status, day of admission and their interaction and Kaplan Meir Survival curves were used to estimate survival rates for day of admission by insurance status

Results:

We analyzed total of 161 patients, 157 met inclusion criteria with 69 (44%) having private insurance, 58 (37%) with public insurance and 30 (19%) were uninsured. Group 1, with 94 (60%) patients, was admitted earlier in the week (Sun–Wed), and group 2, with 63 (40%) patients, was admitted later in the week (Thurs-Sat). The median age at diagnosis was 49 years, 63.7% male 36.3% female. 77.0% white, 10.6% African American, 6.2% Native American and 3.7% Hispanic. 63% of uninsured patients were admitted later in the week (Thurs-Sat) compared to only 35% of insured patients (p=0.0385). There was an interaction between insurance and day of admission with OS (p=0.0378). Patients with insurance who were admitted later in the week Thurs-Sat (Group 2) had a hazard ratio (HR) of death 3.09 (95%CI 1.76-5.42) relative to those admitted earlier in the week Sun-Wed (Group 1) (p<0.0001). Median overall survival (OS) for uninsured patients in Groups 1 and 2 was 0.77 and 1.47 years as compare to median OS for insured patients in Groups 1 and 2 of 1.47 and 0.42 years with a p-value=0.0006 respectively. The proportion of patients achieving CR did not differ by day of admission (p=0.6389) and insurance type (p=0.3611). Relapse was not associated with day of admission (p=0.7316) or by insurance type (p=0.1806).

Conclusions:

For the patients with the diagnosis of AML who presented to our institution, uninsured patients were admitted later in the week in comparison to insured patients. The overall survival was lower for the patients who were admitted towards the weekend as compare to patients who were admitted earlier in the week. This trend is both noteworthy and significant and due to its possible impact on standard of care warrants further investigation.

INHIBITION OF ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3-MEDIATED DRUG TRANSPORT BY PROTEASOME INHIBITOR BORTEZOMIB: IMPLICATIONS IN CANCER THERAPY

Presenter: Khondoker Alam

Khondoker Alam[1], John Powell[1], Kai Ding[2] and Wei Yue[1]

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Purpose OATP1B3 is a drug transport protein expressed at the basolateral membrane of the liver as well as many cancers, it mediates uptake of many clinically important drugs into the cells (e.g., statins and paclitaxel). To date, little is known about how OATP1B3 function is regulated. We hypothesized that OATP1B3 is post-transnationally modified by ubiquitination and that proteasome inhibition affects OATP1B3 transport function. The aim of this study was to determine the ubiquitin-modification of OATP1B3 and the impact of bortezomib, the first-in-class proteasome inhibitor for cancer therapy, on OATP1B3 transport function in a HEK293-OATP1B3 stable cell line and human sandwich-cultured hepatocytes (SCH).

Methods Ubiquitination of OATP1B3 was determined by co-immunoprecipitation of HA-Ub and FLAG-OATP1B3 in HEK293 cells transiently transfected with plasmid vectors expressing HA-Ub, FLAG-OATP1B3 or both. Direct inhibition of bortezomib (0.1 - 5 μM) to OATP1B3-mediated [^{3}H]CCK-8 transport (1 μM, 3 min) was determined in a HEK293-OATP1B3 stable cell line. To determine the potential indirect effect of bortezomib on OATP1B3 transport function, HEK293-OATP1B3 and human SCH were pre-treated with bortezomib, 100 nM and 250 nM, respectively, or vehicle control for up to 7 h. After rinsing with HBSS buffer, [^{3}H]CCK-8 accumulation (1 μM, 3 min) was compared between bortezomib treatment and control. LDH toxicity assay was performed to determine cytotoxicity following bortezomib treatment.

Results HA-Ub and FLAG-OATP1B3 were co-immunoprecipitated in HA-Ub/FLAG-OATP1B3-cotransfected HEK293, indicating that OATP1B3 undergoes ubiquitination. Bortezomib did not directly affect [^{3}H]CCK-8 uptake in HEK293-OATP1B3. However, bortezomib pre-treatment for as short as 2 h significantly decreased [^{3}H]CCK-8 uptake both in HEK293-OATP1B3 and human SCH. In HEK293-OATP1B3 cells, 2 h and 7 h bortezomib pre-treatment significantly decreased [^{3}H]CCK-8 accumulation to 75.6 ± 7.7% and 71.9 ± 2.5% of control, respectively (n=3). In human SCH, 7 h bortezomib pre-treatment significantly decreased [^{3}H]CCK-8 accumulation to 61.6 ± 9.9% of control (n=4 livers). LDH assay indicated negligible toxicity after bortezomib treatment.

Conclusions This is the first indication that OATP1B3 is post-translationally modified by ubiquitin and that proteasome inhibitor inhibits OATP1B3 transport function. The inhibition of OATP1B3-mediated transport by bortezomib occurred in an indirect manner, presumably by affecting ubiquitin modification of OATP1B3. Inhibition of OATP1B3 transport function by bortezomib highlights the clinical significance of proteasome inhibition as a potential determinant for OATP1B3-mediated DDIs affecting the pharmacokinetics and efficacy of OATP1B3 substrates (e.g. statins, paclitaxel).

TARGETING A TUMOR STEM CELL MARKER DOUBLECORTIN-LIKE KINASE FOR THE TREATMENT OF LIVER CANCER AT EARLY STAGE

Presenter: Naushad Ali

Naushad Ali[1,6,7*], Parthasarathy Chandrakesan[1], Charles B. Nguyen[1], Sanam Husain[4,6], Allison F. Gillaspy[5,6], Mark Huycke[2,6,7], William L. Berry[3], Randal May[1], Dongfeng Qu[1], Nathaniel Weygant[1], Sripathi M. Sureban[1,6,7], Danny N. Dhanasekaran[3,6] and Courtney W. Houchen[1,6,7*]

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Introduction: Hepatocellular Carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. Hepatitis C virus (HCV)-induced chronic inflammation and cirrhosis of the liver are recognized as major risk factors for the initiation of HCC. Non-viral factors and signaling dysregulation have also been shown to contribute to HCC. Chemotherapy, surgical resection, radiation and local ablation are not effective in a large group of patients with cirrhosis and HCC. Improving the treatment outcomes in these patients will require early intervention, identification of novel molecular targets and unraveling signaling pathways that confer resistance to current treatment modalities. Our recent studies have revealed a positive correlation between expression of the tumor stem cell (TSC) marker doublecortin-like kinase (DCLK1) and cancer growth in the colon and pancreas. However, the molecular mechanism(s) by which its overexpression impacts key signaling pathways during hepatocarcinogenesis is largely unknown.

Methods: We used transcriptome analysis of DCLK1-overexpressing and HCV replicon co-expressing cell lines, Huh7 hepatoma cells-derived tumor xenografts, patient's liver tissues and normal human hepatocytes-derived hepatospheroids to investigate DCLK1-regulated signaling pathways in the liver. Real-time PCR, and Western blot were used to validate the results. The siRNAs and shRNAs against DCLK1, and a small molecule kinase inhibitor (XMD8-92) were used to investigate the impacts of DCLK1 on HCV replication, hepatoma cell migration and tumor growth.

Results: Unlike the normal liver, DCLK1 overexpression was observed in lymphoid aggregates consisting of T and B cells, bile ducts, and epithelial/stromal cells in HCV-positive patients with cirrhosis and HCC. Normal human hepatocytes expressed DCLK1 when cultured as spheroids in Matrigel, but not in monolayer. These spheroids differentiated into neuronal and hepatic cell lineages upon stimulation with serum. A positive correlation in DCLK1 overexpression with extensive expression of pro-inflammatory S100A9 and c-Myc, and activation of NFκB was observed in xenograft model and patient liver tissues. Silencing of DCLK1 inhibited S100A9 expression, hepatoma (Huh7) cell migration and Huh7 cells-derived tumor growth. The transcriptome-based analysis for differential gene expression revealed that DCLK1 controls signaling network that drives inflammation, formation of tumor-associated SW1/SNF1 chromatin remodeling complexes and tumorigenesis in the liver.

Conclusions: The results underscore the potential role of DCLK1 in signal regulation involving inflammation, chromatic remodeling and tumorigenesis. Thus, DCLK1 is a bona fide therapeutic target for the treatment of HCV-induced inflammation, cirrhosis and HCC.

TUMOR-TARGETED DELIVERY OF DOXORUBICIN IN LUNG CANCER CELL LINE USING MULTIFUNCTIONAL GOLD NANOPARTICLES

Presenter: Narisreddy Amreddy

Narisreddy Amreddy[1,3], Anish Babu[1,3], Ranganayaki Muralidharan[1,3], Meghna Mehta[2,3], Elyse V. Johnson[4], Anupama Munshi[2,3], Rajagopal Ramesh[1,3]

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Effective treatment of lung cancer remains a challenge. Despite advances made in cancer therapy, the five-year survival of patients diagnosed with lung cancer is less than 16%. Conventional chemotherapy poses challenges and is often limited in its use due to poor drug accumulation in the tumor and non-specific cytotoxicity to normal tissues. Therefore, by circumventing these problems and improving drug accumulation in the tumor the therapeutic efficacy of the chemotherapeutic can be improved.

In the present study we have developed tumor-targeted multifunctional gold-based nanoparticles that can selectively deliver Doxorubicin (Dox) to lung cancer cells. Gold nanorods (GNR) **(**3.8 aspect ratio) were conjugated with Dox via pH sensitive hydrazone bond and decorated with transferrin molecules. The rationale to use pH sensitive linker is due to the fact that the nanoparticles after getting internalized into the targeted tumor cell enter the acidic endosome/lysosome compartment where the linker gets cleaved and releases Dox inside the cell. Similarly, transferrin (Tf) was chosen as the tumor targeting ligand towards transferrin receptor (TfR) as lung cancer cells overexpress the receptor. The final synthesized nanoparticles were labeled as GNR-Dox- Tf. The efficacy of GNR-Dox-Tf was compared to GNR-Dox that lacked Tf and free Dox and tested in the non-small cell lung cancer cell line, A549 that expresses high levels of TfR. The nanoparticles were subjected to physico-chemical characterization, specificity assays, cell uptake studies and hyperspectral imaging. The nanoparticles were subsequently tested for efficacy. Cell uptake studies demonstrated GNR-Dox-Tf nanorods specifically targeted TfR overexpressing A549 tumor cells compared to normal lung fibroblast (MRC-9) cells that expressed low levels of TfR. Additionally, higher uptake of GNR-Dox-Tf compared to GNR-Dox was observed in A549 cell line. Cell viability assay demonstrated GNR-Dox-Tf induced greater cytotoxicity (55%) compared to GNR-Dox (37%) in A549 cells. Further, GNR-Dox-Tf-mediated cytotoxicity was enhanced (78%) in the presence of desferrioxamine (DFO). In contrast, the GNR-Dox-Tf-mediated cytotoxicity towards MRC-9 cells was significantly less than that observed for A549 cells demonstrating selectivity towards tumor cells. Molecular studies revealed GNR-Dox-Tf induced G2 phase cell-cycle arrest and apoptosis as evidenced by activation of caspase-9 and PARP in A549 cells. GNR-Dox-Tf also elicited a DNA damage response as evidenced by longer tails in a neutral comet assay and prolonged γ-H2AX foci. GNR-Dox-treated tumor cells also induced a G2 cell cycle arrest, DNA damage response and activation of the apoptotic signaling, the response however was lower than that observed in GNR-Dox-Tf-treated cells. The GNR-Dox-Tf induced minimal toxicity in MRC-9 cells compared to the A549 cells. In conclusion, our *in vitro* study demonstrated the ability of multifunctional nanoparticles to selectively target and deliver chemotherapeutic agents to induce cytotoxicity in tumor cells with minimal toxicity to normal cells.

This study was supported in part by a grant from the National Cancer Institute, 5R01 CA167516.

RESTORATION OF HIPPOCAMPAL VASCULAR DENSITY FOLLOWING BRAIN IRRADIATION: A ROLE FOR ENDOTHELIAL PROGENITOR CELLS

Presenter: Nicole M. Ashpole

Nicole M. Ashpole[1], Junie P. Warrington[1,2], Matthew C. Mitschelen[1], Han Yan[1], Danuta Sosnowska[1], Tripti Gautam[1], Julie A. Farley[1], Anna Csiszar[1], Zoltan Ungvari[1], William E. Sonntag[1,2]

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Whole brain radiation therapy (WBRT) remains the most common form of treatment for metastatic brain tumors. Despite the success of this regimen in reducing tumor growth and increasing cancer survival, studies in human and animal models have demonstrated that WBRT induces significant cognitive deficits after treatment. Previously, we have shown that the WBRT-associated cognitive impairments are associated with significant capillary rarefaction in the hippocampus of mice. Despite the vascular loss and localized cerebral hypoxia, angiogenesis fails to occur within these mice, which subsequently induces the long-term deficits in learning and memory. The mechanisms underlying the absence of vessel recovery following WBRT are unknown. In this study, we tested the hypotheses that vascular recovery fails to occur as a result of loss of angiogenic drive in the circulation, chronic tissue inflammation, and/or impaired endothelial cell production/recruitment. Ten week old C57BL/6 mice were subjected to a clinical series of fractionated WBRT: 4.5Gy fractions twice a week for 4 weeks. Following WBRT, angiogenic factors in circulation were assessed *in vitro*. Plasma from radiated mice increased in vitro endothelial cell proliferation and adhesion to a greater extent than plasma from control mice, indicating WBRT did not suppress the pro-angiogenic drive. Analysis of cytokine levels within the hippocampus revealed that IL-10 and IL-12(p40) were significantly increased one month following WBRT; however, systemic hypoxia (which has been shown to promote vessel recovery) did not reduce these inflammatory markers. Enumeration of endothelial progenitor cells (EPCs) in bone marrow and circulation indicated that WBRT reduced EPC production which was restored with systemic hypoxia. Furthermore, using a bone marrow transplantation model, we determined that bone marrow derived endothelial-like cells home to the hippocampus following systemic hypoxia and contribute to the restoration of vasculature. Thus, the loss of production and homing of EPCs have an important a role in the prolonged vascular rarefaction following WBRT.

ABNORMAL INTEROCEPTIVE INSULA ACTIVITY ASSOCIATED WITH NICOTINE CRAVING IN LONG-TERM SMOKERS

Presenter: Jason A. Avery

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Interoception constitutes the perception of metabolic and visceral signals that collectively contribute to the subjective sense of the body's internal state. The physiological dysregulation associated with nicotine withdrawal promotes an aversive interoceptive state that motivates drug-seeking behaviors aimed at reestablishing homeostasis (i.e., positive alliesthesia). The insular cortex is a cortical destination for interoceptive signals from the body, with demonstrated involvement in neuroimaging studies of interoception and nicotine cue-reactivity. Lesions of the insula are also associated with the dramatic cessation of cigarette craving. This evidence points to a direct role for the insula in manifesting the subjective interoceptive experience of nicotine craving. However, to date there is no human neuroscience evidence demonstrating that nicotine craving is associated with activity in the specific regions of the insula supporting interoception. We therefore recruited long-term cigarette smokers as well as healthy non-smokers to undergo fMRI while performing a task requiring interoceptive attention to visceral sensations or exteroceptive attention in a visual target detection control task. The cigarette smokers were scanned twice, once while nicotine-sated, and once while nicotine-craving.

In a separate group of healthy non-smokers, we observed greater activity within bilateral dorsal mid-insula during attention to visceral sensations compared with the exteroceptive control task. This region has previously been shown to underlie visceral interoception. We used the bilateral dorsal mid-insula clusters for region-of-interest analyses to compare interoception-evoked activity in the smokers between nicotine-craving and nicotine-sated scans. In line with prior findings, we found that nicotine craving was associated with decreased interoception-evoked activity in the mid-insula when compared to the nicotine-sated state. This finding was confirmed in a subsequent whole-brain, voxel-wise analysis, which also identified nicotine-craving-induced reductions in bilateral amygdala and orbitofrontal cortex activity. These findings constitute the first evidence in humans that nicotine craving is associated with alterations in the activity of the specific regions of the insula supporting interoceptive awareness of the body.

AG311 TARGETS THE MITOCHONDRIAL RESPIRATORY CHAIN TO TRIGGER CELL DEATH IN BREAST CANCER CELLS

Presenter: Anja Bastian

Anja Bastian[1], *Lora C. Bailey-Downs[3], Jessica E. Thorpe[2], Aleem Gangjee[4], Kenneth Humphries[5], Michael A. Ihnat[2,3]*

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Chemotherapeutic agents that target mitochondria are emerging as an appealing strategy for the development of new anticancer therapy. The inhibition of the mitochondrial electron transport chain (ETC) provides an alternate and selective mechanism for killing cancer cells, bypassing upstream apoptosis-inducing pathways. This mechanism is based on the concept that cancer cells have higher mitochondrial membrane potential, rendering them inherently sensitive to increased reactive oxygen species (ROS) generation such as superoxide. In addition, pharmacological inhibition of complex I and III at the ubiquinone-binding site could further increase superoxide production. Collectively, this mitochondrial sensitivity represents an attractive approach to selectively kill cancer cells. The purpose of this study was to investigate the mitochondria-associated cell death of AG311, a novel anticancer compound. AG311 (5-[(4-Methylphenyl)thio]-9H-pyrimido[4,5-b]indole-2,4-diamine) is a small molecular weight compound designed by our group. We previously showed that AG311 induces rapid mitochondrial depolarization leading to necrotic cell death in a cancer cell-selective manner. In two mouse orthotopic breast cancer models (MDA-MB-435 and 4T1), AG311 significantly reduced tumor volume by 85% and 81%, respectively (n = 4 - 6), while showing no apparent systemic toxicity.

In this study, we aimed to identify the mitochondrial protein target(s) of AG311 in cancer cells. First, MDA-MB-435 cells, cultured in galactose media to upregulate mitochondrial oxidative phosphorylation, sensitized cells to AG311-induced cell death. Mitochondrial oxygen consumption rate (XFe96 extracellular flux analyzer) drastically decreased by 62.9% (± 12.9, n = 8) in response to AG311 (7.5 µM). The effect of AG311 on mitochondrial ETC complexes was determined by spectrophotometrically measuring NADH oxidation in the presence of antimycin A (complex I), ubiquinol reduction (complex III-IV) or cytochrome c oxidation (complex IV). We found that AG311 inhibited complex I and III activity, but not complex IV. Additional kinetic assays indicated that AG311 competitively inhibited ubiquinone binding and significantly induced generation of mitochondrial superoxide (assessed with MitoSOX Red). Finally, pretreatment with antioxidants (e.g. lipoic acid) partially prevented AG311-induced cell death. In summary, the present results indicate mitochondrial ubiquinone as a likely target for AG311-induced selective cancer cell death through generation of mitochondrial superoxide. This together with the previously demonstrated efficacy further substantiates the use of AG311 as a possible anticancer agent.

PRE-CLINICAL EFFICACY OF RON KINASE INHIBITORS ALONE AND IN COMBINATION WITH PI3K INHIBITORS FOR TREATMENT OF SFRON-EXPRESSING BREAST CANCER

Presenter: Magdalena Bieniasz

Magdalena Bieniasz, Parvathi Radhakrishnan, Alana L. Welm

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Purpose: Most breast cancers display robust and specific activation of the short-form Ron (sfRon) receptor tyrosine kinase, suggesting that sfRon is a potential therapeutic target for treatment of this disease. sfRon-overexpressing breast tumors are characterized by robust activation of the PI3K pathway, and dysregulation of the PI3K signaling network is frequently associated with resistance to tyrosine kinase inhibitors (TKIs). We reasoned that upfront, concurrent inhibition of sfRon and PI3K might enhance the anti-tumor effects of Ron kinase inhibitor therapy while also preventing potential therapeutic resistance.

Experimental design: We first evaluated the effects of candidate Ron kinase inhibitors (OSI-296 and ASLAN002) and PI3K inhibitors (NVP-BKM120 and NVP-BEZ235) to select the best candidates for inhibition of sfRon-expressing breast tumors. Next, we used patient-derived breast tumor xenograft (PDX) models as high-fidelity pre-clinical models to determine the efficacy of single agent or dual Ron/PI3K inhibition. We tested ASLAN002 with and without co-administration of NVP-BKM120 in breast PDX models with and without *PIK3CA* gene mutation.

Results: Breast PDX tumors harboring wild-type *PIK3CA* showed a robust response to ASLAN002 as a single agent. In contrast, PDX tumors harboring mutated *PIK3CA* demonstrated slow, but continued tumor growth in presence of the Ron kinase inhibitor. The H1047R *PIK3CA* mutation contributed to partial resistance to ASLAN002, which was overcome with addition of NVP-BKM120 to the treatment regimen. We further demonstrated that concurrent inhibition of sfRon and PI3K in breast PDX tumors with wild-type *PIK3CA* provided durable tumor stasis after therapy was discontinued, whereas cessation of either monotherapy facilitated tumor recurrence.

Conclusion: Our work provides pre-clinical rationale for targeting sfRon with Ron kinase inhibitors in breast cancer patients, with the important stipulation that tumors harboring *PIK3CA* mutations may be partially resistant to Ron inhibitor therapy. Our data also indicate that tumors with wild type *PIK3CA* are most effectively treated with an upfront combination of Ron and PI3K inhibitors for the most durable response.

AGGRESSIVE REPEAT SURGERY FOR FOCALLY RECURRENT PRIMARY GLIOBLASTOMA: OUTCOMES AND THEORETICAL FRAMEWORK

Presenter: Phillip A. Bonney

Phillip A. Bonney**,** B.S.[1], Michael E. Sughrue, M.D.[1], Charles Teo, FRACS[2]

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Object. The relative benefit of repeat surgery for recurrent glioblastoma is unclear, in part due to the very heterogeneous nature of the patient population and the effect of clinician philosophy on the duration and aggressiveness of treatment. We sought to investigate the role of last progression-free interval on patient outcomes following aggressive repeat surgery for recurrent glioblastoma.

Methods. We present outcomes in 104 patients undergoing repeat surgery for focally recurrent glioblastoma with at least 95% resection and adjuvant treatment at most recent prior surgery. In addition to common variables, we provide data regarding the period of progression-free survival (PFS) following an aggressive lesionectomy for focally recurrent primary glioblastoma (T2), and the next-most recent PFS (T1). We term the ratio T1/T2 the relative aggressivity index (RAI).

Results. The median PFS was 7.8 months, 6.0 months, 4.8 months following 2nd, 3rd and 4-6th craniotomy, respectively. Importantly, there was a wide range of outcomes, with time to post-operative recurrence ranging from 1-24 months in this group. Our analysis found there is no meaningful relationship between T1 and T2, meaning that previous PFS is entirely unable to predict the PFS that the present surgery will provide the patient.

Conclusions. Repeat surgery for glioblastoma is beneficial in many cases, however this is hard to predict pre-operatively. Often, surgery can provide the patient with a good period of disease freedom, but this is variable and we generally lack the ability to predict who these patients are.

Note: The surgeries were performed in Australia. The data were analyzed at this institution.

EQUILIBRATIVE NUCLEOSIDE TRANSPORTERS: A STUDY OF DRUG TRANSLOCATION
Presenter: Rebba C. Boswell-Casteel

Rebba C. Boswell-Casteel, Jennifer M. Johnson, and Franklin A. Hays

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

Equilibrative nucleoside transporters (ENTs) are major pharmaceutical targets responsible for modulating the efficacy of more than 30 FDA/EMA approved drugs that treat an expansive range of disease states (e.g., pancreatic cancer, acute myeloid leukemia, non-Hodgkin lymphoma). In fact, expression levels of human ENT1 have been linked to prolonged survival for pancreatic cancer patients receiving gemcitabine treatment – a nucleoside analog transported by ENTs. However, the molecular mechanism and chemical determinants of ENT-mediated substrate transport, and the atomic resolution topology of ENTs, remains a mystery. The current studies are focused on defining the molecular basis for how therapeutics interact with this class of integral membrane proteins. Function Unknown Number 26 (FUN26) is a yeast ortholog of the human equilibrative nucleoside transporter (ENT) family. FUN26 was expressed and purified to homogeneity and incorporated into proteoliposomes for functional analysis. Gain-of-function mutations have been identified that significantly alter ENT substrate specificity by allowing the transport of nucleotides. An *ab initio* structural model was generated and suggest the mutations play a role in substrate binding and conformational switching/gating of the protein. In addition, the identification of a potential new inhibitor of ENT function has been made and is undergoing characterization.

EXPOSURE TO ELECTRONIC-CIGARETTES' AEROSOL EXTRACTS INDUCE SIGNIFICANT DNA DAMAGE
Presenter: Lacy Brame

Lacy Brame[1,2], Vengatesh Ganapathy[1], Ilangovan Ramachandran[1], Theodore Wagener[3,5], David A. Rubenstein[4], and Lurdes Queimado[1,3, 5,6]

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

Background: E-cigarettes (ECs) have been marketed as an alternative to smoking tobacco cigarettes and their use has been *rapidly* increasing over the last 10 years. All EC products heat a solution that typically contains nicotine turning it into an aerosolized vapor inhaled by the user and subsequently exhaled into the air. Limited evidence suggests that ECs are safer than traditional tobacco cigarettes, however, the risks of EC use are not completely known. Chemical studies of inhaled and exhaled EC aerosols have shown the presence of nicotine, ultrafine particles and low levels of toxins known to cause cancer. Even so, the little research conducted on the effects of EC aerosols has focused almost exclusively on cell death, a parameter that does not correlate with cancer risk.

Aims: To determine whether EC aerosols cause persistent DNA damage in human cells and to define the strand-specific patterns of DNA damage and repair following exposure to EC aerosol extracts.

Methods: EC aerosol extracts from 5 distinct ECs containing selected nicotine concentrations (0-18 mg/ml) were prepared as we previously described for mainstream smoke[1]. Human oral epithelial cells were exposed to escalating doses of EC extracts. All doses used (0.00002 to 0.002 puffs/ml) represent relatively low doses of exposure. DNA damage was quantified in the *p53* gene at 1 and 16 hours post exposure using a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) developed in our laboratory. Cell viability was determined by MTT [3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay. Data were analyzed by Student's *t*-test.

Results: Exposure to EC aerosol extracts for 1 hour resulted in a significant increase in DNA damage in oral epithelial cells for all doses tested. The observed levels of DNA damage were lower than those induced by exposure to mainstream smoke. Sixteen hours after exposure, the levels of persistent DNA damage varied between EC extracts, suggesting that the ability to repair the DNA damage induced by EC aerosol extracts is dependent on their composition. No cell death was observed.

Conclusion: Our study demonstrated that exposure to EC aerosol extracts induces significant DNA damage. Even 1 hour exposure to very low doses of EC aerosol extracts resulted in significant DNA damage. Interestingly, we observed significant differences in the levels of DNA damage and repair following exposure to diverse EC extracts. These data suggest that EC use leads to variable levels of persistent DNA damage and potentially increases cancer risk. Our study emphasizes the need to further investigate the health consequences of exposure to EC aerosols and highlights the extreme importance to regulate EC and the exposure to EC aerosols.

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EPSIN FACILITATES IKK COMPLEX ASSEMBLY TO POTENTIATE NF-KB SIGNALING AND PROMOTE BREAST CANCER PROGRESSION AND METASTASIS

Presenter: Xiaofeng Cai

Xiaofeng Cai,[1] Yong Wei,[3] Hao Wu,[1] Kandice L. Tessneer,[1] Baojun Chang,[1] Satish Pasula,[1] Scott Hahn,[1] Yunzhou Dong,[1] John McManus,[1] Hoogeun Song,[1] Megan L. Brophy,[1,2] Yiyuan Chen,[1] Xiaolei Liu,[1,2] Kai Song,[1] Lijun Xia,[1,2] Yibin Kang,[3,4] and Hong Chen[1,2,]

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Breast cancer is a leading cause of death among women. Although significant advances have been made in delineating the signaling pathways involved in breast cancer progression, studies uncovering regulatory mechanisms are necessary to identify new therapeutic targets. Epsins are a family of endocytic adaptors previously reported to promote tumor angiogenesis. However, the tumor-intrinsic roles of epsins in tumor growth and metastasis still remains an open question. Here, we demonstrate that epsins are not only upregulated in human breast cancer and correlate with poor relapse-free survival, but also required for breast cancer progression and metastasis. Intriguingly, epsin is critical for NF-κB signaling activation by interacting with NEMO via its ubiquitin interactive motif (UIM), facilitating NEMO polyubiquitination and recruiting IKKα/β subunits to promote IKK complex assembly. Our findings establish epsin as a key regulator of NF-κB signaling that drives the progression and metastasis of breast cancer.

CHARACTERIZATION OF A NOVEL TRANSGENIC MOUSE MODEL REVEALS A DUAL TUMOR SUPPRESSIVE AND ONCOGENIC ROLE FOR TMEFF2 IN PROSTATE CANCER

Presenter: JM Corbin

JM Corbin[1,*], JD Wren[2], KM Fung[1], KL Stratton[3] and MJ Ruiz-Echevarria[1,*]

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Prostate cancer (PCa) is the second most common cancer in American men. Surgical methods and radiation therapy are both effective for the treatment of organ-confined PCa; however, late stage castration resistant prostate cancer (CRPC) is currently incurable. While it has become apparent that androgen receptor (AR) signaling remains critical to CRPC, the transition to this form of the disease is not fully understood, and it likely involves additional processes, i.e. the growth stimulatory role of castration resistant neuroendocrine (NE) cells. A better understanding of the mechanisms that drive resistance to castration is essential for the development of effective therapies.

The TMEFF2 protein is expressed in the embryo and in the adult human, mainly in brain and prostate. It has been implicated in a range of cancers, including glioma and PCa, and exhibits both tumor suppressive or oncogenic roles depending on the cellular context. The majority of our studies have demonstrated a tumor suppressor role for TMEFF2 in PCa. TMEFF2 inhibits invasion of PCa cells, which correlates with inhibition of integrin expression and changes in the levels of metabolites of the 1-C metabolism pathway. Data presented here indicate that reduced TMEFF2 expression correlates with decreased disease free survival in a cohort of patients with PCa, suggesting that in fact TMEFF2 can function as a tumor suppressor in the clinical setting. Paradoxically, TMEFF2 is overexpressed in advanced PCa clinical specimens, an observation that is difficult to reconcile with its tumor suppressor role. In order to further analyze the *in vivo* role of TMEFF2 in modulating prostate carcinogenesis, we have developed xenograft models, and a transgenic mouse model that expresses TMEFF2 specifically in the prostate. Expression of TMEFF2 in mouse xenografts prevented subcutaneous tumor formation, confirming its tumor suppressor function. Moreover, characterization of the transgenic TMEFF2 mouse indicated that TMEFF2 expression modulates prostate development but a tumorigenic role was not apparent. Importantly however, when crossed to a transgenic adenocarcinoma of mouse prostate (TRAMP) mouse model, TMEFF2 expression increased the incidence of poorly differentiated neuroendocrine tumors. Consistent with this phenotype, data obtained with GAMMA, a data mining-program, indicated that TMEFF2 positively correlates with the expression of neuroendocrine markers, i.e. chromogranin A. These results indicate that TMEFF2 has a dual role in PCa tumorigenesis, and suggest a model by which TMEFF2 initially functions as a tumor suppressor but switches to an oncogenic role at late stages of the disease. Since TMEFF2 expression is regulated by the AR, and TMEFF2 modulates the activity of the AR (see accompanying poster), it is likely that this constitutes the mechanism by which TMEFF2 exerts its dual function in PCa tumorigenesis.

* Some of these studies were completed by JMC and MJRE while at East Carolina University.

SILENCING ZIP4 SENSITIZES PANCREATIC CANCER TO CHEMOTHERAPY

Presenter: Xiaobo Cui

Xiaobo Cui[1,2,3,5], Yuqing Zhang[4], Shunrong Ji[5], Jingxuan Yang[1,2,3], Liuyan Jiang[6], Qiang Zhang[3,7], Xiaotian Sun[1,2,3], Wenyan Xu[5], Bo Zhang[5], Jiang Long[5], Jin Xu[5], Quanxing Ni[5], Putao Cen[8], Lei Zheng[9], Kai Ding[10], Russell G. Postier[2], Xianjun Yu[5], and Min Li[1,2,3,5]

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Background: Pancreatic cancer is characterized by a high degree of chemoresistance. However, the underlying molecular mechanism is not well understood. ZIP4, a membrane-associated zinc transporter, is overexpressed in most pancreatic cancers and has been found to be involved in pancreatic cancer pathogenesis and progression. The role of ZIP4 in regulating pancreatic cancer chemoresistance has not been investigated previously.

Method: In order to elucidate the relationship of ZIP4 and gemcitabine resistance, we measured the sensitivity of pancreatic cancer cells to chemodrugs by manipulating ZIP4 expression in MIA PaCa-2, AsPC-1 and BxPC-3 cells and in orthotopic xenograft mouse models.

Result: Our findings demonstrated that ZIP4 levels affect both sensitivity and cellular proliferation in response to the chemotherapy agents gemcitabine and cisplatin. Specifically, our cell culture results showed that ZIP4 overexpression confers gemcitabine- and cisplatin-resistance of pancreatic cancer cells. Conversely, silencing ZIP4 sensitizes pancreatic cancer cells to gemcitabine and cisplatin. Using orthotopic xenograft mouse models, we showed that gemcitabine treatments were more effective, as evidenced by overall survival, in the ZIP4-silenced group than in controls. We also found that ZIP4 level is correlated with overall survival in gemcitabine-treated human pancreatic cancer patients. Western blot analysis indicated that ZIP4 may partially regulate gemcitabine resistance by upregulating ENT1.

Conclusion: These results suggest that ZIP4 plays a critical role in pancreatic cancer chemoresistance and may serve as a novel therapeutic target in pancreatic cancer treatment.

FUNCTIONAL GENOMICS CHARACTERIZATION OF *CNOT3* - A NOVEL GENE IMPLICATED IN APC-DRIVEN COLON CANCER PROGRESSION

Presenter: Richard Glenn C. Delacruz

Richard Glenn C. Delacruz[1], Imelda T. Sandoval[1], Ester Borras[2], Eduardo Villar[2] and David A. Jones[1]

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Colon cancer is the fourth most commonly diagnosed cancer in Oklahoma. It arises through successive histological changes that reflect specific underlying genetic alterations in the intestine. Inactivation of the tumor suppressor gene, adenomatous polyposis coli (APC), is responsible for most cases of, and drives the gradual progression of, colorectal cancer. Whole exome sequencing of adenomas from patients with the heritable type of colon cancer predisposition, familial adenomatous polyposis (FAP), identified a novel gene, CNOT3, being recurrently mutated in these adenomas with inactivated APC. *In silico* analyses predict that two CNOT3 mutations, E20K and E70K, are probably damaging. We are using the developing zebrafish embryo as an *in vivo* model system to understand whether APC inactivation and CNOT3 mutation are genetically linked. *In situ* hybridization against zebrafish *cnot3a* mRNA shows that *cnot3a* is present early in development in the brain region and at low levels in the gut. Quantitative RT-PCR analyses in adult zebrafish organs indicate that mRNA expression is highest in brain and testis but detectable in most other tissues. Knockdown of *cnot3a* using a splice blocker antisense oligonucleotide reveal a requirement for cnot3a in brain development and gastrointestinal differentiation. Rescue of these defects was achieved by coinjection of wildtype human CNOT3 (hCNOT3) along with cnot3a morpholino. Similar rescue experiments using the novel E20K and E70K variants show that E20K rescues cnot3a knockdown but E70K does not. These studies suggest that the hCNOT3 E70K mutation has a deleterious functional consequence and may therefore contribute to tumor development.

RON SIGNALING IN LCMV AND CANCER VACCINE SETTINGS

Presenter: Christa I DeVette

Christa I DeVette, H Atakan Ekiz, Alana L Welm

Immunobiology and Cancer Department, Oklahoma Medical Research Foundation, OK, USA

Resident macrophages are important mediators of immune response. Our lab studies the Ron receptor, a tyrosine kinase (TK) expressed primarily in peritoneal macrophages (PM). Mice deficient in the TK domain of Ron are susceptible to lipopolysaccharide-induced sepsis, suggesting that Ron activity is required for attenuating host immune activity. When challenged with tumors overexpressing Ron ligand, hosts lacking Ron TK domain are *more resistant to metastatic outgrowth*. This effect was dependent on CD8+ T cell expansion in Ron TK knockout (TKKO) mice. Therefore, we hypothesize that Ron signaling in PMs helps attenuate cytotoxic T cell responses in the host. Similarly, we propose loss of Ron will be beneficial in cancer vaccine settings where cytotoxic antitumor responses are desirable.

First, we characterized Ron expression in mice. Consistent with published findings and ImmGen microarray data, we detected high levels of Ron protein in PMs compared to other lymphoid tissues. Next, Lymphocytic choriomeningitis virus (LCMV) infection of wild-type and TKKO mice was used to test functional consequences to Ron inhibition. Tissues isolated from infected TKKOs had greater CD8+ T cell activation. Interferon gamma, TNFα and markers of effector T cell differentiation were consistently increased in LCMV-infected TKKO mice. Thus, in a highly infectious setting, the absence of Ron TK produces robust activation of CD8+ T cells.

In the tumor setting, we tested if Ron TK deletion would prolong the cytotoxic T cell response of a cancer vaccine. Protein vaccination decreased primary tumor growth and metastatic outgrowth, with TKKOs being more resistant to metastases compared to their vaccinated cohorts. We plan to validate our results with a DNA vaccine against similar tumor antigens. Together, these results provide exciting avenues for cancer vaccine research and set precedence for studying Ron signaling in cancer and infectious settings.

DOD Breast Cancer Research Program Innovator and Scholar Concept Award
#W81XWH1210499 (to ALW)

EFFECTS OF CHEMOTHERAPY AND RADIATION EXPOSURE ON BRACHIAL ARTERY BLOOD FLOW DURING DYNAMIC HANDGRIP EXERCISE

Presenter: Kaylin D. Didier

Kaylin D. Didier[1], Landon K. Reiter[1], Austin K. Ederer[1], Jacob T. Caldwell[1], James C. Knudson1, Rachel Hardy[1], Carl J. Ade Ph.D [1]

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Cardiovascular Disease (CVD) presents a major concern for cancer survivors treated with chemotherapy and radiation and is one of the leading causes of death in this population. Chemotherapy and radiation treatments have previously been shown to alter central and peripheral cardiovascular function, but the precise etiology is not yet completely understood. However, one type of vascular change that may contribute to the therapy-associated increase in CVD is impairments in endothelium dependent dilation of the peripheral resistance vessels and conduit arteries. Therefore, the purpose of this study was to investigate if the vascular responses to dynamic handgrip exercise are blunted in individuals who have undergone chemotherapy and/or radiation treatment.

To date, 2 cancer survivors (CS) and 4 untreated control(UTC) have completed two dynamic handgrip exercise protocols at relative (10 and 20% maximal voluntary contraction (MVC)) and absolute (3 kg) workloads. Simultaneous measurements of forearm blood flow (FBF; Doppler Ultrasound), and mean arterial pressure (MAP) were taken during each of the exercise workloads. Forearm vascular conductance (FVC) was calculated from MAP and FBF.

Preliminary results: FBF was similar in CS compared to UTC at 10% MVC (168.24 vs. 147.46 ml min^{-1}) and decreased at 20% MVC (177.12 vs. 260.93 ml min^{-1}). FVC was increased in CS when compared to UTC at 10% MVC (177.41 vs. 131.03 ml min^{-1} 100 $mmHg^{-1}$) and reduced at 20% MVC (167.08 vs. 221.62 ml min^{-1} 100 $mmHg^{-1}$). During absolute workloads FBF and FVC of the CS compared to UTC was decreased at 3 kg (131.88 vs. 183.92 ml min^{-1} and 134.26 vs. 165.05 ml min^{-1} 100 $mmHg^{-1}$, respectively). In conclusion, chemotherapy and radiation treatment in cancer survivors results in alterations to exercise blood flow regulation during dynamic exercise, particularly at higher exercise workloads.

MOTIF MIMETIC OF EPSIN SUPPRESSES TUMOR GROWTH AND METASTASIS THROUGH DYSREGULATED VEGFR2 SIGNALING

Presenter: Yunzhou Dong

Yunzhou Dong, Hao Wu, Satish Pasula, Lili Yu and Hong Chen

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Tumor angiogenesis is critical for cancer progression. Genetic endothelial epsin deficiency in mice abrogates tumor progression by shifting the balance of VEGFR2 signaling towards uncontrolled tumor angiogenesis and resulting in dysfunctional tumor vasculature. We adopted a strategy to design a tumor endothelium-targeting chimeric peptide (UPI) for the purpose of inhibiting endogenous tumor endothelial epsins by competitively binding activated VEGFR2. UPI peptide specifically targets tumor endothelial VEGFR2 through an unconventional binding mechanism driven by unique residues present only in the epsin ubiquitin interacting motif (UIM) and VEGFR2 kinase domain. UPI peptide increases VEGF-driven angiogenesis and neovascularization but spares quiescent vascular beds. Further, UPI peptide markedly impairs functional tumor angiogenesis, tumor growth and metastasis, resulting in a significant increase in survival. Equipped with localized tumor endothelium-specific targeting, our UPI peptide provides potential for an effective and alternative cancer therapy.

TGF-β RI INHIBITOR LY2157299 IN UCS PRECLINICAL MODELS
Presenter: Shailendra Kumar Dhar Dwivedi

Shailendra Kumar Dhar Dwivedi*, McMeekin Scott D*, Resham Bhattacharya*

*Department of Obstetrics and Gynecology, Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma

Uterine carcinosarcomas (UCSs) are highly aggressive, rare (4-9% of uterine cancers), biphasic tumors composed of epithelial (carcinosarcomatus) and mesenchymal (sarcomatous) elements. Arising mainly in the uterus, UCS has a high rate of extra-uterine spread at diagnosis and high rate of recurrence responsible for 16.4% of all deaths caused by uterine malignancies. UCS are thought to arise from epithelial or monoclonal cells, sarcomatous regions thus may represent true examples of complete epithelial-mesenchymal transition (EMT). TGFβ is a multifunctional cytokine that not only regulates EMT, but in epithelial cells suppresses growth and proliferation. Contrastingly, aberrations in TGFβ signaling regularly occur inducing the cancer cells to proliferate, invade and metastasize beyond their tissue of origin. The EMT nature and a report demonstrating amplification of the TGFβ locus at 19q13.1 in UCS prompted us to investigate the role of TGFβ signaling in this malignancy.

Using patient samples and cell lines we demonstrate that the components of the TGFβ pathway are expressed and functional in UCS. Importantly mRNA levels of TGFβ-I, TGFβ-II, TGFβR-I and TGFβR-II were higher in recurrent compared to the non-recurrent patient samples. Using FUMMT-1, FUMMT-3 and CS-99 we demonstrated that TGFβ induced significant Smad2/3 activation and migration. TGFβ induced significant proliferation in FUMMT-1 that was cMYC dependent. The EMT response was variable with only CS-99 expressing the epithelial membrane antigen (EMA) that was potently downregulated upon TGFβ treatment. Fibronectin was induced in all the cell lines and potent upregulation of Snail1 was observed in FUMMT-1 and CS-99 both at the mRNA and protein level upon TGFβ treatment.

We next evaluated the efficacy of inhibiting TGFβR-I (LY2157299) or TGFβR-I/II (LY2109761) in mediating TGFβ induced proliferation, migration and EMT. Both LY2157299 and LY2109761 inhibited Smad2/3 activation and TGFβ dependent migration similarly. However though TGFβ dependent proliferation was inhibited by both inhibitors, the RI/RII inhibitor also increased proliferation in absence of exogenous TGFβ. The EMT markers such as Snail1, Slug and Fibronectin were all similarly downregulated upon RI or RI/II treatment.

Importantly the TGFβ induced cMYC when attenuated by either pharmacological or genetic approaches abrogated the proliferation response in FUMMT-1. Though conventionally TGFβ signaling inhibits cMYC expression, a previous report demonstrated that TGFβ through NFAT upregulated cMYC transcription. In accordance we found that downstream of TGFβ, NFAT activation is responsible for cMYC induction and inhibition of either, NFAT, Smad3 or TGFβR-I could inhibit cMYC induction and proliferation. In corroboration mRNA levels of cMYC were elevated in the recurrent compared to non-recurrent group of patient samples. In summary inhibition of TGFβR-I could be efficacious in inhibiting both TGFβ mediated proliferation and migration in UCS cells and induction of cMYC could be a significant prognostic factor predicting poor outcome.

DOES SURGICAL RESECTION ALLEVIATE PRESENTING SYMPTOMS FOR PATIENTS WITH GLIOMAS?
Presenter: Peter A Ebeling

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Introduction: Gliomas are the most common primary intraparenchymal neoplasms of the central nervous system. It has been well-established that surgery is critical to alleviating symptoms and obtaining a definitive diagnosis in glioma patients. While surgery for gliomas is often undertaken to relieve symptoms, there exist very little data regarding how frequently these symptoms actually improve post-operatively. Here, we present a retrospective analysis of symptom relief following surgical resection of intracranial gliomas.

Methods: We performed retrospective chart review on patients undergoing surgical resection of gliomas at our institution between January 2005 and December 2011. Seventy-seven patients with follow-up information available were included in the analysis. Symptom improvement was determined by review of clinical examinations within the first 3 months of surgery. Univariate and multivariate analyses were performed.

Results: Pre-operative symptom incidences were as follows: Headache—41 (53%), seizures—27 (35%), weakness—18 (23%), altered mental status—15 (19%), visual disturbance—14 (18%), nausea/vomiting—13 (17%), ataxia—10 (13%), and others experienced by less than 10 patients (numbness, speech difficulty, syncope, cranial neuropathy, hearing loss). Symptom improvement after surgery was as follows: Headache—53%, seizures—35%, weakness—63%, altered mental status—67%, visual disturbance—64%, nausea/vomiting—77%, ataxia—70%. On univariate analysis, extent of resection, adjuvant therapies, tumor size, and tumor grade were not associated with improvement of individual symptoms.

Conclusions: We present a directed analysis of rates of improvement in various symptoms with surgery. Surgery is often indicated to prolong overall survival in this population, yet patients with gliomas commonly ask if their symptoms will resolve following resection. This study provides some data for pre-operative counseling and decision making.

ALTERATIONS IN ENDOTHELIAL FUNCTION AND FRACTIONAL O_2 EXTRACTION IN LONG-TERM CANCER SURVIVORS TREATED WITH CHEMOTHERAPY AND RADIATION

Presenter: Austin K. Ederer

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Chemotherapy and radiation cancer therapeutics increase arterial stiffness and decrease aerobic exercise capacity, which may be the consequence of altered peripheral cardiovascular function. During exercise, the profile of microvascular fractional O_2 extraction measured via near-infrared spectroscopy (NIRS) derived muscle deoxygenation (Δdeoxy-[Hb+Mb]), which provides information on the dynamic matching of O_2 delivery-to-O_2 utilization. Typically in healthy exercise trained individuals Δdeoxy-[Hb+Mb] slowly increases as the exercise workload progressively increases. However, if O2 delivery is not appropriately matched to O2 utilization, like that experienced with decreased cardiovascular function, the Δdeoxy-[Hb+Mb] will increase rapidly relative to healthy controls. Therefore, we tested the hypothesis that cancer survivors would have an altered profile of Δdeoxy-[Hb+Mb] during exercise.

To date, 2 cancer survivors (CS) and 1 untreated control (UC) completed a ramp exercise test on a cycle ergometer. During exercise Δdeoxy-[Hb+Mb] of the vastus lateralis and rectus femoris was measured, normalized from baseline (0%) to the gas exchange threshold (GET) (100%). The adipose thickness at the site recorded was measured by ultrasound.

The power output at GET (PO_{GET}) was lower in CS compared to UC. Both groups displayed a linear increase in %Δdeoxy-[Hb+Mb]. The %Δdeoxy-[Hb+Mb] slope of the vastus lateralis was greater in CS compared to UC when plotted as a function of PO_{GET} (2.04 vs. 0.80 % W^{-1}, respectively) and %PO_{GET} (1.84 vs. 1.17 % %W^{-1}, respectively). A greater %Δdeoxy-[Hb+Mb] slope of the rectus femoris was also observed in CS compared to UC (1.29 vs. 0.74 % W^{-1} and 1.17 vs. 1.09 % %W^{-1}, respectively). In conclusion, the greater reliance on fractional O_2 extraction displayed in CS during exercise suggests an impaired matching of O_2 delivery-to-O_2 utilization relationship during exercise compared to UC, which may be the result of decreased endothelial function.

OKLAHOMA AMERICAN INDIAN PREFERRED SMOKELESS TOBACCO CESSATION STRATEGIES, PERCEIVED BARRIERS, FACILITATORS, AND MOTIVATORS

Presenter: Valerie Eschiti

Valerie Eschiti, PhD, RN, Janis Campbell, PhD, Lancer Stephens, PhD; Nasir Mustaq, PhD; Jessica Blanchard, PhD, Mike Peercy, MT(ASCP)H, PMP, *MPH* **;** Teresa Davis, RN; Jana Lauderdale, PhD, RN; Stacey Sanford, LPN, Stacey Berg

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Oklahoma American Indians (AIs) have high rates of smokeless tobacco (ST) use. Use of ST is associated with periodontal disease, precancerous oral lesions, oral cancer, kidney cancer, pancreatic cancer, and cancers of the digestive system. The purpose of this study was to determine ST cessation preferences of adult AIs in Oklahoma, as well as barriers, facilitators, and motivators. Because of the spiritual significance of tobacco to AI people, as well as cultural and social factors, an initial step was to find out from the AI people themselves what their preferences are regarding cessation strategies**.**

An Integrative Model of Behavior Prediction served as the framework for the study. A community-based participatory research approach was utilized This mixed methods, descriptive study was conducted using focus groups and individual interviews. Male and female adult participants (n = 30) were recruited from the seven tribal nations of southwest Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita & Affiliated Tribes), Choctaw Nation, Chickasaw Nation, and the Indian Health Care Resource Center of Tulsa.

Demographic data are being analyzed, and will be completed in January 2015. Preliminary qualitative analysis reveals four themes: Why Smoke: More than just a Habit?Kicking the Habit: Barriers to Cessation; Living Tobacco Free: Cessation Success; and Somebody Cares: Strategies for Cessation.

Findings indicate that tobacco use practices are more than just habits, rather they are patterns of behaviors linked to generations of learned behavior. Participants commented on the lack of available cessation tools designed for ST. Motivation to quit tobacco use was varied and ranged from the importance of making cessation a priority, having individual will power, and differentiating between quitting for oneself and quitting for others. Family emerges as the most prominent motivator for cessation. Health concerns appear to be a leading facilitator for tobacco cessation; however, ideas about the relationship between smokeless tobacco use and negative health impacts were not consistent.

This study funded by Oklahoma Stephenson Cancer Center/Tobacco Settlement Endowment Trust.

EXECUTIVE-FUNCTION AND CHEMOTHERAPY EFFECTS ON SENSITIVITY TO THE EMOTIONAL TONE OF VERBAL COMMANDS

Presenter: Blas Espinoza-Varas

Blas Espinoza-Varas, Sudha Lakhwani, Ashan Khan, and Kai Ding

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Rationale. Adherence to treatment plans has a major impact on outcomes and depends heavily on fluid communication between patients and health-care professionals. An important component of treatment adherence entails complying with verbal commands (e.g., "quit smoking!" or "go on a diet!") issued by nurses and physicians to impede or instigate treatment-relevant behaviors; the commands emotional voice tone (VT), lenient or stern, signifies optional or mandatory adherence. Adherence could increase if the patient has keen sensitivity to the emotional VT; however, information or response conflict could decrease the sensitivity pre or post adjuvant chemotherapy (CHT), and decrease adherence. The ability to identify the commands VT in information- or response-conflict conditions that impose on executive functions (EF) could serve as in index of how compliant is a patient with verbal commands.

Method. Between surgery and CHT cycle 1, and between cycles 3 and 4 of gynecological cancers (n=14), we assessed the effects of three EF demands on VT identification for impeding and instigating commands. 1) Inhibitory control trials presented the cue word "left" or "right" followed by impeding commands in lenient or stern tone, mapped onto a left or right response; the cue and ear side could be congruent or in conflict with the correct response side. Trials presenting instigating commands ("go!") mapped lenient or stern onto a right or left response. 2) Response-mapping switching conditions interleaved impeding and instigating commands within the same trial block, and required switching the mapping rule depending on the command, impeding or instigating. 3) Working-memory conditions asked whether the command presented on the current trial was equal to or different from the one presented two trials back.

Results. Compared to that of healthy young adults, the patients' VT identification accuracy was significantly lower, both prior to and after three CHT cycles. With impeding and instigating commands, the patients' VT identification errors were small in conditions free of EF demands, but increased significantly when EF demands were imposed, being largest in condition 2. Relative to conditions without EF demands, identification latencies increased significantly only in condition 2. CHT effects did not reach significance, but individual differences were large.

Conclusions. Even prior to CHT, the ability to process the VT of verbal commands is significantly diminished in cancer patients; as a result, they could have difficulty assessing how mandatory a command is. This deficit could decrease treatment adherence and lead to poor outcomes.

RON KINASE SIGNALING IN BREAST CANCER PROGRESSION AND METASYTASIS
Presenter: Najme Faham

Najme Faham and Alana Welm

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Metastasis is one of the major challenges of tumor biology and accounts for the main cause of death from breast cancer. Metastatic breast cancer is mostly resistant to current treatment options which are mainly designed to target the primary tumor. Therefore, a deeper understanding of the mechanisms behind metastasis is critical for the development of novel therapies. RON (also known as MST1R), a receptor tyrosine kinase with significant homology to c-Met, exhibits increased expression in about 47% of human breast cancers, and deregulated expression of the RON signaling axis has been correlated with poor prognosis and reduced metastasis-free survival of the patients. RON is known to activate multiple signaling pathways *in vitro*, including MAPK, phosphatidylinositol-3 kinase (PI3K), Src tyrosine kinase, phospholipase C-□ (PLC-□□□ and catenin, largely through direct binding of its the C-terminal docking site to SH2-domain containing adaptor proteins. However, the contributions of each signal transduction pathway to specific biologic responses relevant to cancer progression and metastasis are still poorly defined. To this end, we have taken advantage of a mutational strategy used for c-Met in order to guide the signaling through one specific pathway at the expense of the others.

The C-terminal part of RON contains two tandem tyrosines in a degenerate motif that when phosphorylated bind to different SH2-containing molecules in a competitive manner. To amplify the signaling through particular pathway, we mutated the multifunctional docking site of RON to optimal binding motifs for PI3K, Src, Grb2 or PLC-γ. Mutations were introduced to the docking site using a lentivirus expressing human wild type Ron cDNA. As negative controls, we generated a signal dead mutant which the two tyrosines in the docking site were replaced by phenylalanine and is therefore unable to recruit signal transducers, as well as a kinase dead mutant to eliminate the transforming capability of RON. We generated these mutants in a Tet-inducible lentiviral system to be able to titer the expression levels of RON and therefore address both MSP-dependent and independent RON activation. The mutants were stably introduced into T47D breast cancer cells. Analysis of mRNA and protein showed the same expression levels among the mutants and wild type infected cells, indicating similar stability of the mutants compared with WT-RON. We were able to show RON activation in the presence and absence of its ligand. Based on our results, ligand-activation of RON leads to activation of signaling pathways with different kinetics. Our data indicate that different mechanisms of RON activation (MSP-dependent vs MSP independent) can result in differential stimulation of downstream signaling pathways in T47D breast cancer cells.

EFFECT OF VAPING POWER ON AEROSOL SIZE DISTRIBUTION AND E-JUICE CONSUMPTION IN A TYPICAL E-CIGARETTE

Presenter: Evan L. Floyd

Evan L. Floyd*, PhD, David L. Johnson, PhD, Jun Wang, PhD, James L. Regens, PhD,

University of Oklahoma - Health Sciences Center

E-cigarette technology has rapidly evolved toward higher powered devices that produce denser vapor and a more satisfying vaping experience. This research characterizes the effect of vaping power on mass of e-juice vaporized as well as particle size and particle mass distributions.

Vaping aerosol was produced with a tank-style e-cigarette equipped with an adjustable voltage battery set from 3.3 to 11.2 Watts. Aerosol particle size distributions were measured simultaneously with a Scanning Mobility Particle Sizer (SMPS) and an Aerodynamic Particle Sizer (APS), providing a combined size measurement range of 16 nanometers (nm) to 19.8 micrometers (µm). This instrument ensemble was also used to characterize conventional cigarette smoke aerosol for direct comparison. Additionally e-juice vaporization mass was measured at 9 points between 3.0–11.9 watts.

Consistent with prior studies, vaping aerosol size distributions were bimodal in the ultrafine region; however, a previously unreported third mode was observed around 900 nm comprising approximately 95% of aerosol mass. Particle mass distribution shifted toward larger particle sizes at the higher vaping power but actually reduced in the ultrafine ranges, likely due to increased kinematic coagulation. Increasing power from 3.0 and 11.9 watts resulted in an 86-fold increase in e-fluid consumption.

Vaping device power has a dramatic effect on vaping aerosol concentration and mass distribution across particle sizes. Vaping aerosol mass spans a much wider particle size range than previously reported, although the major portion of the mass is still well within the respirable size range. Because e-cigarette technology continues to evolve toward higher output devices, these results demonstrate need for further research to inform the design and regulation of e-cigarette products.

Realizing that small differences in vaping power can result in large differences in e-juice vaporized as well as shifts in aerosol size distribution should inform public health and clinical research seeking to compare e-cigarette devices against each other; studies should be standardized by vaping power and not voltage since voltage omits a critical factor in the equation (the heating element’s resistance).

THE MACROPHAGE-STIMULATING PROTEIN (MSP)/RON PATHWAY IN BREAST CANCER BONE METASTASIS

Presenter: Jaime Fornetti

Jaime Fornetti, Kelsi Andrade, and Alana L Welm

Immunobiology and Cancer, Oklahoma Medical Research Foundation

Skeletal metastases are a significant cause of morbidity in breast cancer, affecting an estimated 70% of patients with metastatic disease. Currently, therapies targeting bone metastasis are limited. One pathway implicated in progression of breast cancer to the bone is that of macrophage-stimulating protein (MSP) and its receptor, Ron. In women, overexpression of the MSP/Ron pathway in breast tumors is associated with an increase in both overall metastasis and metastasis to bone. Further, preclinical models demonstrate that MSP overexpression in mammary tumor cells is sufficient to promote spontaneous metastasis to the bone. In this model, bone metastases were characterized as osteolytic, or bone destructive, which recapitulates the predominant type of bone metastasis in breast cancer patients. Recent work from our lab has further characterized MSP as an important mediator of tumor cell-driven osteolysis by osteoclasts. Using an experimental metastasis model in which tumor cells were injected directly into the bone, tumors from MSP-overexpressing cells were associated with greater destruction of the surrounding bone compared to controls. Osteolysis downstream of MSP was dependent on Ron expression in the host and did not require RANKL or TGFβ signaling, two pathways with known roles bone metastasis. Notably, pharmacological inhibition of Ron prevented both the development of osteolysis and the progression of existing osteolysis in this model. In vitro, MSP significantly increased the osteolytic capacity of wild type osteoclasts, but had no effect on osteoclasts lacking the tyrosine kinase domain of Ron. Moreover, in wild type osteoclasts, MSP-induced osteolysis was decreased by Ron inhibitors. Altogether, these data support the hypothesis that MSP activation of Ron on osteoclasts promotes bone destruction and increased bone metastasis. The current goals of this work are to further understand the role of the MSP/Ron pathway in osteolysis and breast tumor metastasis to bone using mouse models and in vitro osteoclast cultures. It is anticipated that further understanding the mechanisms of bone metastasis will contribute to the identification of new treatment options for metastatic disease.

NICOTINE INCREASES THE STEMNESS OF HEAD AND NECK CANCER CELLS

Presenter: Vengatesh Ganapathy

Vengatesh Ganapathy[1], Jimmy Manyanga[1], Lacy Brame[1,2], Dana Mowls[1,2] and Lurdes Queimado[1,3-6]

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Background: Smoking is the main risk factor for lung and head and neck cancer. Nicotine replacement therapies (NRT) have been developed to aid smoking cessation, which decreases cancer incidence. Nonetheless, there is controversy about the safety of NRT. Nicotine has been shown to induce DNA damage but appears unable to initiate tumorigenesis in humans and rodents. In contrast, nicotine has been shown to promote tumor growth and metastasis in lung cancer models. The mechanisms associated with these discrepancies are unknown.

Aims: (1) To define the strand-specific patterns of DNA damage in human epithelial cells following exposure to nicotine. (2) To investigate the effects of nicotine on epithelial stem cell number and function.

Methods: Human epithelial normal and cancer cell lines were exposed for 1 hour to escalating doses of nicotine (0.03 – 300 μM) and evaluated for DNA damage. DNA damage was quantified in the *p53* gene using a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) developed in our laboratory. Cell viability was determined by MTT [3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay. To determine the effects of nicotine on stem cells, normal and cancer cells were exposed to 30 μM nicotine for 2 weeks and stem cells evaluated by ALDEFLOUR assay and spheroid formation assay. Data were analyzed by Student's *t*-test.

Results: Exposure of normal and cancer cells to nicotine for 2 weeks resulted in a small but significant increase in DNA damage in cancer cells, but not in normal epithelial cells. No significant difference in DNA damage was observed between DNA strands. No significant change in cell viability was observed following 1 hour of exposure to diverse doses of nicotine. Exposure of head and neck cancer cells to nicotine for 2 weeks resulted in a significant increase in the number and size of spheroids, a measure of stem cell functionality. Preliminary data suggests that the nicotine effects in stem cell functionality are specific to cancer cells.

Conclusion: Our study demonstrates that nicotine exposure leads to persistent DNA damage and an increase in stemness in cancer cells, but not in normal cells. These findings could explain the reported inability of nicotine to initiate tumorigenesis and provide a novel mechanism by which nicotine might contribute to tumor progression and therapy resistance. Most importantly, they emphasize the need to further investigate the health consequences of NRT in cancer patients.

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

HEALTH AND FITNESS APPS: OBESITY RELATED CANCER PREVENTION TOOLS?
Presenter: Mary Gowin

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Introduction: Overweight and obesity in young adults is around 40% and estimates are that 20% of cancers are linked to obesity. Weight gain during the transition from adolescence to young adulthood is a growing public health concern as this is an influential time in the lifespan. Universities are an ideal setting to intervene in this segment of the population as 21 million young Americans will attend college. Most college students own a smartphone (79%) and 24% of them have downloaded a health and fitness application (app), which makes this technology a potential modality for health promotion efforts. Yet little is known about how college students use these apps. The purpose of this study was to describe college student use of smartphone health and fitness applications.

Methods: College students ages 18-30 (n=27) from a large public university were recruited to participate in one on one interviews regarding their current use of a health and fitness app. Participants were asked open-ended questions about app choice and use, how the app contributed to behavior change, acceptable/unacceptable features, and reasons for discontinued use. Interviews were recorded, transcribed, and then analyzed using Nvivo 10.

Results: Most participants downloaded an app with a specific behavior goal and felt the app helped them meet that goal. Two distinct groups emerged from the study: those who used the app as a tool to support an established behavior and those who used the app as an attempt to adopt a new behavior. Participants reported that they would not pay for apps and that ease of use was the most important feature of an acceptable app. Acceptable apps provided visual/auditory cues, easy access to desired features, game-like rewards or challenges, and few start up requirements. Most participants opposed linking their social media with apps. Participants described apps providing both positive and negative reinforcement for behavior.

Discussion: Ease of use, cost, and social media findings were consistent with previous research in this area. The emergence of two distinctive groups of users provides a new level of explanation regarding the types of users. In addition participants' descriptions of positive and negative reinforcements provide guidance on how to appropriately operationalize apps in programming. Furthermore, participants had strong opinions about the apps and how they used them. This indicates that they should be included in any decision making regarding operationalizing apps in programming, otherwise they may not utilize apps as health promotors intend. App use is an emerging area of interest for researchers and practitioners looking to use this technology in the prevention and maintenance of health habits. Obesity related cancers could be prevented if weight gain in young adults was reduced or eliminated. Apps could be a viable tool for addressing obesity in this segment of the population and should be researched further.

BASE STACKING STABILIZES CONSECUTIVE TERMINAL G-U PAIRS
Presenter: Xiaobo Gu

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Background: Consecutive terminal guanosine-uracil (G-U) pairs occur naturally in miRNA-mRNA interactions in cancer gene regulation. G-U base pairs have different contributions to RNA helix stability when G-U base pairs are located in different positions. Internal tandem G-U pairs are often thermodynamically destabilizing. In contrast, consecutive terminal G-U pairs are energetically stabilizing and show more sequence dependence than other consecutive terminal mismatches in RNA duplexes. Therefore, we present crystallographic and NMR studies of RNA duplexes with consecutive terminal G-U pairs. The base stacking contributes to the sequence dependent thermodynamic stabilities of consecutive G-U pairs, and cobalt hexamine ions saturate the major groove of the helix.

Methods: Crystallography, NMR spectroscopy, and molecular modeling were used to determine the structural basis for the sequence dependence of consecutive terminal G-U pairs.

Results: The RNA sequence (5'-GGUGGCUGUU-3')$_2$ forms a self complementary duplex with a series of G-U wobble base pairs. The very high resolution of the crystal structure (1.32 Å) provides a detailed view of the hydrogen bonding and metal ion interactions. The helix is overwound but retains the overall features of *A*-form RNA. The penultimate base steps have high base overlap and explain the favorable energetic contribution from terminal G-U pairs. In RNA prediction programs that include favorable energetics for terminal G-U pairs, the predicted structure agrees well with the crystal structure and supports the hypothesis that the stacking of G-U pairs makes favorable energetic contributions. The consecutive G-U wobble base pairs bind cobalt hexammine ions in the major groove, which break the molecular symmetry of the self-complementary RNA duplex. G-U pair formation and cobalt hexammine ion binding were confirmed in solution NMR studies on three RNA duplexes.

Conclusions: This new RNA structural motif provides insight into RNA structure-energetics relationships and will facilitate *de novo* predictions of RNA structure from sequence and fundamental physical principles. Consecutive terminal G-U pairs may have previously been underpredicted. Thus, these results will aid future searches for functional sites in noncoding RNAs and target sites of small RNAs in gene regulation.

ANNEXIN-DIRECTED β-GLUCURONIDASE FOR THE TARGETED TREATMENT OF VASCULAR SOLID TUMORS

Presenter: Katrin P. Guillen

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To improve the power and clinical relevance of annexin-directed enzyme prodrug therapy, we have created a new family of fusion proteins centered about the human beta-glucuronidase (βG) enzyme. When tethered to the tumor cell surface, βG is capable of converting relatively harmless prodrugs into the chemotherapeutics SN-38, doxorubicin, and p-hydroxyaniline mustard; however, in healthy tissue, βG is compartmentalized within lysosomes, thus posing little risk of prodrug activation by endogenous βG. By targeting βG to the surface of tumor cells and their vasculature, we aim create high titers of chemotherapeutics only in the direct vicinity of the tumor and therefore mitigate chemotherapeutic side effects. To target βG, we have exploited the ability of annexin A1 and A5 to tightly bind phosphatidylserine (PS), an anionic membrane phospholipid which is strictly segregated to the cytoplasmic leaflet in healthy cells but robustly and consistently translocated to the outer leaflet of tumor cells, their metastases, and tumor vasculature.[1] We genetically fused human annexin A1 and A5 to human wild type βG and the 16a3 βG mutant (which confers improved activity at a physiological pH),[2] created stable producer cell lines, and produced/purified all constructs. To date, we have examined the fusion proteins' enzymatic activity along with binding to non-confluent endothelial cells (HAAE-1), which mimic the tumor vasculature, and binding to breast (MCF-7) and pancreatic (Panc-1) cancer cell lines.

Constructs were expressed in stably transfected Cho Flp-In cell lines for two weeks via fed-batch culture. Fusion proteins were purified to >95% purity (SDS-PAGE) by a series of immobilized metal affinity, hydrophobic interaction, and gel filtration chromatography. A1, A5, βG, and His_6 identities were confirmed via dot blots. Yields achieved were 710, 470, and 140 μg/L for hA5-16a3, hA1-16a3, and hA1-βG, respectively. Activity of both mutant fusion proteins was significantly improved ($p < 0.01$) at a pH of 7.4 over activity of the wild type, with hA5-16a3 retaining 28% and hA1-16a3 retaining 8% specific activity compared to pH 4.5. Both hA5-16a3 and hA1-16a3 were determined to bind strongly to MCF-7, Panc-1, and HAAE-1 cells, with dissociation constants ranging from 0.55-1.1 nM for hA5-16a3 and 2.1-3.0 nM for hA1-16a3. βG activity at a pH of 7.4 and strong cell binding capabilities lend proof of concept to these powerful, novel fusion proteins. Current work aims to validate hA1/hA5-16a3 in simulated *in vitro* enzyme prodrug therapy with SN-38 Glucuronide/SN-38 (prodrug/drug). Future work will investigate other prodrug/drug systems including DOX-GA3/doxorubicin and compound 2,[3] a prodrug which a therapeutic index $>10^6$.

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SHOC1, A NOVEL XPF ENDONUCLEASE/HELICASE- RELATED PROTEIN REQUIRED FOR PROPER REPAIR OF DOUBLE-STRAND BREAKS

Presenter: Michel F. Guiraldelli

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Homologue recombination (HR) is the only error free DNA repair system to repair double-strand breaks in both mitotic and meiotic cells. HR requires the action of nucleases and helicases in several steps of the pathway. Resolution of Holliday junctions (HJ), metastable DNA intermediates of the HR pathway, is required for proper error free DNA repair and maintenance of genome stability. In the past decade, several endonucleases able to process HJs have been identified. However, neither the individual nor the combined action of these proteins can account for resolution of most HJs. We recently identified human and mouse orthologs of SHOC1, a novel protein showing conserved domains expected for a helicase and an endonuclease. Purified recombinant human SHOC1 binds DNA with higher affinity for branched DNA structures. More importantly, SHOC1 exhibits both ATPase and helicase activities. We hypothesize that the SHOC1 protein is a novel endonuclease participating in the resolution of HJs. Our goals are to reveal the in vivo requirement of SHOC1 in mouse meiosis and to determine the biochemical mechanism of SHOC1 action.

Our work will provide critical new insights into the poorly understood process of HR, the mechanisms involved in DNA repair, and maintenance of genome stability. This information is fundamental for delineating causes of malignant cell transformation and has the potential to accelerate the approaches for treatment and/or prevention of cancer.

GLYCOLYTIC SHIFT INDUCED BY LPA IN OVARIAN CANCER
Presenter: Ji Hee Ha

Ji Hee Ha[1,2], Rangasudhagar Rhadhakrishnan[1], and Danny N. Dhanasekaran[1,2]

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Lysophosphatidic acid (LPA), a bioactive phospholipid, is present at elevated levels in the serum and malignant ascites of ovarian cancer patients. LPA functions through its cognate receptors, which are seven transmembrane G protein-coupled receptors (GPCR). It has been known as an oncogenic growth factor in ovarian cancer and other types of human malignancies. However, the precise biological functions of LPA in ovarian oncogenesis remain to be fully elucidated. Increased glucose uptake mediated by glucose transporters and reliance on glycolysis for energy, is a common feature in malignant cells. Accumulating evidence points to Hypoxia-inducible factor-1α (HIF-1α), as a critical mediator of the glycolytic shift observed in many cancer cells. Previously, we have shown that under normoxic and hypoxic conditions, LPA induces HIF-1α expression in ovarian cancer cells. Furthermore, either stable or transient silencing of $G\alpha_{i2}$, a downstream signaling effector, abrogates LPA induced increase in HIF-1α expression. In the present study, we found that LPA stimulated an increase in the expression of Hexokinase-2 (HK2) and Glucose transporter 1 (GLUT1), which are targets of HIF-1 alpha, are also mediated via $G\alpha_{i2}$ signaling pathway. To determine the outcome of LPA induced increase in HK2 and GLUT1 on glycolytic rates, we measured the extracellular acidification rate (ECAR) in ovarian cancer cells following treatment with LPA, using an extracellular flux (XF) analyzer. In both SKOV3-ip and OVCA429 cells, LPA increased ECAR in a dose-dependent manner. Silencing $G\alpha_{i2}$ as well as HIF-1α in ovarian cancer cells reduced ECAR, indicative of reduced glycolytic rate. The current study, points to the identification of LPA(R)-$G\alpha_{i2}$–HIF-1α-signaling axis as potential metabolism-targets in ovarian cancer treatment.

IMPROVING THE QUALITY OF AND STANDARDIZING RESIDENT OPERATIVE REPORTS FOR TRANSURETHRAL RESECTION OF BLADDER TUMOR SURGERY

Presenter: Joseph A. Haddad

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Introduction and Objective: Ensuring surgical quality is receiving increasing attention and transurethral resection of bladder tumor (TURBT) is a target for quality improvement. One indicator of surgical quality is the completeness and accuracy of the operative report. Surprisingly, there is a paucity of standardized operative templates for TURBT and little formalized instruction for learners. Our objective was to assess the quality of resident dictations for TURBT and to determine areas of improvement using a "TURBT checklist" of 10 critical procedural elements.

Methods: After obtaining IRB approval, we performed a retrospective review of the last 50 TURBT operative reports dictated by residents. A "TURBT checklist" was developed assessing 10 key factors in documentation (Figure 1). Postgraduate year of the dictating resident was identified. For each procedure, we measured the number of critical procedure elements from the TURBT checklist included in the operative report.

Results: 43 of 50 dictations were performed by first and second year urology residents. Tumor characteristics was the only element that was included consistently (52%). Dictations frequently lacked other procedural elements, including clinical stage (4%), bimanual examination (8%), and presence or absence of carcinoma in situ (10%). Among the 7 operative reports performed by senior residents, all dictations described tumor characteristics (compared to 44% of junior residents), 86% commented on a complete resection (compared to 33%), 71% described the size of the largest tumor (40%), and 57 % described the number of tumors (30%).

Conclusions: Our study demonstrates TURBT operative dictations performed by residents lack many of the critical components required for a quality TURBT. Checklist implementation can be a teaching tool for residents early in training to ensure critical procedural elements are documented.

Source of Funding: None

DOCOSAHEXAENOIC ACID (DHA) ALTERS BREAST CANCER EXOSOME MICRORNA CONTENTS AND SIGNALING TO ENDOTHELIAL CELLS

Presenter: Bethany Hannafon

Bethany Hannafon[1], Karla Carpenter[1], William L. Berry[2], Ralf Janknecht[2,4], William Dooley[3,4] and Wei-Qun Ding[1,4]

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DHA is a long-chain omega-3 polyunsaturated fatty acid that has anticancer properties, including the ability to suppress tumor angiogenesis. The mechanism of DHAs anti-angiogenic activity is not well understood. It has recently been recognized that the intercommunication between cancer cells and their microenvironment is essential to tumor growth and angiogenesis. Exosomes are small (50-100 nm) extracellular vesicles that are important mediators of intercellular communication by encapsulating proteins, lipids and small RNA cargo and transporting them to adjacent cells or to the circulation to act at distant sites. In recent years, the role of tumor-derived exosomes in cancer progression has been realized. However, ways to limit or change their influence on cancer progression has not been demonstrated. In addition, very little is known about the role of breast cancer exosomes in contributing to breast cancer progression or whether breast cancer exosomes mediate DHAs anticancer activity.

Breast cancer exosomes were collected from the conditioned media of MCF7 and MDA-MB-231 breast cancer cells engineered to express GFP-tagged CD63 (a marker of exosomes) after treatment with DHA. Overall, exosome secretion from the DHA-treated cells was increased. Total RNA was extracted from the DHA-treated and control MCF7-derived exosomes and analyzed by small RNA sequencing. The expression of 83 exosome microRNAs was altered by DHA (>2-fold) and several of the most abundant exosomal microRNAs (miR-23b, miR-27a/b, miR-21, and miR-320b) are known to have anti-angiogenic activity. When DHA-treated MCF7 cells were co-cultured with or the collected exosomes were directly applied to endothelial cell cultures, we observed an increase in the expression of these microRNAs in the endothelial cells. Furthermore, overexpression of miR-23b and miR-320b in endothelial cells decreased the expression of their pro-angiogenic target genes (PLAU, AMOTL1, NRP1 and ETS2) and significantly inhibited tube formation by the endothelial cells, an effect that could be reversed by inhibition of exosome secretion via Rab27A knockdown. These results indicate that the microRNAs transferred by exosomes mediate DHAs anti-angiogenic action.

In conclusion, our data demonstrates that DHA alters breast cancer exosome secretion and microRNA contents, which leads to the inhibition of endothelial tube formation. To our knowledge, this is the first study to provide evidence that the microRNA contents of cancer-derived exosomes can be altered thereby influencing their biological activity. These results provide insight into our understanding of DHA's anticancer activity and potential new cancer therapeutic strategies targeting exosome secretion and content transmission.

TARGETING CYSTATHIONE-γ-LYSASE TO THE TUMOR VASCULATURE IN ENZYME PRODRUG THERAPY OF BREAST CANCER IN AN IMMUNE-COMPETENT MOUSE MODEL

Presenter: Roger Harrison

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Enzyme prodrug systems attempt to circumvent the issues created by the systemic administration of current cancer drugs by localizing cytotoxic compounds to the tumor. An enzyme converts a nontoxic prodrug to a cytotoxic drug at the tumor. This study utilizes a targeted approach to enzyme delivery by capitalizing on the externalization of phosphatidylserine on cancer cells and tumor vasculature. The enzymes are fused to annexin V (AV) or annexin I (AI), proteins with strong binding affinity for phosphatidylserine. Three fusions have been evaluated using bacterial purine nucleoside phosphorylase (PNP), yeast cytosine deaminase (CD), or bacterial methionine-γ-lyase (MET). The most efficient system, MET-AV, has been selected for transition to immune-competent models using mammalian cystathionine-γ-lyase (CGL) engineered to have MET activity.

Active fusion proteins were recombinantly produced and purified in *Escherichia coli*. Binding strength and stability studies were performed with human endothelial cells HAAE-1 and breast cancer cell lines, MCF-7 and MDA-MB-231. Results were qualitatively confirmed with confocal microscopy. The same cell lines were used for a cytotoxicity analysis of the enzyme prodrug treatment. *In vivo* studies were conducted using SCID mice and MDA-MB-231/GFP xenografts or BALB/c mice with 4T1 mammary tumors.

In vitro results show successful binding and killing of breast cancer and endothelial cells representative of tumor vasculature. *In vivo,* all three fusion proteins were cleared from circulation in SCID mice within 8 hours. Binding to tumor vasculature was confirmed with immunohistochemistry. The CD system yielded unsatisfactory *in vivo* results; however both the PNP and MET systems achieved tumor growth suppression for the duration of the treatment period with the strongest effect shown with MET. Preliminary studies combining rapamycin (Rap) with MET-AV yielded a >80% reduction in tumor volume.

Mouse CGL (mCGL) was mutated in three positions to impart MET activity and fused to mouse AV and AI, resulting in mCGL-AV and mCGL-AI fusion proteins with activity equivalent to MET-AV. Neither fusion triggered adverse immunological effects in BALB/c mice. mCGL-AV was found to be more effective than mCGL-AI in inhibiting the growth of 4T1 mammary tumors in BALB/c mice. In combination with cyclophosphamide (for immunostimulation) and rapamycin (to downregulate HIF-1α and thus block the response of the tumor to hypoxia created by the enzyme prodrug therapy), enzyme prodrug therapy using mCGL-AV and selenomethionine prodrug enhanced survival, reduced primary tumor volume, reduced metastatic progression, increased apoptosis, decreased proliferation, and reduced the hypoxic response in BALB/c mice with 4T1 tumors.

LIPID DEPENDENT SUPPRESSION OF CANCER CELL MIGRATION BY CD82
Presenter: Chao Huang

Chao Huang

Department of Physiology, University of Oklahoma Health Sciences Center

CD82 is a membrane protein which belongs to the tetraspanin family, and the expression of CD82 is associated with decreased migratory potential of solid tumor cells. In recent years, more and more studies suggest that CD82's inhibitory effect on cell migration is lipid dependent, such as ganglioside located in the outer leaflet of the plasma membrane. However, how CD82 is associated with outer leaflet membrane ganglioside remains unknown. Though it was demonstrated that CD82 is physically associated with ganglioside such as gm2 and gm3, but there was no known ganglioside binding motif found in CD82 amino sequence. We proposed that CD82 binds to ganglioside in a cholesterol dependent manner and we designed a CD82 mutant that lacks one particular cholesterol binding motif in the transmembrane domain, and we overexpressed CD82 and CD82 mutant in Du145 cells to see if the function is altered or not upon the cholesterol binding motif mutagenesis. The CD82 mutant completely lost its function as a metastasis suppressor, however, the localization of CD82 to light membrane fractions, and CD82's co-localization with other tetraspanin protein such as CD9, as well as lipid raft marker such as gm1, were not altered by the mutation. So this mutant is still functioning as a membrane scaffold, which can interact with multiple membrane domains, but the downstream pathway was not altered and the suppressing effect on cell migration was not observed.

DUAL CXCR4/CCR5 CHEMOKINE RECEPTOR ANTAGONISTS
Presenter: Hubin, T. J.

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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. As 20 chemokine receptors and 46 chemokines are known, with few of these participants exclusive to their partners, a huge number of targets for antagonists are possible. Indeed, progress towards the development of a number of single-chemokine receptor antagonists has been steady. However, the promiscuity native to chemokines provides for the possibility of the defeat of a single-receptor antagonist, as alternate chemokine/receptor interactions can circumvent the blocked signal.

The two most studied chemokine receptors, due to their function as required co-receptors for HIV infection, are CXCR4 and CCR5. However, CXCR4 and CCR5 are linked through a number of other diseases: arthritis, inflammatory states, and a growing number of cancers. Researchers needing tools with which to study these diseases might benefit greatly from dual CXCR4/CCR5 antagonists. Notably, specific calls for dual CXCR4/CCR5 antagonists have appeared recently in the literature in the contexts of the study and treatment of HIV, the study and treatment of cancer, and the general study of chemokine receptors. For these reasons, we have chosen to design, synthesize, and screen the biological activity of dual CXCR4/CCR5 antagonists. These antagonists are based on topologically constrained tetraazamacrocycle transition metal complexes. The synthesis and characterization of these complexes, along with preliminary screening data on their CXCR4 and CCR5 antagonism will be presented.

BACTERIAL COLONIZATION AND DIFFERENTIAL EXPRESSION OF TOLL LIKE RECEPTOR 4 IN HCV-RELATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

Presenter: Janaki K. Iyer

Janaki K. Iyer[1], Jay Bullard[2], Elizabeth Tran[1], Tyler Ellington[1], Elliot Rigsby[1], Tejal Desai[1], Shafiq Al-Rifai[1], Bret Haines[1], Mohamad Khattab[1], Anjali Sundaramoorthy[1], Anil Kaul[3], Richard T Glass[2], and Rashmi Kaul[1]

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Livers chronically infected with Hepatitis C virus (HCV) are at high risk to develop hepatocellular carcinoma (HCC), the most common type of liver cancer. Chronic inflammatory states are associated with malignancies but the role of other factors that contribute to HCV-related chronic liver inflammation are undetermined. We have shown that aerobic bacteria are present in normal and cirrhotic liver tissues (Singh et al, 2011). Host cells recognize microorganisms and their components through cell surface receptors like Toll like receptors (TLRs). TLRs are key molecules of the innate immune system and their activation results in production of cytokines and chemokines that cause inflammation. Aberrant expression or activation of TLRs without regulation results in chronic inflammation.

The contribution of specific liver microbiome populations and TLR activation in the progression of HCV-related cirrhosis and cancer development are poorly understood. We hypothesize that qualitative and quantitative changes in the liver microbiome population can result in altered expression of TLRs that influence HCV-related cirrhosis and cancer development. In the present study, we identified the microorganisms present in normal liver tissues, HCV-related cirrhotic tissues (HCV) and HCV-related HCC tissues (HCV/HCC); and the expression of TLR2 and TLR4 receptors in these livers. We identified both Gram positive and Gram negative organisms in all the livers using the API system kit. Normal, HCV and HCV/HCC liver tissues showed ~40%, 64% and 86% respectively of Gram positive bacteria. TLR2 and TLR4 expression was observed by immunohistochemistry and the staining intensity was quantified in hepatocyte and portal regions. There were no changes in the expression of TLR2 in the hepatocytes or portal regions in different liver tissues. TLR4 expression was reduced in HCV cirrhotic (median 39.8, range 32.3-54.2) and HCV/HCC hepatocytes (median 40.8, range 28.0-54.3) compared to the normal liver hepatocytes (median 47.7, range 20.2-54.9). In portal regions, HCV/HCC tissues (median 11.7, range 4.8-23.7) showed the lowest expression of TLR4 followed by HCV cirrhotic tissues (median 20.0, range 6.3-50.4) and normal tissues (median 23.8, range 2.4-28.0). The reduction in TLR4 expression in cirrhotic and HCC tissues could be a reflection of increased innate immune suppression during cirrhosis and cancer development and also due to altered microbial flora in these tissues. Our findings suggest that there might be a potential contribution of microbial communities towards immunosuppression of TLR4-mediated innate immunity in cirrhotic livers undergoing progression to HCC. Manipulating bacterial communities through probiotics or TLR4 agonist treatments may provide therapeutic benefits and prevent HCV-related liver cancer development. [Cancer Sucks, Bixby,OK; NIH LTCDS (#DK92310)].

DELINEATING STROMAL CONTRIBUTION TO TUMOR RESISTANCE AGAINST ANTIANGIOGENIC THERAPY
Presenter: Pharavee Jaiprasart

Pharavee Jaiprasart, Bharat Devapatla and Sukyung Woo

Department of Pharmaceutical Sciences, College of Pharmacy, OUHSC

Angiogenesis is required for tumor progression and metastasis and a valid target for anticancer therapy; however the clinical benefit from antiangiogenic therapies is limited due to the rapid development of resistance after an initial response phase. Tumor microenvironment is increasingly recognized as an important determinant for tumor progression and response to therapeutics. We aimed to elucidate the tumor-stromal interactions that mediate resistance to anti-VEGF treatment, with the ultimate goal to devise better treatment strategies to improve therapeutic outcomes.

We identified tumor stromal gene signature correlated with emerging phenotypic tumor resistance to anti-VEGF therapies. A series of *in vitro* experiments was conducted to examine the role of the identified stroma-derived pathway, apelin, in tumor adaptive resistant to anti-VEGF therapy. We also generated SKOV3 human ovarian cancer cells stably transfected with apelin receptor (SKOV3-APLNR). Mitogenic and chemoattractant properties of apelin were studied in endothelial cells and SKOV3-APLNR in normoxic and hypoxic (1% O_2, 5% CO_2) conditions. The apelin-mediated functions were perturbed using pharmacological inhibitors of apelin receptor. To determine the *in vivo* relevancy of apelin expression and treatment resistance, we compared plasma apelin concentrations from mice bearing bevacizumab-resistant and -sensitive tumors. Further, correlation of apelin and apelin receptor expression levels to treatment outcome and/or prognosis were validated with clinical gene expression profiling data of various tumor types deposited in GEO.

In vitro results showed that apelin 10-100 ng/ml has a mitogenic effect on endothelial cells, increasing cell proliferation as compared to vehicle treated control (1.6 fold; $P<0.001$). Apelin-mediated cell migration was more prominent on cancer cells (2.2 folds; $P<0.01$) and was particularly enhanced in hypoxic condition. Further, we observed apelin and VEGF worked synergistically in promoting cell migration under hypoxic condition that is not present in normoxic condition. In confirmation of apelin roles *in vivo*, we found a four-fold elevation of apelin peptide in plasma of mice bearing bevacizumab-resistant tumors as compared to those bearing bevacizumab-sensitive tumors ($P<0.05$). High apelin gene expression also correlated with poor prognosis in neuroblastoma patients ($P = 2.9 \times 10^{-6}$).

Our results suggest that in the hypoxic centers of solid tumors, particularly after antiangiogenic drugs is given, paracrine signaling *interactions* between *tumor* cells-secreted alternative angiogenic factors and *stromal* cells play a greater role in promoting angiogenesis and metastasis. Apelin may serve as an important mediator of this tumor-stromal interactions and disruption of apelin signaling may improve outcomes of anti-VEGF therapy.

USING THE ELECTRONIC CIGARETTE FOR IMMEDIATE SMOKING REDUCTION IN PATIENTS AT RISK FOR CERVICAL DYSPLASIA AND ASSOCIATED DIAGNOSES

Presenter: Shirley A. James

Shirley A. James, MS, Ellen Meier, MS, Theodore Wagener, PhD, Laura A. Beebe, PhD

Immediate smoking cessation is critical in women diagnosed with cervical dysplasia, a condition that is exacerbated by smoking. Recent studies have reported some success with smoking reduction and cessation for people using electronic nicotine delivery systems (ENDS), even when the individuals originally had no desire to stop smoking. In this pilot study 31 women with cervical dysplasia and associated diagnoses sampled NRT (nicotine gum or lozenge) and ENDS (Blu e-cigarette) and chose the method they preferred to try for a 6 week intervention period designed to reduce the number of cigarettes smoked. A certified Tobacco Treatment Specialist (TTS) trained in motivational interviewing delivered education about the risks of smoking and behavior change strategies, and trained women in the intervention method of their choice. The primary outcome measure was reduction in the average number of cigarettes smoked per day at the 12-week follow-up visit. Twenty-eight women chose the ENDS product, thus comprise the study population for this analysis. Although 2 women were lost to follow-up, they were included in the analysis, and no change in cigarette smoking from baseline was assumed. At the 12-week follow-up, eight of 28 (28.6%) women were abstinent from cigarette smoking for at least 7 days, with 5 continuing to use the electronic cigarette. An additional 4 had reduced daily cigarette consumption by 75% or more (cumulative 12/28 or 42.9%), and another 7 had reduced by 50 percent or more (cumulative 19/28 or 67.9%). At the 12 week follow-up 21 women (75%) continued to use the electronic cigarette and 12 (42.9%) were dual users. This pilot study adds to the growing body of literature that suggests that the use of electronic cigarettes may reduce cigarette consumption and may assist individuals in smoking cessation.

This work was done at the University of Oklahoma Health Sciences Center from the Oklahoma Tobacco Research Center in conjunction with the Stephenson Cancer Center.

CANDIDATE CISPLATIN-RESISTANT BIOMARKERS FROM OVARIAN CARCINOMA
Presenter: Saghar Kaabinejadian

Saghar Kaabinejadian, Andrea Patterson, Wilfried Bardet, Kenneth W Jackson, Curtis P McMurtrey, William H Hildebrand.

Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States of America

Background: Ovarian cancer is the fifth leading cause of cancer-related death among women, and the deadliest of the gynecologic cancers. Cisplatin is widely used as a chemotherapeutic drug in the treatment of ovarian cancer. Resistance to cisplatin occurs in about one-third of women during the primary course of treatment and in all patients treated for recurrent disease. In this study we hypothesized that the HLA class I of cisplatin resistant ovarian cancer cells presents peptides distinct to these cells as compared to sensitive cells. The overall goal is to identify HLA/peptide complexes unique to the cell surface of cisplatin resistant cancers for immunotherapeutic intervention.

Methods: To identify the peptides that are uniquely presented on the surface of cisplatin resistant ovarian cancer cells, resistant and sensitive ovarian cancer cell lines (A2780/Cis and A2780, respectively) were transfected with soluble HLA-A*02:01. Transfected resistant and sensitive cells were grown in separate bioreactors, and harvested HLA molecules were purified by immunoaffinity chromatography, mapped by comparative mass spectrometry, and peptide sequences distinct to cisplatin-resistant cells were identified.

Results: The HLA class I of A2780 cells sampled peptides from 8905 proteins, providing a thorough representation of the cancerous cell proteome. When cisplatin sensitive and resistant HLA peptides were compared, 52 HLA/peptide complexes were distinct to or upregulated on resistant cells. These putative ciaplatin-resistant HLA/peptide biomarkers include topoisomerase II-alpha (TOP2A) and others that were significantly more abundant (≥ 1.5 log) in the platinum-resistant cells compared to sensitive cell lines. We were able to identify two TOP2A peptides (K1 and Y1) that are presented by HLA-A*02:01 of the cisplatin resistant cells 56 and 42 times more than the sensitive cells, respectively.

Conclusion: Proteomics analysis of cisplatin resistant ovarian cancer cells resulted in the identification of novel candidate biomarkers, K1/HLA-A*02:01 and Y1/ HLA-A*02:01. The gene encoding these peptides (TOP2A) is the major target of several anticancer agents including anthracyclines and mutations in this gene have been associated with the development of drug resistance. Therefore, these peptide/HLA complexes would be attractive candidates for further validation as biomarkers of cisplatin resistance on tumor cells and primary tissues.

OVEREXPRESSION AND PURIFICATION OF AFFINITY TAGGED HUMAN JMJD4 FOR STRUCTURAL STUDIES

Presenter: Chiedza Kanyumbu

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

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University of Oklahoma Health Sciences Center

Jumonji domain-containing protein 4 (JMJD4) belongs to the Jumonji C (JmjC) family of oxygenases, members of which have been shown to have demethylase activity on the methyllysines located along the N-terminal tails of histones. JMJD4 has recently been shown to catalyze the lysyl hydroxylation of eukaryotic release factor 1 (eRF1), a key mediator of accurate termination of eukaryotic translation and thus maintaining the proper length of polypeptide chains. Premature or improper termination of translation has been linked to several inherited diseases such as cystic fibrosis and muscular dystrophy, as well as cancers including colorectal, breast and ovarian cancers. Consequently, structural data from JMJD4 will be valuable for structure-based drug design and development.

No three-dimensional structural data on JMJD4 are currently available, so our immediate aim is to get sufficient amounts of pure JMJD4 for structural studies in solution by small angle X-ray scattering (SAXS) and in crystals by X-ray diffraction. We made homology models of JMJD4 isoforms 1 and 2, and we used these to design several maltose binding protein (MBP)–JMJD4 fusion proteins to enhance the solubility of JMJD4 when overexpressed in *E. coli*. Some of these constructs produced high yields of soluble fusion protein with no protein aggregation or oligomerization (verified by size exclusion chromatography and dynamic light scattering analysis) and are, therefore, suitable for preliminary structural studies. We are focused on optimizing SAXS and crystallization conditions. Selected constructs will be used in further biophysical experiments to elucidate the interaction between JMJD4 and eRF1.

HISTONE DEMETHYLASE JMJD2A IS A NOVEL INITIATOR OF PROSTATE CANCER

Presenter: Tae-Dong Kim

Tae-Dong Kim, Ralf Janknecht

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

Histone demethylase upregulation has been observed in human cancers, yet it is unknown if this is a bystander event or drives tumorigenesis. Here, we found overexpression of the histone demethylase JMJD2A (also called KDM4A) in human prostate tumors that positively correlated with Gleason score and metastasis. Transgenic mice in which we mimicked this overexpression developed prostatic intraepithelial neoplasia, establishing JMJD2A as a novel driver of prostate cancer development. In addition, we demonstrated that JMJD2A cooperated with the ETV1 transcription factor to increase expression of Hippo pathway transcriptional cofactor YAP1 and proteasome-associated PSMD10, both of which promoted prostate cancer cell growth and were associated with prostate tumor aggressiveness. ETV1 bound to the YAP1 promoter in vitro and in vivo and facilitated the recruitment of JMJD2A leading to changes in histone lysine methylation.

Further, YAP1 expression largely rescued the growth inhibitory effects of JMJD2A depletion in prostate cancer cells, indicating that YAP1 is a seminal downstream effector of JMJD2A. Taken together, these data reveal a previously unrecognized JMJD2A/ETV1-YAP1 axis whose inhibition may represent a novel treatment strategy for prostate and possibly other cancers.

THE HISTORY OF CIGARETTE TAXATION IN OKLAHOMA
Presenter: Fritz L. Laux

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Topic key words: Public Policy, Taxation, Oklahoma, Cigarettes

State taxation of cigarettes in Oklahoma began, and was almost immediately repealed, in 1933. Temporary taxes on cigarettes were then enacted and lifted throughout the 1930's until 1941, when the state rate was permanently set at 5 cents per pack. From there, state taxation of cigarettes paralleled national trends with increases in the 60's and 70's leading to a below average rate in the 90's partially corrected for with an 80-cent increase to $1.03 per pack in 2005.

Oklahoma's more interesting developments in recent years have been in the area of state taxation of tribally-regulated cigarette sales. This began after the Supreme Court's 1991 decision in the Citizen Band Potawatomi case, establishing rules for how allowances for a state-tax-free quota of cigarette sales for tribal members could practicably be administered for Oklahoma tribes. After the Pottawatomi decision, the state negotiated a wave of tax treaties, called "compacts" with the tribes establishing tribal rates at 25% of nontribal rates. At the expiration of this first wave of compacts, a second wave was negotiated beginning in 2003, so as to adapt to an anticipated 80-cent increase in nontribal tax rates. Following enforcement problems with state taxation of tribal cigarettes from 2005 through 2007, a subsequent wave of compacts was negotiated in 2008. A prominent feature of these third-wave compacts is that they, for the first time, specified levels for the taxation of cigarettes by the tribes themselves (in addition to state-level taxation). Finally, a fourth wave of compacts has been negotiated in 2013-2014. The focus of this latest round of compacts has been to consolidate the 5-level variation in state taxation of tribally regulated cigarette sales to one level, ultimately to be standardized at 50% of the nontribal rate. With 36 of Oklahoma's 39 federally recognized tribal nations having at one time compacted with the state over cigarette taxation, this is a detailed and complex history.

SYNTHESIS OF DISACCHARIDE MOIETY OF ANTI-CANCER COMPOUND OSW-1

Presenter: Anh T. Le

Anh T. Le and Anthony W. G. Burgett, Ph.D.

Department of Chemistry and Biochemistry, University of Oklahoma

OSW-1 is an anti-proliferative natural product compound isolated from the bulb of the *Ornithogalum saundersiae* flower (NCI-60 GI_{50} average = 0.78 nM). OSW-1 was determined to inhibit the cancer cell proliferation through targeting the oxysterol binding protein (OSBP) family. The OSBPs are a class of cytosolic proteins present in all eukaryotes with a poorly defined cellular function, although recent results suggest the OSBPs could serve as master sensors for sterols and/or lipid molecules. Multiple OSBP protein family members have been associated with the pathologies of different types of cancer, including pancreatic and blood cancers. ORP4, an OSBP family member, was shown to be overexpressed in blood cancer cells and to drive cancer cell proliferation. Our research goal is to develop compounds that specifically target ORP4 over the other OSBP protein family members. These ORP4-targeting compounds will be used to further study ORP4 cellular function and be explore as potential personalized anti-cancer lead therapeutic compounds.

In order to derivatize the OSW-1 structure, first the OSW-1 compound must be accessed through total synthesis. Currently, we are working to synthesize OSW-1 through a convergent approach, in which the molecule can be assembled from two major subunits: the steroidal aglycon and the disaccharide moiety. This synthetic approach, based on known chemistry, will allow for rapid generation of multiple OSW-1 analogs for biological evaluation.

BRIEF FEEDBACK INTERVENTION FOR CURRENT HOOKAH BAR PATRONS

Presenter: Eleanor L. Leavens

Eleanor L. Leavens[1,2], Alayna P. Tackett[1,2], Noor N. Tahirkheli[2,3], Dana S. Mowls[2,3], Sarah Johnston[1], Emma I. Brett[1], Leslie M. Driskill[2,3], Ellen Meier[1] , Mary Beth Miller[1,2], Theodore L. Wagener[2,3]

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Hookah use has been on the rise in the US and abroad in recent years. Studies have illustrated the harmful effects of hookah use and users' limited knowledge regarding its negative effects. Given the limited research on hookah cessation, the purpose of the current study was to examine the efficacy of a brief feedback intervention in a sample of current hookah bar patrons. Participants (N = 35) in a Midwestern Metropolitan area were recruited as they entered hookah bars and asked to complete a brief questionnaire and carbon monoxide (CO) testing, and were then randomized into assessment-only control (n = 18) or feedback (n = 17) conditions. Upon exiting the hookah bar, the feedback condition received educational information about the harmful effects of hookah as well as personalized feedback regarding their pre- and post-hookah session CO levels. Both conditions completed a brief exit survey at the end of their ad-lib hookah session assessing their hookah use, perceptions, and knowledge. A 3-month follow-up survey will be conducted in order to assess changes in hookah use. On average, participants spent 1.70 hours in the hookah bar and reported smoking 1 (SD = .42) bowl of shisha among 3.10 (SD = 1.76) people and using 3.84 (SD = 3.29) pieces of charcoal. Participants rated perceptions of absolute harm (1=not at all harmful, 10=extremely harmful) and relative harm (1= less harmful, 2= equally harmful, 3= more harmful). Post intervention, the feedback condition demonstrated higher perceptions of absolute harm caused by hookah (Control: M = 4.94; SD = 2.36; Feedback: M = 8.21; SD = 1.57; $t(29) = -4.43$, $p < .001$). Further, participants in the feedback condition were more likely to view hookah as equally or more harmful than cigarettes post feedback (Control=72.2%, Feedback=100%; Chi-square= 10.03, p = .007). This study begins to address the lack of research on hookah cessation interventions. The current research supports the use of educational and personalized feedback as a feasible intervention for correcting misperceptions regarding hookah.

This study was conducted at the University of Oklahoma Health Sciences Center, Department of Pediatrics.

Funding: Funding for the current project was provided by the Oklahoma Tobacco Research Center (OTRC) and intramural funds through Dr. Theodore Wagener.

TOBACCO AND PREGNANCY: AN ANALYSIS OF MAJOR COMORBIDITIES OR COMPLICATIONS, PRETERM BIRTHS, AND ECONOMIC OUTCOMES IN THE U.S. FROM 2001-2010

Presenter: Philip E. Looper

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Introduction: The adverse effects of tobacco are well-established and, in turn, contribute to poor health outcomes. Research continues to document the substantial maternal and neonatal risks incurred by tobacco use or exposure.

Objectives: To compare clinical outcomes of major complications or comorbidities and premature births plus economic outcomes of length of stay and charges for tobacco users and nonusers among maternal inpatient cases involving births in the U.S. from 2001-2010.

Methods: National hospital discharge data from the Agency for Healthcare Research and Quality's Health Care Utilization Project were used in this retrospective cross-sectional study. Inclusion criteria included all maternal cases of Cesarean section or vaginal births from 2001-2010 in the U.S. Clinical outcomes analyzed were major complications or comorbidities (MCC/CC, based upon diagnosis related groups) and preterm labor, while economic outcomes included lengths of stay and inflation-adjusted charges (US$, 2014). Generalized linear models (binomial/logistic, negative binomial, gamma) were utilized for outcomes, controlling for diagnoses of current tobacco use disorders/dependence, patient characteristics (age, race, income quartile, rural residence), clinical case-mix (Deyo-Charlson Comorbidity Index), hospital characteristics (bedsize, teaching status, geographic region, rural location), primary payer, and year.

Results: Among the 40.3 million births from 2001-2010, current tobacco use disorders were recorded among 4.0% of births (n=1,594,160) of which 23.3% involved MCC/CC and 11.1% premature births, versus 17.1% and 7.1% among cases not involving tobacco use, respectively ($p<0.05$). Multivariable analysis indicated that current tobacco use was associated with 36.0% higher odds of MCC/CC (OR=1.360, 95th CI:1.326,1.395) and a 48.6% higher odds of premature birth (OR=1.486, 95th CI:1.445,1.528) ($p<0.001$). Across all pregnancies, disparities of poorer clinical outcomes were also observed based upon increasing age, primary payer (i.e., Medicaid), micropolitan or rural residence, race (i.e, African American), and income quartile below the median ($p<0.05$). While no differences between either lengths of stay or charges were observed solely with current tobacco use, a worsening case-mix disease severity capturing several tobacco-related illnesses (e.g., cardiopulmonary disease) was associated with poorer economic outcomes ($p<0.001$).

Conclusion: Across over 40 million births, the harmful impact of tobacco use and related illnesses during pregnancy is associated with markedly higher odds of poor outcomes, worsened by observed disparities. Continued work to mitigate the public health impact of tobacco and improve maternal-child care across vulnerable and underserved communities is clearly warranted.

PATIENT-DERIVED XENOGRAFT AND PRE-CLINICAL THERAPEUTICS (PDX-PCT) CORE
Presenter: David H. Lum

David H. Lum, Yoko DeRose, Bryan Welm and Alana Welm

Oklahoma Medical Research Foundation

Accumulating evidence from recent genomics data has reinforced the view that tumors can display exceptional heterogeneity between patients, between tumors from the same patient and even within a single tumor. These findings, together with decades of clinical experience with varied drug responses, strongly suggest that *personalized* approaches to assess cancer risk and treatment will be essential to reduce mortality.

New experimental models of human tumor initiation, progression, metastasis, and therapeutic response/resistance are critical to improve cancer treatments. Current models often fail to predict the efficacy of drugs in the clinical setting. This disconnect leads to disappointing clinical trial results that do not considerably improve patient survival, to failure of the FDA to approve new therapies, and to the loss of time and money. The ideal cancer model(s) would: 1) replicate the spectrum of tumor pathologies and subtypes, 2) reproduce genetic and epigenetic alterations found in human tumors, 3) grow in the correct developmental and anatomic context, 4) have an appropriate tumor microenvironment and an intact immune system, and 5) exhibit patterns of metastasis observed in patients.

Dr. Alana Welm (OMRF) was the first to establish a collection of patient-derived orthotopic breast xenografts by implanting patient tumor tissue into mice. Significant evidence demonstrates that patient-derived xenografts (PDX) recapitulate the genomic and phenotypic features of their corresponding patient tumors, and that tumor graft growth and metastasis mirrors clinical outcome in the corresponding patients. We propose that patient-derived tumor grafts may provide a remarkable opportunity to predict the best therapy regimens for individuals, a concept termed ‘personalized’ or ‘precision’ medicine.

The Patient-Derived Xenograft and Preclinical Therapeutics Core will provide high-quality services for basic and translational cancer research, drug discovery and personalized cancer therapy.

The mission of the core will be to:

- Generate the most current and sophisticated patient-derived in vivo cancer models.
- Bridge the gap between basic scientists and clinicians to facilitate seamless bench to bedside research.
- Improve pre-clinical drug efficacy evaluation and examine personalized chemotherapy with patient-derived xenografts.
- Enable the classification of patient-derived xenografts into previously unappreciated categories to improve clinical utility regarding patient diagnosis, prognosis, and treatment.

OKN-007: SEEKING A LICENSE TO KILL PEDIATRIC GLIOMAS
Presenter: Samantha Mallory

Samantha Mallory[1], Patricia Coutin deSouza[2], Rene McNall-Knapp[1], Nataliya Smith[3], Debra Saunders[3], Kar-Ming Fung[4], Shanna Smartwood[5], Rheal A. Towner[3]

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Brain tumors are the most common solid tumor in children, and despite current treatment options including surgical resection, chemotherapy, and radiation for pediatric high-grade gliomas, survival in these patients remains very poor. This research represents promising pre-clinical data of a novel compound, OKN-007 (OKlahoma Nitrone 007, a disulfonyl derivative of α-phenyl-tert-butyl nitrone (PBN)), as a new clinical therapy for pediatric high-grade gliomas (pHGGs). The objective is to establish if pHGGs, which are often hard to surgically resect, can be treated with OKN-007, either as a single agent or in combination with currently used chemotherapeutic agents. OKN-007 may be an ideal candidate that can have an anti-cancer effect on pHGG cells, due to its multiple anti-cancer effects, including induction of apoptosis, and inhibition of cell proliferation and angiogenesis, and may play an important role in the anti-cancer activity against pHGGs. Morphological magnetic resonance imaging (MRI) of xenograft nude athymic and SCID mice injected with pHGG cells TCCC3752 and KNS42 is used in this study to assess brain tumor volumes for response to therapy. Preliminary data regarding the regression of pHGGs in mice following treatment with OKN-007 is presented. Mean animal survival was found to be significantly increased with OKN-007 treatment in responsive animals compared to an untreated group, $p<0.05$. Immunohistochemistry and microarray will be used to assess levels of angiogenic (VEGF (vascular endothelial growth factor), HIF-1α (hypoxia inducible factor-1α), MVD (microvessel density)), cell differentiation (CAIX (carbonic anhydrase IX)), cell proliferation (Glut-1 (glucose transporter 1), MIB-1), apoptosis (cleaved caspase 3) markers and assess inhibition of TGFB and PDGFR complexes and downstream pathways, which are overexpressed in tumors and thought to play a role in oncogenesis and progression. OKN-007 is currently an investigational drug undergoing clinical trial evaluation for recurrent gliomas in adult patients but will still require FDA approval for use in pediatric glioma patients. An outcome of the proposed research is to incorporate the pre-clinical data in an IND application to the FDA in order to translate this research to the clinic and benefit children with pHGGs.

DEFINITIVE RADIATION THERAPY FOR SALIVARY GLAND MALIGNANCIES: THE STEPHENSON CANCER CENTER EXPERIENCE

Presenter: Jonathan Mani

Jonathan Mani; Christina Henson, M.D.; Abeer Arain, M.D.; Terence Herman, M.D.; Chance Matthiesen, M.D.

Department of Radiation Oncology, Stephenson Cancer Center, University of Oklahoma

Purpose: Salivary gland cancers (SGC) make up < 5% of head and neck cancer in the U.S. Ideal management is excision followed by radiation therapy (RT). We reviewed our institutional experience in treating SGC definitively with RT in patients not candidates for definitive surgery.

Materials/Methods: We performed a retrospective review of 14 SGC treated definitively with radiation from 2007 to 2014. Median patient age at diagnosis was 73.5 years (range 29-91). Eleven (79%) patients were male, 3 female. Thirteen (93%) presented with a facial mass, 5 (36%) with facial weakness, 3 (21%) with pain, and 2 (14%) with numbness. Five (36%) were initially staged T2, 4 (29%) T3, and 5 (36%) T4. Five patients were initially staged N0, 3 (21%) N1, and 6 (43%) N2 [5 N2b, 1 N2c]. Patients with M1 disease were excluded. Thirteen (93%) cases were parotid gland primaries, and 1 was submandibular. Three (21%) had squamous histology, 2 (14%) acinic, 1 (7%) adenoid cystic, 1 carcinoma ex-pleomorphic adenoma, 1 carcinoma NOS, 1 malignant mixed tumor, 1 mucoepidermoid cyst, 1 small cell vs Merkel cell, and 1 squamous vs mucoepidermoid cyst. Seven (50%) patients had high-grade lesions. Five (36%) had CNVII involvement; 3 (21%) had CNV involvement. One (7%) had perineural invasion of a non-named nerve. The median prescribed dose was 72 Gy (range 18-74) in 34 fractions (range 9 – 37). Thirteen patients were treated with IMRT; 1 was treated with conventional treatment planning. Two (14%) received concurrent chemotherapy. Median follow-up was 4 months (range 0-32.4).

Results: Eleven patients (79%) completed therapy as planned. Seven (50%) patients had no evidence of recurrence at last follow-up. Three (21%) patients did not complete definitive RT; 2 completed 18-30 Gy and opted for hospice; 1 converted to neoadjuvant therapy (underwent resection) after only partial response was noted at 50 Gy. Of 5 (36%) that recurred, 2 (14%) opted to receive hospice care, 1 required RT and chemo for an axillary recurrence, 1 underwent chemotherapy, and 1 required surgery. Three (21%) patients underwent resection after definitive radiation therapy; all 3 were found to have residual tumor. One maintained a positive margin after resection. Two patients had expired at time of analysis, 1 from liver metastases and 1 from aspiration pneumonia. Their survival times from RT initiation were 35 and 7.5 months.

Conclusions: Definitive RT is an option in patients not candidates for initial surgical resection. Patients with T1-2 lesions with minimal nodal involvement had better outcomes in this series. Overall, 50% of our patients have no evidence of recurrence. Prognosis in these patients, however, remains poor. Further investigations are necessary to determine the optimal treatment approach for SGC patients when initial surgery is declined or contraindicated.

EXPOSURE TO MAINSTREAM AND SIDESTREAM SMOKE INCREASES THE STEMNESS OF EPITHELIAL NORMAL AND CANCER CELL LINES

Presenter: Jimmy Manyanga

Jimmy Manyanga[1], Vengatesh Ganapathy[1], David A. Rubenstein[2], and Lurdes Queimado[1, 3-6]

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

Background: Cigarette smoking is the leading cause of preventable cancer death. Furthermore, continuing smoking after cancer diagnosis contributes to therapeutic resistance and poor prognosis. Almost one-half of non-smokers are exposed to secondhand smoke. Mainstream (MS) smoke, the main smoke inhaled by active smokers, and sidestream (SS) smoke, the main component of secondhand smoke, are qualitatively similar with respect to chemical composition. However, many carcinogens are present in greater amounts in SS than in MS smoke. This suggests that passive smoking may elicit molecular mechanisms that differ from those induced by active smoking. Stem cells are a small subset of cells with the unique capacity of self-renewal and multi-potency. Cancer stem cells drive tumor initiation, progression, metastasis and therapeutic resistance. The effects of cigarette smoke in stem cells are poorly studied. Nonetheless, recent data suggest that MS smoke decreases the number of mesenchymal stem cells and increases the number of cancer stem cells. No studies have reported the effects of SS smoke in stem cells.

Aims: To determine the effects of MS and SS smoke on the number and functionality of epithelial normal and cancer stem cells.

Methods: Human epithelial normal and cancer cells were exposed every other day to 3 □M of MS and smoke extracts (~ 1 cigarette/5 L) for 2 weeks. Stem cell number and function was evaluated respectively by ALDEFLOUR assay and spheroid formation assay. Cell viability was determined by MTT assay. MS and SS extracts were prepared as we previously described. Data was normalized to mock treated cells and analyzed by Student's *t*-test.

Results: Exposure of head and neck cancer cells to MS and SS smoke extracts for 2 weeks resulted in a significant increase in stem cell number. Additionally, exposure to MS and SS smoke extracts caused a 4 fold and a 1.5 fold increase in head and neck cancer cells spheroid formation, respectively. A smaller but significant increase in spheroid formation (~ 1.5 fold) was observed in normal epithelial cells exposed to MS and SS smoke extracts for 2 weeks. Interestingly, we observed that the spheroids formed in the presence of SS smoke extracts are morphologically different from those formed in the presence of MS smoke extracts.

Conclusion: Our study demonstrates for the first time that exposure to MS and SS smoke leads to a significant increase in spheroid formation in normal and cancer cell lines. These data provides a novel mechanism by which active and passive smoking might contribute to tumor initiation and progression, as well as therapy resistance. Importantly, we observed significant differences in the morphology of spheroids originated by cancer cells exposed to SS and MS smoke extracts. The molecular events behind these differences and their potential implications for human health are currently being investigated in our laboratory.

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

SMOKERS WITH A GED WHO CALL A STATE QUITLINE

Presenter: Sydney Martinez

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The inverse association between educational attainment and smoking is well established; however, analyses with refined categories of educational attainment indicate those with a General Educational Development (GED) certificate do not fit this pattern and smoke at higher rates than even high school (HS) dropouts.

Oklahoma Tobacco Helpline registration data from July 1, 2012 to June 30, 2014 were used to compare age, income, tobacco use patterns, and past quit attempts among registrants with a GED compared to HS dropouts and HS graduates. Adult tobacco users ages 25 or older who enrolled in a single or multiple call intervention were included in analyses.

During the two year study period, 8.3% (n=3,823) of registrants ages 25 or older reported a GED as their highest educational attainment. Twenty-two percent (n=9,964) reported less than a HS diploma and 28.0% (n=12,946) had a HS diploma. Callers with a GED were significantly younger than both HS dropouts and graduates (45.9 years vs. 47.6 and 47.5 years, $p<.0001$). For each increase in education level, the proportion of callers with low income decreased steadily, with 88.9% of HS dropouts, 85.1% of adults with a GED, and 74.5% of HS graduates reporting an annual income of less than $25,000. Adults with a GED (29.4%) were less likely to smoke a pack or more cigarettes per day compared to HS dropouts (33.3%, $p<.0001$) and more likely than HS graduates (26.5%, $p=.0004$). There were no significant differences in the proportions of someday smokers ($p=.80$) or the number of previous quit attempts ($p=.57$).

Although recent smoking prevalence data indicate adults with a GED do not follow the education gradient established for smoking and have significantly higher rates than both HS graduates and HS dropouts, tobacco users with a GED who called the Helpline fell between HS dropouts and HS graduates for most characteristics and tobacco use patterns. More research is needed to determine what factors might contribute to higher smoking prevalence in the general population of adults with a GED and whether tobacco quitlines are effective in the GED population seeking treatment.

SCF^{FBW7} REGULATES CILIOGENESIS BY TARGETING NDE1 FOR UBIQUITYLATION AND DESTRUCTION
Presenter: Dipak Maskey

Dipak Maskey[1], Matthew C. Marlin[2], Seok-Ho Kim[1], Sehyun Kim[1, 3], Guangpu Li[2], and Leonidas Tsiokas[1]

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Primary cilia start forming within the G1 phase of the cell cycle and continue to grow as cells exit the cell cycle (G0). They start resorbing when cells re-enter the cell cycle (S phase) and are practically invisible in mitosis. The mechanisms by which cilium biogenesis and disassembly are coupled to the cell cycle are complex and not well understood. We previously identified the centrosomal phosphoprotein NDE1, as an inhibitor of ciliogenesis and showed that its levels inversely correlate with ciliogenesis. Here, we identify the tumor suppressor FBW7 as the E3 ligase that mediates the destruction of NDE1 upon entry into G1. CDK5, a kinase active in G1/G0 primes NDE1 for FBW7-mediated proteolysis. Cells depleted of FBW7 or CDK5 show enhanced levels of NDE1 and a reduction in ciliogenesis, which is corrected in cells depleted of both FBW7 or CDK5 and NDE1. These data show that cell cycle-dependent mechanisms can control ciliogenesis through a CDK5-FBW7-NDE1 pathway.

THE RNA-BINDING PROTEIN HUR RADIOSENSITIZES HUMAN TNBC CELLS BY MODULATING THE CELLULAR RESPONSE TO DNA DAMAGE AND OXIDATIVE STRESS

Presenter: Meghna Mehta

Mehta M, Griffith J, Basalingappa K, Babu A, Amreddy N, Muralidharan R, Gorospe M, Herman T, Ding WQ, Ramesh R, Munshi A.

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The RNA-binding protein human antigen R (HuR) associates with U-/AU-rich mRNAs encoding proteins that control cell proliferation, metabolism and the stress response. HuR is overexpressed in several human cancers and its overexpression is associated with poor prognosis and resistance to therapy. While the role of HuR in drug resistance has been studied, its contribution to radiation resistance has not been examined. Therefore, we investigated the role of HuR in radiation resistance of triple negative breast cancer (TNBC) cells: MDA-MB-231, MDA-MB-468 and Hs578t. Reduction of HuR expression using small interfering (si) RNA decreased cell proliferation and sensitized TNBC cells to ionizing radiation. Clonogenic assays indicated that silencing HuR suppressed the clonogenic survival of all three TNBC cell lines with survival at 2 Gy (SF2) reduced from 59%, 49%, 65% in control cells to 40%, 33%, and 46% in siHuR-treated MDA-MB-231, MDA-MB-468 and Hs578t cells, respectively. To delineate the underlying mechanism of radiosensitization and to identify candidate mRNAs showing altered levels after silencing HuR, we undertook a ribonomic approach. First, since ionizing radiation enhances the production of reactive oxygen species (ROS), causing DNA damage, we investigated the possible involvement of ROS in siHuR-mediated radiosensitization. ROS production in control or HuR-silenced cells treated with or without radiation was measured using the fluorescent dye 2'-7'-Dichlorodihydrofluorescein diacetate (DCFDA). Radiation significantly increased ROS generation in HuR knockdown cells compared to control cells. To further test the involvement of ROS in radiosensitivity, control and HuR-silenced cells were pre-treated with N-Acetyl-L- cysteine (NAC), an ROS scavenger, prior to radiation. The presence of NAC completely prevented radiation sensitivity and ROS production, indicating the involvement of ROS in HuR-mediated radiation sensitivity. Second, we directly tested the involvement of the DNA damage response (DDR) pathway in radiosensitivity after silencing HuR by evaluating the number of □-H2AX foci (a common indicator of DNA damage) in control and HuR-silenced cells following irradiation. Our results showed that the number of □-H2AX foci was significantly greater in HuR-silenced cells than in control cells at 1 h, 2 h and 24 h after irradiation. The persistence of □-H2AX foci suggests that radiosensitization by HuR silencing involves inhibition of the repair of damaged DNA. This hypothesis was supported by the comet assay, which showed that HuR-silenced cells had larger and longer-lasting tails than control cells, in keeping with the higher levels of DNA damage seen after silencing HuR. Our studies indicate that radiosensitization upon HuR knockdown is linked to suppression of the cellular response to genotoxic and oxidative damage.

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THE EFFECT OF RURAL RESIDENCE AND ACCESS TO UROLOGIC SPECIALISTS: AN INVESTIGATION ON THE MORTALITY OF KIDNEY CANCER IN MINORITIES

Presenter: Adamantios M. Mellis

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Introduction: Previous studies have found differing kidney cancer mortality rates among minority groups. Several factors may contribute to these findings including rural residence and presence of specialty care. In this study, we used a state administered cancer registry to investigate kidney cancer mortality in minority groups based on urban/rural residence and presence of urologists.

Materials and Methods: Using the Oklahoma State Department of Health's web−based public health query system, OK2SHARE, the incidence and mortality of kidney cancer was evaluated in the state of Oklahoma from 2000 to 2010 across counties of residence. Mortality rates were evaluated among Caucasians, Hispanics, African−Americans, and American Indians. Within these groups, rates were compared across gender. Urban/rural residence and presence of urologist were evaluated at a county wide level. Urologists were identified from the Oklahoma State Urology Association membership directory. Rural counties were identified using U.S. Department of Agriculture data.

Results: Of the 77 counties in Oklahoma, 17 were classified urban (22%). Of these, 6 had a practicing urologist. 11 rural counties had a practicing urologist. Between 2000 and 2010, 6,587 cases of kidney cancer and 2,185 deaths were observed in Oklahoma. Counties with a urologist reported 1,269 (58%) kidney cancer mortalities. Overall, the mortality rate in men (7.21) was higher than women (4.06), consistent with national trends. Analyzing mortality rates stratified by race, American Indians had a higher mortality rate (5.32) compared to all other minority races (2.93). African American and American Indian populations living in rural areas of the state had higher mortality rates (8.37 and 6.10) than their urban counterparts (3.14 and 4.49). Furthermore, increased mortality rates in African Americans was seen in counties where there were no urologic specialists (9.38 vs. 3.17).

Conclusions: In this preliminary study we found that kidney cancer mortality rates in Oklahoma were highest among American Indians in minority races. Further, we found that rural residence and lack of urologist to be associated with increased mortality rates, particularly among African Americans and American Indians. Additional factors not evaluated may contribute to these findings. Further studies are warranted to evaluate the differences in kidney cancer mortality among these minority populations.

RECENT TRENDS IN TOBACCO-RELATED CANCER BY GENDER, OKLAHOMA

Presenter: Dana S. Mowls

Dana S. Mowls, MPH; Lacy S. Brame; Laura A. Beebe, PhD

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Despite substantial declines, cigarette smoking is responsible for one in three cancer-related deaths. This research examines recent trends in tobacco-related cancer incidence rates by gender in the state of Oklahoma.

Incident rates for bladder, buccal cavity and pharynx, cervix (female only), esophagus, kidney and renal, lung and bronchus, pancreas, and stomach cancer from 2001-2010 were obtained from the Oklahoma Central Cancer Registry via the Oklahoma State Department of Health OK2SHARE public use database. Incidence rates were per 100,000 population and age-adjusted to the 2000 US standard population. Annual percent change (APC) was estimated by least-squares linear regression to describe trends in cancer incidence rates over time. Rates were considered to increase or decrease if the p-value for trend <0.05.

Males had higher incidence rates for all tobacco-related cancers examined, excluding female cervical cancer. During 2001-2010, no declines in tobacco-related cancer incidence rates were observed among females. Incidence rates declined for lung cancer and stomach cancer among males only. Among males, incidence rates declined the most per year for lung cancer (APC: -2.67%; p-value: 0.0003) followed by stomach cancer (APC: -1.52%; p-value: 0.0276). During 2001-2010, incidence rates increased for buccal cavity and pharynx cancer (APC: 2.49%; p-value: 0.0270) among males and for kidney cancer among both males (APC: 2.62%; p-value: 0.0149) and females (APC: 5.23%; p-value: 0.0002). All other tobacco-related cancer incidence rates, including female cervical cancer, were stable during 2001-2010.

Reflecting historical patterns of cigarette smoking, males had higher incidence rates for all tobacco-related cancers examined, excluding female cervical cancer, during 2001-2010 in Oklahoma. Although several factors may have accounted for the observed trends, recent shifts in smoking behaviors likely contributed to the reductions in lung and stomach cancer among males. Tobacco-related cancers with increasing trends should be closely monitored to understand factors associated with their rise.

EXAGGERATED NEGATIVE EMOTION PROCESSING BIAS IN SMOKING MDD

Presenter: Ikuko Mukai

Mukai, I.[1], Simmons, W.K. [1], and Bellgowan, P.S. [2]

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Introduction: Although the overall smoking rate has declined in the last 50 years, there has been much less progress among those with major depressive disorder (MDD) (Cook, et al., 2014). Support and treatment for smoking cessation are often not provided to smokers with MDD (Cook et al., 2014), because of a belief among health-care providers that smoking works as self-medication for mental illness (Prochaska, 2011). However, epidemiological studies have linked the level of smoking dependence and the severity of mood symptoms in MDD (Jamal et al., 2012; Kendler, 1997; Breslau et al., 1993). In addition, a study by Taylor et al. (2014) demonstrated that smoking cessation leads to improvement in depressive illness in the long term. These results indicate that smoking likely exacerbates MDD, and thus it is doubly important to promote smoking cessation among those with MDD. In this study we present human neuroimaging evidence that smoking results in an exaggerated negative bias in facial emotion processing in MDD patients. This study thus provides a biological basis for the deleterious effects of smoking on MDD symptoms found in epidemiological studies.

Methods: 17 non-smoking healthy controls (HCns), 17 non-smoking MDD patients (MDDns) and 7 smoking MDD patients (MDDsm) were studied. The age and gender of the HCns were matched with the MDDns. Subjects were assessed with the Hamilton Depression Rating Scale and Fagerstrom Nicotine Dependence Test. We employed a repetition suppression experimental paradigm and conducted an event-related fMRI experiment on processing of sad (S) and happy (H) facial emotion. In each trial, subjects were exposed to two consecutively presented faces (emotion repeated: HH or SS, or emotion changed: HS or SH) or only one face (H or S). The repetition suppression (RS) for sad or happy was assessed by contrasting these conditions. We conducted voxel-to-voxel whole brain analyses and regions of interest (ROI) analyses to compare the RS between groups.

Results: For the HCns, the whole brain analyses showed significant RS for sad in seven brain areas: right middle and superior temporal gyri, left fusiform gyrus, right anterior and posterior fusiform gyri, right pons and right amygdala. The analyses also revealed significant RS to happy in the left amygdala. In contrast, no areas showed significant RS to either sad or happy in the MDDns and MDDsm groups. Furthermore, in the ROIs defined by the results noted above, the HCns group showed stronger RS to sad than both MDDns and MDDsm groups, and the MDDns group showed stronger RS to sad than the MDDsm group.

Discussion: Regions showing repetition suppression to sad faces included not only the typical face-responsive regions but also the amygdala, which is associated with mediating responses to negative emotional stimuli. Differences in RS to sad may reflect a processing bias for negative emotion stimuli in individuals with MDD, and smoking may enhance this negative emotion processing bias.

The study was performed at the Laureate Institute for Brain Research in Tulsa, OK.

TARGETED DELIVERY OF HuR siRNA BY TRANSFERRIN RECEPTOR TARGETED LIPID-BASED NANOPARTICLES EXHIBIT ENHANCED ANTI-TUMOR EFFICACY *IN VITRO*

Presenter: Ranganayaki Muralidharan

Ranganayaki Muralidharan[1,3], Narsireddy Amreddy[1,3], Anish Babu[1,3], Anupama Munshi[2,3], Rajagopal Ramesh[1,3]

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Objective: HuR, a nucleo-cytoplasmic shuttling protein plays a role in mRNA stabilization and protein translation. It specifically binds to AU-rich (ARE) sites at the 3' end of the mRNA and transports it to the cytoplasm for protein translation. HuR expression has been demonstrated to be a poor prognostic marker in patients diagnosed with cancers of the lung, ovary, breast and colon. On the basis of these reports we hypothesized that inhibition of HuR will result in down regulation of several HuR regulated oncoproteins that play an essential role in tumor progression. To test our hypothesis we have developed and tested the efficacy of a lipid-based tumor-targeted nanoparticle containing HuR specific siRNA against human lung cancer cell lines.

Methods: Human lung cancer cells (A549, HCC827) and normal lung fibroblast (MRC-9) cell lines were used in the present study. Transferrin receptor (TfR) targeted nanoparticles (NP) were prepared by conjugating transferrin (Tf) into 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[folate(polyethylene glycol)-2000] which is post inserted into the liposomes (DOTAP:chol). The resulting nanoparticles were labeled as Tf-NP. Scrambled siRNA (control siRNA) and HuR-siRNA containing Tf-NPs were labeled as Tf-NP\C and Tf-NP\HuR respectively. Size, charge and shape of the NPs was determined using dynamic light scattering (DLS), zeta potential analyzer and transmission electron microscope. Specificity and transfection efficiency was determined using a fluorescent plate reader. Cell viability was measured by trypan blue exclusion assay; HuR knockdown was evaluated by using quantitative real-time (qRT-PCR) and western blotting. Cell migration was determined using the Boyden chamber assay and flow cytometry.

Results: Differential protein expression of HuR and transferrin receptor was detected in the lung cancer cell lines and normal lung fibroblast by western blotting. The synthesis of Tf-NP was confirmed by dot blot analysis. Size of the Tf-NP was 200-300nm and charge was +1.0 mV. Reduced uptake of Tf-NP was observed upon addition of exogenous human transferrin whereas pre-incubation with Desferoximine (DFO) resulted in enhanced uptake of Tf-NP in A549 cells demonstrating the specificity of Tf-NP towards the transferrin receptor. Transfection efficiency studies using fluorescently labeled HuRsiRNA showed that A549 cells had higher uptake of the Tf-NP when compared to the HCC827 cells whereas MRC-9 cells showed minimal uptake of the Tf-NP. Significant suppression of cell viability was observed in the A549 cells at 24 h and 48 h compared to the HCC827 and MRC-9 cells. This suppression correlated with reduced levels of HuR mRNA and protein expression in Tf-NP\HuR treated cells along with G1phase cell cycle arrest, decreased expression of cyclinD1 and increased p27 protein. Knockdown of HuR also caused a down-regulation of some of its target proteins: Bcl2, cyclinD1 and cyclin E. Finally, tumor cell migration was significantly inhibited in Tf-NP\HuR treated cells compared to Tf-NP\C treatment.

Conclusion: Our results demonstrate that tumor-targeted delivery of HuR-RNAi in lung cancer cells selectively inhibits the expression of HuR and HuR-regulated oncoproteins resulting in decreased cell

proliferation and cell migration. Our results provide the impetus for conducting *in vivo* studies which will lead to the development of HuR-targeted therapeutics for lung cancer.

Acknowledgments. This study was supported by a grant from the National Cancer Institute, 5R01 CA167516.

ASSESMENT OF TOBACCO DEPENDENCE SCREENER AMONG SMOKELESS TOBACCO USERS
Presenter: Nasir Mushtaq

Nasir Mushtaq, Ph.D.*and Laura A. Beebe, Ph.D.

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

Variants of the FTQ and FTND are widely used to study dependence among ST users. However there is a need for dependence measure which is based on the clinical definition of dependence and is easy to administer. Tobacco Dependence Screener (TDS), a self-administered 10-item scale, is based on the DSM-IV and ICD-10 definitions of dependence. It is commonly used as a tobacco dependence screening tool in cigarette smoking studies but it has not been evaluated for dependence in ST users.The purpose of this study is to evaluate the TDS as a measure of tobacco dependence among ST users.

Data collected from a community based sample of exclusive ST users living in Oklahoma (n=95) was used for this study. TDS was adapted to be used for ST dependence as the references for smoking were changed to smokeless tobacco use. Concurrent validity and reliability of TDS were evaluated. Salivary cotinine concentration was used as a criterion variable. Overall accuracy of the TDS was assessed by ROC curve and optimal cutoff scores for dependence diagnosis were evaluated.

There was no floor or ceiling effect in TDS score (mean = 5.42, sd = 2.61). Concurrent validity of TDS as evaluated by comparing it with FTND-ST was affirmative. Study findings showed significant association between TDS and salivary cotinine concentration. The internal consistency assessed by cronbach's alpha indicated that TDS had acceptable reliability (alpha = 0.765). TDS was negatively correlated with time to first chew/dip and positively correlated with frequency (number of chews per day) and years of ST use. Results of logistic regression analysis showed that at an optimal cutoff score of TDS 5+, ST users classified as dependent had significantly higher cotinine concentration and FTND-ST scores.

TDS demonstrated acceptable reliability and concurrent validity among ST users. These findings are consistent with the results of previous cigarette smoking studies evaluating TDS. A self-administered tobacco dependence measure based on a clinical definition of dependence is an effective tool in research setting.

BMI-1 REGULATES CELLULAR BIOENERGETICS BY STABILIZING MITOCHONDRIAL TRANSCRIPTS
Presenter: Soumyajit Banerjee Mustafi

Soumyajit Banerjee Mustafi[1], Shailendra Kumar Dhar Dwivedi[1], Prabir Kumar Chakraborty[2], Rumki Basak[1], Michael T Kinter[3], Priyabrata Mukherjee[2] and Resham Bhattacharya[1#]

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The pre-dominantly nuclear protein Bmi-1 has been mainly studied as a chromatin modifier and through regulation of INK4A/ARF can partially rescue phenotypes in cancer cells, stem cells and knockout mice. An INK4A/ARF independent role of Bmi-1 in regulating mitochondrial function and ROS production has been described but the mechanism remains elusive. Here, we provide evidence for a direct role of Bmi-1 in regulating mitochondrial RNA metabolism orchestrating mitochondrial bioenergetics. Subcellular fractionation and confocal imaging revealed a previously unidentified presence of Bmi-1 in the mitochondria in addition to the nucleus. Silencing Bmi-1 in cancer cells significantly inhibited mitochondrial oxidative phosphorylation, cytochrome C oxidase activity and ATP production while mitochondrial mass and integrity remained unaltered. Importantly all of these phenotypes could be reverted by the expression of extra-nuclear Bmi-1. Bmi-1 positively regulated the steady state level of the mitochondrial mRNA transcripts. Bmi-1 interacted with the stabilizing complex LRPPRC/SLIRP and the degradation complex PNPase/SUV3A respectively and prevented mitochondrial mRNA degradation. Loss of Bmi-1 enhanced the nuclease activity of PNPase towards specific mitochondrial transcripts thereby altering their steady state that was reflected at the protein level. Together these data explain why Bmi-1 is indispensable in the normal and cancer stem cells that are reportedly quiescent and dependent on mitochondrial OxPhos for survival and suggest that silencing Bmi-1 will restrict expansion of stem cells and increase glucose dependence that can be exploited for therapeutic purposes. Collectively these results establish a new and fundamental role of Bmi-1 in regulating mitochondrial bioenergetics and purport possible applications in restricting stem cell expansion, premature brain aging and mitochondrial respiratory chain linked metabolic diseases.

A CLINICAL AND DOSIMETRIC ANALYSIS OF THE USE OF 3D CONFORMAL VERSUS RAPID ARC RADIATION THERAPY FOR T1 GLOTTIC LARYNGEAL CANCER

Presenter: Zachary Nicholas

Zachary Nicholas, MD, Carl Bogardus, MD, Elizabeth Syzek, MD, Terence Herman, MD, Salahuddin Ahmad, PhD, Chance Matthiesen, MD

Introduction: The established technique for T1 larynx RT utilized small, parallel opposed lateral fields. With the advancement of IMRT, beam modulation techniques have gained attention due to their ability to limit dose and potential toxicity to surrounding tissues. Our previous investigation comparing these techniques showed rapid arc IMRT to be the most successful in normal tissue dose reduction with adequate PTV coverage. Here we report our early experiences of treating patients with rapid arc IMRT in comparison to a cohort of 3D conformal patients.

Methods: A retrospective review of 10 patients was performed who were treated from 2010-2012 for a T1N0M0 glottic carcinoma. Five patients were treated with rapid arc, another five by 3D conformal. Treatment planning was performed using Eclipse External Beam Planning with a single arc for the rapid arc group and two opposed lateral coplanar or non-coplanar beams for 3D conformal. CTV delineation included the arytenoid cartilages, false vocal cords, anterior and posterior commisures, true vocal cords, and 1-1.5 cm of subglottis. A PTV was generated expanding the CTV 5 mm. Organs at risk contoured included the spinal cord, carotids, and thyroid. Median treatment dose was 2.25 Gy to 63 Gy (range 2.0-2.25 Gy to 63-70 Gy). Plans were compared using generalized equivalent dose and dose volume parameters for the PTV and OAR. Acute toxicities were recorded during treatment and reported in this study.

Results: Median follow-up for all patients was 6.7 months (range 0-23 months). One recurrence occurred in the rapid arc cohort and no recurrences were documented in the 3D group. All treatment plans covered the V95 adequately. The mean dose delivered to the carotids, spinal cord and thyroid favored rapid arc vs. 3D plans, and was (35.0 vs. 68.7 Gy, 8.2 vs. 1.2 Gy, 20.9 vs. 41.0 Gy respectively). Severe skin reactions (brisk painful erythema / desquamation) occurred in 3 patients (60%) treated 3D conformal. Mild to moderate erythema reported in all (100%) of rapid arc patients. One case of grade 3 dysphagia occurred in the 3D conformal group. Both groups also equally reported Grade 3 mucositis in3 patients (60%), and one patient (20%) with > grade 1 xerostomia.

Conclusion: Rapid arc IMRT has been dosimetrically determined to be superior to 3D conformal treatment approaches for T1 glottic cancer. Here we report our early experience using this technique and a comparison of outcomes. The largest difference in patient acute reactions was noted regarding skin toxicity. Rapid arc dose comparisons also show decreased dose delivered to the carotids and thyroids, with a small increase in cord dose. Further follow-up is necessary to determine if these dosimetric differences correlate to improved clinical outcomes. A prospective study is warranted.

A NOVEL ONCOGENIC ENZYME, RCL, PROMOTES TUMORIGENESIS POSSIBLY BY REGULATING TUMOR ANGIOGENESIS

Presenter: Sangphil Oh

Sangphil Oh, Sook Shin, Ralf Janknecht

Department of Cell Biology, University of Oklahoma Health Sciences Center

RCL is an enzyme that cleaves the N-glycosidic bond of dNMP yielding deoxyribose 5'-monophosphate and a free base. Conceivably, free bases may increase dNTP levels through the salvage pathway, while deoxyribose 5'-monophosphate may stimulate angiogenesis. However, these predictions have remained untested and the physiological roles of RCL unexplored. Here we found that RCL is overexpressed in multiple cancer cell lines and human tumors, suggesting that RCL has oncogenic potential. To investigate its role in vivo, we generated RCL-deficient mice and crossed them with MMTV-HER2/Neu transgenic mice, which are known to develop breast tumors within one year. RCL expression was highly upregulated in HER2/Neu-induced breast tumors but not in normal mammary gland. Mice lacking RCL showed delayed HER2/Neu-induced breast tumor onset, reduced tumor multiplicity and metastasis. Intriguingly, while murine Lewis lung cancer cells expressing enzymatically inactive mutant RCL showed no gross defects in cell proliferation and long term survival in vitro, their growth was suppressed and tumor vessel density decreased in mouse xenografts in vivo. This suggests that RCL may affect tumorigenesis possibly by regulating tumor angiogenesis through secreting deoxyribose, a conversion product of deoxyribose 5'-monophosphate. Altogether, our findings and its enzymatic function suggest that RCL is an oncogenic enzyme and, therefore, could be exploited as a new drug target in the treatment of especially breast cancer patients.

IL-24 INHIBITS LUNG CANCER CELL MIGRATION AND INVASION BY DISRUPTING THE SDF-1/CXCR4 SIGNALING AXIS

Presenter: Janani Panneerselvam

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Introduction: The stromal cell derived factor (SDF)-1/chemokine receptor (CXCR)-4 signaling pathway plays a key role in lung cancer metastasis. Therefore, disrupting the SDF-1/CXCR4 signaling axis will reduce the incidence of lung metastasis. In the present study we investigated whether interleukin (IL)-24 can inhibit the SDF-1/CXCR4 axis and suppress lung cancer cell migration and invasion *in vitro*. Further, the efficacy of IL-24 in combination with CXCR4 antagonists was investigated.

Methods: Human H1299 lung tumor cell line was stably transfected with a tetracycline-inducible plasmid vector carrying the IL-24. Upon addition of doxycycline (Dox; 1μg/ml), cells were induced to express IL-24 protein. The expression levels of CXCR4 and its downstream molecular mechanisms in H1299 cells were analyzed. The inhibitory effect of IL-24 on SDF-1/CXCR4 axis is determined by RT-qPCR, western blot, luciferase reporter assay, flow cytometry and immunocytochemistry and the consequence of its inhibition on cell migration, and invasion.

Results: Endogenous CXCR4 protein expression levels varied among four human lung cancer cell lines with H1299 cells showing the highest expression. Doxycycline-induced IL-24 expression in the H1299-IL-24 cell line resulted in reduced CXCR4 mRNA and protein expression. IL-24 post-transcriptionally regulated CXCR4 mRNA expression by decreasing the half-life of CXCR4 mRNA (>40%). Associated with CXCR4 inhibition was the reduced protein expression of $pAKT^{S473}$, $pmTOR^{S2448}$, $pPRAS40^{T246}$ and HIF-1α. IL-24 inhibited tumor cell migration and invasion both in the presence and absence of the CXCR4 agonist, SDF-1. However, the combinatorial effect of either IL-24 combined with CXCR4 inhibitors (AMD3100, SJA5) or with CXCR4 siRNA demonstrated enhanced inhibitory activity on tumor cell migration.

Conclusions: Our study results demonstrate that IL-24 inhibits lung tumor cell migration and invasion by disrupting the SDF-1/CXCR4 signaling pathway and exhibits enhanced anti-metastatic activity when combined with CXCR4 inhibitors.

TARGETING MIF IN OVARIAN CANCER THROUGH THE HLA/PEPTIDE COMPLEX
Presenter: Andrea Patterson

Andrea Patterson[1], Saghar Kaabinejadian[1], Curtis McMurtry[1], Wilfried Bardet[1], Ken Jackson[1], Oriana Hawkins[2], Jon Weidanz[2], and William Hildebrand[1]

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Background: T cells recognize cancer cells via human leukocyte antigen (HLA)/peptide complexes, and class I HLA-restricted tumor infiltrating lymphocytes correspond to favorable prognosis in ovarian cancer (OC)—the most deadly gynecologic cancer [1, 2]. Direct sequencing of these cancer-associated HLA/peptide complexes identified a peptide derived from macrophage migration inhibitory factor (MIF), a pleiotropic cytokine with multiple tumor-promoting functions and dramatic overexpression in the majority of OCs [3, 4]. We originally discovered this peptide in breast cancer, and developed an antibody (RL21A) against the MIF/HLA-A2 complex that specifically targets a portion of invasive breast tissues [5]. However, the prevalence of MIF in OC led us to the current hypothesis that this complex also represents an efficient target for OC immunotherapy.

Methods and Results: Expression of a secreted HLA-A2 molecule (sHLA) in cancerous ovarian cell lines enabled high-sensitivity HLA peptide retrieval and mass spectrometric analysis, identifying the MIF peptide in all four cell lines tested. In addition, RL21A was shown to stain all four cell lines in the context of HLA-A2 by flow cytometry. We then generated a toxin-conjugated version of RL21A, and a tetrazolium (MTT) cytotoxicity assay showed dose-dependent killing of ovarian cancer cells only when the cells expressed surface HLA-A2. Next, 26 ovarian cancer and 21 normal fallopian tube tissues underwent immunohistochemical staining with RL21A to assess differential MIF/HLA-A2 complex expression. Epithelial OC tissues showed significantly increased RL21A staining ($p<0.001$) compared to normal fallopian tube epithelium, with minimal staining of normal stroma and blood vessels ($p<0.002$ compared to tumor cells). As a next step, we are currently isolating tumor-associated lymphocytes from ovarian ascites fluid samples to investigate natural anti-MIF immunity in OC patients using interferon-γ ELISpot assays.

Conclusions: The MIF-derived peptide is prevalent among OC cell lines, and RL21A recognizes OC cell lines in an HLA-A2-dependent manner. We have shown OC cytotoxicity by the toxin-conjugated RL21A, and an OC-specific staining pattern among patient tissues. Ascites lymphocyte reactivity would further validate this complex as an 'altered self' ligand recognized by OC-associated T cells, but regardless the MIF peptide is a promising target for OC immunotherapy.

SINGLE-FIBER REFLECTANCE SPECTROSCOPY OF AY-27 ORTHOTOPIC BLADDER TUMOR *IN VIVO*: INDICATION OF METHEMOGLOBIN AS A SPECTRAL MARKER OF DISCRIMINATING NEOPLASTIC FROM NORMAL TISSUES

Presenter: Daqing Piao

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Introduction and Objectives: Urinary bladder cancer is among the most expensive cancers per patient to treat because of the high incidence of tumor recurrence that entails life-long surveillance and frequent intervention. Cystoscopy provides direct imaging of macroscopic morphological abnormalities of bladder urothelium within the visible spectrum. However, it is limited in diagnosing non-muscle invasive flat lesions such as carcinoma *in situ* that has a high malignant potential. The objective of this pilot project is to demonstrate if a single-fiber reflectance spectroscopy (SfRS) method has the potential to discriminate neoplastic bladder tissue from normal tissue.

Materials and methods: Orthotopic AY-27 bladder tumors were developed in two female Fisher rats (CDF® [F-344]) by urethral catheterized instillation of a suspension of DiI-labeled AY-27 cells into the urinary bladder. At 7 days post-instillation, the animals were anesthetized with an intraperitoneal injection of sodium pentobarbital and placed in a supine position on a water-warmed heating pad (37°C). The bladder was bisected to two connected halves to expose the inner bladder wall. An optical fiber-probe of 320 μm in diameter with a 15°angle-polished tip was brought in contact with the bladder wall by a translation stage with five degrees of freedom. SfRS measurements over 520-920 nm were taken from three types of visually differentiated tissues: (1) peripheral fat; (2) normal bladder mucosa; and (3) a focal tumor lesion. A total of 13 measurements from rat #1 correspond respectively to 1 from fat, 6 from normal tissue, and 6 from tumor. A total of 11 SfRS measurements from rat #2 correspond respectively to 1 from fat, 4 from normal tissue, and 6 from tumor.

Results: All 22 measurements from the bladder wall revealed a near-100% hemoglobin oxygenation, a result consistent with diffuse reflectance spectroscopy on the serosal side of human bladder *in vivo* [Amelink et al., J. Biophotonics 4 (10): 715-720 (2011)]. The 5 measurements from different sites of the same tumor-laden region of rat #1 and from a similar 5 measurements from rat #2 were remarkably different when comparing to a total of 8 measurements from normal tissue. Those from tumor tissue displayed a distinct spectral mark around 630nm. The mark corresponded to methemoglobin (MetHb), a dysfunctional phase of Hb as was reported for AY-27 bladder tumor models [Larsen et al, J. Biomedical Optics, 13(4): 044031 (2008)]. Three other measurements from neoplastic lesions and two from normal tissue were not differentiable based on the MetHb spectral mark.

Conclusions: SfRS may be a simple viable method for assessing neoplastic tissue of bladder wall. A MetHb spectral mark was found associated with neoplastic tissue development in the bladder wall of an AY-27 orthotopic rat bladder tumor model. Further study is warranted.

FABRICATION OF CARBON NANOTUBE-SCREEN PRINTED ELECTRODES FOR THE DETECTION OF A LUNG CANCER BIOMARKER IN SERUM

Presenter: Gayan Premaratne

Gayan Premaratne, Sadagopan Krishnan
Oklahoma State University, Stillwater, OK – 74078

Lung cancer is the leading cause of death among cancer types in the United States and in the entire world. One of the ways to reduce the fatality caused by lung cancer could be to identify the lung cancer specific markers at an early stage of the disease. Formaldehyde has been recently recognized as one of the volatile organic biomarkers of lung cancer. Our goal is to develop an electrochemical biosensor for detection of low levels of formaldehyde in clinical samples. Our biosensor design involves the pi-pi stacking of carbon nanotubes (CNTs) with pyrene compounds to covalently attach formaldehyde dehydrogenase (FDH) by carbodiimide chemistry. CNTs-modified screen-printed electrodes (SPEs) were used for this experiment for the ease of use and cost effectiveness. The FDH catalyzed oxidation reaction of formaldehyde, using NAD^+ as the electron acceptor, yields formic acid and NADH. The main advantage of using NAD-dependent dehydrogenase-based biosensors is that O_2 does not interfere in the electrochemical formaldehyde detection. The drawback of inefficient oxidation of NADH that could foul the reaction can be eliminated by using quinone (1, 2-Naphthoquinone-4-sulfonic acid sodium salt) as the electrochemical mediator. The sensitivity and efficiency of the sensor depends on the electron transfer from NADH via the quinine mediator to the electrode. All experiments were conducted in anaerobic phosphate buffer (pH 7.4). The sensor is able to detect formaldehyde levels of 1, 10, 50 ppm and the goal is to achieve ppb levels in serum or blood samples upon further optimization and by tuning the surface nanochemistry. The future research will focus on developing a common platform with a multiplexed electrode system for the immobilization of various enzymes that would enable detecting a pool of key volatile organic biomarkers of lung cancer in clinical matrices.

EARLY PREDICTION OF CLINICAL BENEFIT FOR TREATING OVARIAN CANCER USING QUANTITATIVE CT IMAGE FEATURE ANALYSIS

Presenter: Yuchen Qiu

Yuchen Qiu[a], Maxine Tan[a], Scott McMeekin[b], Theresa Thai[c], Kathleen Moore[b], Kai Ding[d], Hong Liu[a], Bin Zheng*[a]

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Ovarian cancer is the second most common gynecologic cancer with the highest mortality rate. Given that majority of ovarian cancer patients are diagnosed at advanced stage (Stage III-IV) with metastatic tumors, chemotherapy treatment is very important after the primary ovarian tumor are removed by surgery. However, in the current clinical practice, Response Evaluation Criteria in Solid Tumors (RECIST) guideline has very limited ability to early evaluate or predict patients' response to the chemotherapy, which may generate the lower association with the actual clinical outcome, such as 6-month progression-free survival (PFS). Thus, to help improve clinical efficacy, the purpose of this study is to investigate and test the feasibility of using a new quantitative image analysis method for early prediction of the tumor response to the chemotherapy of ovarian cancer patients participated in the clinical trials for testing new drugs. In this study, we retrospectively selected 30 cases of ovarian cancer patients previously treated in OUHSC underwent a variety of clinical trials. For each patient (case), we collected two sets of perfusion CT examinations taken pre-treatment and post-treatment (4-6 weeks after start of treatment), as well as the associated clinical record (including RECIST evaluation result and 6-month PFS of the patient) for analysis. A computer-aided diagnosis (CAD) scheme was developed for the study. The scheme first applied a hybrid four stage segmenting algorithm to segment tumor previously tracked by the radiologists on the CT images and then computed three image features including the change of tumor volume, average tumor CT number (density) and variance depicting between the pre- and post-treatment CT images. These quantitative image features were combined by feature fusion method or decision-tree based classifier to predict 6-month PFS. The results indicate that the areas under ROC curve (AUC) are 0.773±0.086, 0.680±0.109 and 0.668±0.101 for using each of the above three features, respectively. A maximum AUC of 0.831±0.078 was achieved by fusing these features. When using the decision-tree classifier, we yielded a prediction accuracy of 76.7% (23/30 cases), which is significantly higher than the prediction accuracy of 60% (18/30) accomplished by the RECIST guideline. In summary, this preliminary study demonstrated the feasibility of applying quantitative image feature analysis to assist improving the early prediction accuracy of the tumor response to the new testing drugs or therapeutic methods for treating ovarian or other gynecologic cancer patients in the clinical trials.

Keywords: Computer aided detection (CAD), ovarian cancer, quantitative CT image analysis, efficacy of clinical trials, early chemotherapy response evaluation, Response Evaluation Criteria in Solid Tumors (RECIST).

DNA DAMAGE IN PERIPHERAL BLOOD CELLS PREDICTS OROPHARYNGEAL CANCER RISK
Presenter: Lurdes Queimado

Vengatesh Ganapathy[1], Clifton Woods[1], Majd A. Kabbani[1], Ilangovan Ramachandran[1], Greg Krempl[1], Dini Chissoe[1], Yan D Zhao[2], Lurdes Queimado[1, 3-6]

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Background: The levels of DNA damage caused by specific genotoxics are modulated by genetic and epigenetic factors, as well as life-style choices and are expected to be a major determinant of the individual susceptibility to cancer. Existing assays to detect DNA damage are quite limited in the types of DNA damage they can detect, and are not practical for population-based screenings. We developed a novel technique named primer-anchored DNA damage detection assay (PADDA) that reliably quantifies nucleotide and strand specific DNA damage *in vivo*. PADDA measures a wide-range of DNA damage lesions, has higher sensitivity than other available assays and is practical for population-based screening.

Aims: (1) To determine whether the levels of persistent DNA damage in oropharyngeal cancer patients differ from a control cohort. (2) To determine the DNA damage threshold that can optimally distinguish between cancer patients and controls. (3) To correlate the levels of DNA damage with known risk factors such as tobacco-smoking habits.

Methods: PADDA was used on a real-time PCR setting to quantify *in vivo* DNA damage in the *p53* of the peripheral blood nucleated cells from 50 patients with oropharyngeal cancer and 50 non-cancer controls. To determine the damage threshold that could optimally distinguish between patients and controls, we constructed a receiver operating characteristic curve (ROC). Linear regression models were used to determine whether *in vivo* persistent DNA damage is associated with known risk factors for head and neck cancer.

Results: Our data show that oropharyngeal cancer patients have very high levels of DNA damage in both transcribed and non-transcribed strands of the *p53* in peripheral blood cells at time of diagnosis. This damage is significantly higher than in non-cancer individuals ($p<0.001$). The ROC curve showed that DNA damage is an excellent diagnostic test with an accuracy of 93%. In addition, we were able to use the ROC curve to define the DNA damage threshold that optimally distinguishes between oropharyngeal cancer patients and non-cancer controls with 88% sensitivity and 84% specificity. A possible correlation between the *in vivo* levels of DNA damage and individual parameters is currently being analyzed.

Conclusion: Our study shows for the first time that oropharyngeal cancer patients have very high levels of DNA damage in peripheral blood cells at time of diagnosis. Of major clinical importance, our study documents that measuring DNA damage in peripheral blood cells has a high potential to assess the risk of oropharyngeal cancer. PADDA is a sensitive and affordable assay for the routine evaluation of DNA damage and repair with an unprecedented ability to quantify strand specific DNA damage. PADDA may become a critical tool to assess cancer risk and guide prevention strategies.

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IMPACT OF CHEMOTHERAPY AND RADIATION TREATMENT ON ENDOTHELIAL-DEPENDENT VASODILATION AND CIRCULATING ENDOTHELIAL MICROPARTICLES

Presenter: Landon K. Reiter

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Advancements in early detection coupled with the development of adjuvant therapies (i.e., chemotherapy and radiation treatment) have facilitated a decrease in cancer mortality; however, these improvements have been off-set by increases in cardiovascular disease (CVD) mortality and morbidity. Although the central cardiotoxic effects of these treatments are well documented, the impact on the peripheral cardiovascular system is not completely understood. To date a common method used to evaluate endothelial function is to measure the vasodilation of an artery following an increase in shear rate and luminal blood flow (i.e. flow-mediated dilation (FMD)). Briefly, when there is an increase in blood flow, like during following a short period of ischemia or during dynamic exercise, the resulting increase in shear stress causes the endothelium to produce vasodilator substances that diffuse from the endothelium into the surrounding smooth muscle and cause vasodilation. However, FMD does not provide a systemic assessment of endothelial function throughout the body. Measurements of endothelial microparticles (EMPs) in plasma, which are small vesicles released into the blood when endothelial cells undergo activation or apoptosis, have provided a new method of gaining an overall evaluation of systemic endothelial status. Therefore, we tested the hypothesis that subjects previously treated with chemotherapy and/or radiation would have a (i) decreased brachial artery FMD and (ii) increased concentration of circulating EMPs compared to age-and gender-matched controls.

To date, 3 cancer survivors (CS) and 3 untreated controls (UTC) have completed a FMD test and given blood for EMP analysis. During FMD testing, measurements of forearm blood flow (FBF) were recorded via Doppler Ultrasound. We quantified EMPs via flow cytometry using CD62E+, which provides an index of endothelial activation/inflammation.

Preliminary Results: The FMD response was decreased in CS compared to UTC (5.69% vs. 10.40%, respectively). When normalized to shear stress, the FMD remained decreased in the CS group. The time to peak diameter was longer in CS compared to UTC (107.5 sec vs. 78.5 sec, respectively). Due to time constraints plasma EMP concentrations are pending at this time. In conclusion, it appears that chemotherapy and radiation treatments may result in a decrease in endothelial function in long-term cancer survivors.

Tanning Beliefs and Behaviors among Rural American Indian and Non-Hispanic White Youth
Presenter: Dorothy A. Rhoades

Dorothy A. Rhoades[1,2], Ardis L Olson[3], Martina Hawkins[4], Dannielle Branam[4], Tammie Cannady[4], Barbara Norton[5], Kai Ding[6], Justin Dvorak[6], Paul Spicer[7], Vanessa Simonds[8], Mark P. Doescher[2,5]

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Purpose Skin cancer rates are increasing among American Indians (AI), and melanoma is diagnosed at an advanced stage for more often in AI than in other racial groups. Exposures to ultraviolet (UV) light during adolescence are strongly associated with skin cancer but have never been reported for AI youth.

Procedures In 2013 we conducted a survey of UV exposure, behavior, and attitude in a racially diverse sample of middle and high school (HS) students in rural Oklahoma. Associations between demographic and UV exposure variables were assessed with chi-square testing. Multivariate associations with race and sex were explored with a proportional odds model for ordinal response variables and logistic regression for binary outcomes.

Summary of Data Our sample included 134 students who indicated any AI (n=68) or non-Hispanic White (NHW) race (n=66). Most (82%) were HS students and 66% were female.

Most students (59-67%) spent > 2 hours/day outdoors in summer, with no difference by race or gender. The prevalence of ≥ 1 sunburn in 1 year was 69%, with a median of 3 (range 1-99), and was more frequent among girls than boys (74% vs 58%; p = .05). However, NHW girls were more likely to report sunburn compared to AI girls (Odds ratio [OR] 6.3, 95% confidence interval [CI] 2.1, 19.1). No association with race was found in boys.

The proportion who used an indoor tanning device in 12 months was 33%, with 12% using ≥10 times. In contrast, the prevalence of indoor tanning among HS students in the US is 13-16%. Girls in our sample reported indoor tanning much more often than boys (45% vs 9%, p< .0001), with no difference or interaction seen by race. Intentional sun tanning was reported frequently: 66% overall, with 76% among girls and 45% for boys (p=.0003), and no difference or interaction seen by race.

While 85% of the students reported a propensity to burn, only 9% always use sunscreen outdoors. Girls more often reported sunscreen use compared to boys (79% vs 61%; p=.02) but AI girls were much less likely to use sunscreen compared to NHW girls (OR 0.24; CI 0.1, 0.7). No significant difference was found by race among boys. However, AI males had significantly higher odds of a positive attitude towards putting on sunscreen than NHW boys (OR 3.9; CI 1.1, 13.5); no race effect was seen for girls. Girls were less likely than boys to always cover their shoulders in the sun (23% vs 38%, p=.05), and less likely to wear hats (14% vs 86%; p<.0001), with no difference or interaction by race. Overall, 27% strongly agreed that tanning makes people look more attractive. Although 32% of the AI and 21% of the NHW strongly agreed, the difference was not statistically significant.

Conclusion UV exposure risks in this rural sample of students are higher than reported nationally, particularly for indoor tanning, for both AI and NHW students. Interventions to reduce harmful UV exposure must include AI youth and address indoor tanning.

OXYSTEROL BINDING PROTEIN 2 (OSBP2/OPR4L): A POTENTIAL THERAPEUTIC TARGET FOR LEUKEMIA
Presenter: Brett L. Roberts and Nicholas A. Wasinger

Naga Rama Kothapalli, Nicholas A. Wasinger, Brett L. Roberts, Anthony W. Burgett

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The oxysterol-binding proteins (OSBP/ORPs) are a family of cytosolic and membrane proteins recently identified as being potentially druggable targets for anti-cancer chemotherapeutic development. One member of this protein family, ORP4L, was initially discovered by its high levels of expression in cancer cells. Normal ORP4L expression is limited to a select few tissues of the body, and therefore its aberrant expression in cancer cells suggests it could be linked to oncogenesis. ORP4L expression has been particularly linked to some leukemias, but the expression of ORP4L in different cancer cell lines have not been systematically determined, nor has the potential role of ORP4L expression in leukemia pathology or cancer biology been definitively explored. We currently have a multi-dimensional research program focused on the organic synthesis and biological validation of OSBP/ORP-targeting anti-cancer small molecules. The goal of the current research project is to determine if ORP4L is a cancer-specific drug target, especially for targeting for leukemia cell lines that highly overexpress this protein. We have, for the first time systematically characterized expression of ORP4L and other OSBP/ORP proteins in a panel of cancer cells, both at the mRNA transcript and the protein level. Our results show marked difference in ORP4L expression levels and clear evidence of ORP4L post-translational modifications in the panel of different cancer cell lines. Future research will determine if the ORP4L expression level or ORP4L state are is critical to cancer cell proliferation.

CONCURRENT HYPERTHERMIA SENSITIZATION AND RADIATION-GUIDED NANOCHEMOTHERAPY
Presenter: Kaustuv Sahoo

Ruchika Fernando[1], Kaustuv Sahoo[1], Danny Maples[1], Yuanshui Zheng[2], Jerimy C Polf [3], Eric R. Benton[3], Kenneth E. Bartels[4], Daqing Piao[5], and Ashish Ranjan[1*]

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The objectives of this study were to: 1) determine if mild hyperthermia (40–42 °C) can sensitize tumor cells for more effective proton beam radiotherapy (PBRT); 2) characterize the survival fraction of cells exposed to PBRT; and 3) characterize release of the drug doxorubicin (Dox) from low temperature sensitive liposomes (LTSLs) without exposure to mild hyperthermia in combination with PBRT.

Dox was actively loaded in LTSLs. A549 monolayer cells were incubated with 100–200 nM of Dox-LTSL (± mild hyperthermia). Cell irradiation (0–6 Gy) was performed by placing the cell culture plates inside a solid water phantom and using a clinical proton treatment beam with energy of 150 MeV. End points were survival fraction, radiation-mediated Dox release, and reactive oxygen species (ROS) production. Hyperthermia effectively sensitized cells for PBRT and lowered the cell survival fraction (SF) by an average of 9.5%. The combination of 100 nM Dox-LTSL and PBRT (1–6 Gy) achieved additive to synergistic response at various dose combinations. At higher radiation doses ($\geq$ 3 Gy), the SF in the Dox and Dox-LTSL groups was similar (~20%), even in the absence of hyperthermia. In addition, 30% of the Dox was released from LTSLs and a 1.5-2 fold increase in ROS level occurred compared to LTSL alone therapy. The combination of LTSLs and PBRT can achieves additive to synergistic effect at various dose combinations *in vitro*.

Concurrent PBRT and Dox-LTSL treatment significantly improved the cytotoxic outcomes of the treatment compared to PBRT and Dox chemotherapy without LTSLs. We hypothesize that PBRT may induce drug delivery from LTSL in the absence of hyperthermia, and provide a novel means of radiation guided nanotherapy.

MITOCHONDRIAL PYRUVATE CARRIER 1 (MPC1) IS DOWNREGULATED IN *apc^{mcr}* AND ESSENTIAL FOR NORMAL VERTEBRATE DEVELOPMENT

Presenter: Imelda T. Sandoval

Imelda T. Sandoval[1], Richard Glenn C. Delacruz[1], Christeena Satterfield[1], Kristofor A. Olson[2], Jared Rutter[2] and David A. Jones[1]

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Colon cancer is the third leading cause of cancer deaths in the US. It is estimated that there will be approximately 97,000 new cases and 50,000 deaths resulting from colon cancer in 2014. It has been proposed that colon tumors undergo a series of genetic changes as it progress from normal tissue to carcinoma, with mutations in the tumor suppressor *Adenomatous Polyposis Coli* (*APC*) as the primary initiating mutation. Germline mutations in *APC* are found in a majority of familial adenomatous polyposis (FAP), an inherited form of colon cancer, while somatic mutations in *APC* occur in 80% of sporadic colon tumors.

Mitochondrial Pyruvate Carrier 1 (MPC1) is a member of the mitochondrial carrier family and has just been recently identified. It forms a heterocomplex with MPC2 and is responsible for transporting pyruvate, a critical player in cellular metabolism, into the inner mitochondrial matrix. Recent studies have shown that *MPC1* expression is downregulated in various types of cancers, particularly in colon adenocarcinoma, and exhibits a positive correlation with *APC*. We, therefore, investigated whether APC regulates MPC1 and whether *MPC1* downregulation contributes to intestinal differentiation and development of colon cancer.

To explore the relationship between APC and MPC1, we turned to the zebrafish to further study *mpc1*. We found that *mpc1* is expressed primarily in the gut in the developing embryo. Utilizing a zebrafish genetic mutant of *apc* (*apc^{mcr}*), we demonstrate that *mpc1* expression is reduced in *apc^{mcr}* compared to *apc$^{+/mcr}$* and wild type siblings. Antisense knockdown of *mpc1* in wild type embryos resulted in an array of developmental defects that most notably included failed intestinal differentiation. Knockdown of *mpc1* recapitulated other phenotypes of *apc* loss including enlarged hindbrain, pericardial edema, loss of pectoral fins, reduced pigmentation, body curvature and defective jaw formation. Interestingly, the phenotypic abnormalities that we have observed with *mpc1* morphants are strikingly similar to those reported for *neckless* mutant embryos (*nls*), which has an inactivating mutation in retinaldehyde dehydrogenase type 2 (*aldh1a2*) and exhibits a retinoic acid (RA)-deficient phenotype. Further studies into the regulation of MPC1 may lead to a new role for APC in metabolism and tumorigenesis.

CYCLIN DEPENDENT KINASE REGULATES THE LENGTH OF S-PHASE THROUGH TICRR/TRESLIN PHOSPHORYLATION

Presenter: Courtney G. Sansam

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S-phase cyclin-dependent kinases (CDKs) stimulate replication initiation and accelerate progression through the replication timing program, but it is unknown which CDK substrates are responsible for these effects. CDK phosphorylation of the replication factor TICRR/TRESLIN is required for DNA replication. We show here that phosphorylated TICRR is limiting for S-phase progression. Expression of a TICRR mutant with phosphomimetic mutations at two key CDK-phosphorylated residues ($TICRR^{TESE}$) stimulates DNA synthesis and shortens S-phase by increasing replication initiation. This effect requires the TICRR region that is necessary for its interaction with MDM Two Binding Protein. Expression of $TICRR^{TESE}$ does not grossly alter the spatial organization of replication forks in the nucleus, but it does increase replication clusters and the number of replication forks within each cluster. In contrast with CDK hyperactivation, the acceleration of S-phase progression by $TICRR^{TESE}$ does not induce DNA damage. These results show that CDK can stimulate initiation and compress the replication-timing program by phosphorylating a single protein, suggesting a simple mechanism by which S-phase length is controlled.

RNA STRUCTURES AND ENERGETICS ENABLING CANCER RESEARCH
Presenter: Susan Schroeder

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Background: The power of RNA to regulate gene expression has the potential to cure cancer. RNA interference (RNAi) has tremendous capacity for elucidating the aberrant gene expression in cancer cells and successfully treating cancer through small RNA therapeutics. The energetics of RNA duplexes and imperfect matches play an important role in the specificity and efficacy of microRNAs (miRNAs) that regulate expression of cancer genes and of RNA therapeutics with the potential to cure cancer. Understanding the energetic stability of imperfect RNA helices is a key step toward understanding off-target effects of small RNA therapeutics. Energetic stabilities form the foundation for RNA structure predictions, which are a useful tool for determining microRNA target site accessibility. The network of changes in small RNA and mRNA expression in cancer biology may be described by the competing endogenous RNA (ceRNA) hypothesis. The competing endogenous RNA (ceRNA) hypothesis presents a systems view of small RNA-mRNA networks where multiple RNA effectors, such as mRNA, long noncoding RNA, and pseudogenes, present multiple binding sites for small RNA regulators. Testing the ceRNA hypothesis will require accurate RNA energetics and structure predictions. Our lab has focused on improving the predictions of terminal mismatches that occur in small RNA-mRNA duplexes.

Methods: The free energies for the formation of duplexes containing terminal mismatch motifs were measured using optical melting experiments. The enthalpic and entropic contributions to the stabilities of terminal adenosine mismatches were examined using substitutions with locked nucleic acids and solutions with polyethylene glycol, a co-solute that mimics cellular crowding. A variety of biophysical studies were used to explore the structural basis for the thermodynamic stabilities of terminal mismatches.

Results: New rules for the thermodynamic stabilities of terminal mismatches improve the correlation between thermodynamic stability and effective small RNA gene silencing. Our measurements provide benchmarks for adjusting free energy parameters to different salt concentrations and molecular crowding conditions, and thus improve predictions in experimental conditions.

Conclusions: These results contribute to the ongoing improvement of the thermodynamic database of RNA motifs that forms the core of RNA structure prediction tools. Accurate structure predictions will be essential for discovering the complex network of RNA interactions that regulate gene expression in cancer biology.

UTILIZATION OF CIRCULATORY ANGIOGENIC BIOMARKERS FOR DOSE OPTIMIZATION OF ANTIANGIOGENIC THERAPY

Presenter: Satish Sharan

Satish Sharan and Sukyung Woo

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Purpose: Several antiangiogenic drugs are approved for treatment of cancer patients but availability of validated biomarkers for prediction of clinical outcome is still elusive. Various circulating cytokines & angiogenic factors (CAF) like VEGF, PlGF and sVEGFR2 are upregulated upon treatment with angiangiogenic therapy and extensively explored as biomarkers; however it has resulted in limited success. We aimed to quantitatively characterize dynamics of circulatory biomarkers in response to antiangiogenic therapy at various dosages and thus to guide finding biologically optimal doses to improve therapeutic benefits.

Methods: We developed a quantitative systems pharmacology (QSP) model to investigate CAF modulation by tumor and host cells, and the relationship between overall CAF changes and antitumor efficacy in response to sunitinib, a VEGF receptor tyrosine kinase inhibitor, as the model drug. Time profile of *in vivo* drug concentrations, tumor growth, CAFs modulation after sunitinib treatment were obtained preclinically and clinically. Key features of our QSP model included VEGF-induced VEGFR2 activation, signal transduction, tumor growth kinetics, antitumor response and feedback compensatory mechanism, and circulatory biomarkers emanated from tumor and host cells. The model was developed using preclinical data from tumor-bearing animals and then translated to explain VEGF modulation in cancer patients receiving sunitinib with different treatment outcomes (progressive vs. stable disease).

Results: Daily administration of sunitinib (20-80 mg/kg/day) led to stimulation of VEGF, PlGF and inhibition of sVEGFR2. Our model successfully predicted the time- and dose-dependent changes in CAF induced by anti-VEGF therapy in both animals and patients. The model also provided mechanistic insight about recognition of relative contribution of host derived CAF for better interpretation of biomarker data from anti-angiogenic therapy. Dose-dependent change in CAFs was closely correlated with antitumor activity; higher doses led to not only a greater tumor reduction but also greater stimulation of compensatory proangiogenic factors that potentially confer tumor escape mechanism. We developed an "Inhibition Index" using CAF changes and antitumor response that would be valuable in finding biologically optimal doses for antiangiogenic therapy.

Conclusion: The present study outlined the importance of finding optimal doses that balance between antitumor activity and anti-vascular effects by antiangiogenic therapy and circulatory biomarkers can be effectively utilized for this purpose. Our findings suggest that optimizing dose intensity will improve the therapeutic benefits of anti-VEGF therapy (e.g., avoid the higher doses that induce CAF and cause accelerated development of resistance).

THE ROLE OF RIF1 AND THE REPLICATION TIMING PROGRAM IN VERTEBRATE DEVELOPMENT
Presenter: Joseph Siefert

Joseph Siefert[1], Amnon, Koren[3], Courtney Sansam[2], Emily Clowdus[1], Duane Goins[2], Chris Sansam[1,2]

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DNA replication timing is the coordinated manner in which different sequences of DNA are replicated during S-phase of the cell cycle. The DNA replication timing program is stable and very reproducible among individual cell types, and the spatiotemporal order of replication is highly conserved among metazoans. In spite of this, the mechanisms and determinants of replication timing have remained largely elusive and the biological significance is unknown. However, replication timing changes have been observed to occur during embryonic stem cell differentiation in vitro as well as in multiple types of cancer. Using zebrafish as a model of vertebrate development, we have generated replication timing profiles from various stages of development corresponding to different transcriptional and differentiation statuses. Our results indicate that lineage-independent replication timing can be observed at the whole organism level and suggest that changes in replication timing occur in vivo coincident with differentiation. Ongoing analysis will examine the correlations between replication timing, transcription, and epigenetic marks, which can reveal conserved mechanisms of replication timing. Furthermore we are planning experiments to investigate replication timing changes in cancer using a zebrafish model of T-cell cancer in collaboration with the Frazer Lab.

To date, the only metazoan protein shown to have global effects on replication timing is Rif1. Our Rif1 knockdown in zebrafish has demonstrated that Rif1 is required for vertebrate development and has revealed defects in hematopoiesis and vascular development. Using knockdown and overexpression methods, we are investigating the role Rif1 plays in cell differentiation during vertebrate development. Additionally, Rif1 has known roles in DNA damage response and collapsed replication fork repair, and several mutations in Rif1 have been identified in breast cancer. Therefore, we have used TALENs, a precise genome editing technology, to create an allelic series of Rif1 mutants, including a null and several modified versions of the protein, in order to generate separation of function mutants and elucidate mechanisms of its biological functions.

NATIONAL STUDY OF CHRONIC DISEASE SELF-MANAGEMENT: SIX- AND TWELVE-MONTH FINDINGS AMONG CANCER SURVIVORS AND NON-CANCER SURVIVORS

Presenter: Alicia L. Salvatore

Alicia L. Salvatore[1], SangNam Ahn[2], Luohua Jiang[3], Kate Lorig[4] and Marcia G. Ory[5]

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Objective: This study examined the applicability of the Chronic Disease Self-Management Program (CDSMP) for cancer survivors and compared outcomes among cancer survivors and participants with other chronic diseases (non-cancer survivors).

Methods: Participants were older adults (n=1,170) enrolled in the National Study of CDSMP. Detailed information about physical and psychosocial health status and health care behaviors was collected from participants (n=116 cancer survivors and n=1,054 non-cancer survivors) via self-report before CDSMP participation and at six- and twelve-month follow-ups. Linear and generalized linear mixed models were used to assess baseline-to-six-month and baseline-to-twelve-month changes.

Results: Among cancer survivors, general health, depression, and sleep significantly improved from baseline to six-months. These significant changes were sustained at twelve months. Communication with physicians, medication compliance, pain, days in poor physical health, days in poor mental health, and days kept from usual activities also improved significantly from baseline to twelve months. Among non-cancer survivors, all outcomes except medication compliance and stress improved significantly from baseline to six months. At twelve months, medication compliance also improved significantly.

Conclusions: Findings suggest that participation in CDSMP, an evidence-based chronic disease self-management intervention not specifically tailored for cancer survivorship, may significantly improve physical and psychosocial health status and key health care behaviors among cancer survivors. Additional research is needed to elucidate cancer survivors' unique needs and examine the benefits of tailored versions of CDSMP. Nevertheless, CDSMP, available at-scale nationally and internationally, is a promising intervention for cancer survivors and should be considered a valuable component of survivorship care plans.

DEVELOPMENT OF A TARGETED GADOLINIUM CONTRAST FOR NONINVASIVE OF MAGNETIC RESONANCE (MR) IMAGING OF NON-MUSCLE INVASIVE BLADDER CANCER

Presenter: Joel Slaton

Joel Slaton, MD, Carole Davis, MS, Nataliya Smith, Debbie Saunders, Robert Hurst, Rheal Towner

Department of Urology, OUHSC, and Advanced Magnetic Resonance Center, OMRF

INTRODUCTION AND OBJECTIVES: Development of methods to noninvasively detect bladder cancer and eliminate cystoscopy remains the golden ring of urology research. While muscle invasive cancer is relatively easily imaged with standard CT and MRI technology, the ability to image non-muscle invasive bladder cancer (NMIBC) in a noninvasive manner remains a challenge. We report our experience with a tumor-targeted gadolinium contrast agent for MR imaging NMIBC.

METHODS: The peptide ligand (CSNRDARRC) has previously been reported as having strong specificity for urothelial cancer. The peptide linked to a FITC was tested against a panel of human and rodent malignant and benign urothelial cell lines and imaged fluorescently. The peptide ligand was then conjugated to Gadolinium-DOTA (Gd). The linked Gd-ligand was studied in vitro against urothelial cell lines and compared to a scrambled peptide linked to Gd and visualized with MRI. The linked Gd-ligandide ligand was delivered intravesically into a murine model of non-muscle invasive bladder cancer for 90 minutes and then washed clear with saline and then imaged with MR. This approach was repeated using a intravenous (IV)delivery and renal filtering into the bladder to image the surface cancer. Intravenous delivery was also used to image the same tumor growing in the subcutis of the mouse.

RESULTS: The FITC-ligand reproducibly bound to the surface of the various cancer lines but no to the benign immortalized urothelial and nonurothelial cell lines increasing fluorescence in cells 2.5-fold. The ligand-linked Gd was bound to the cancer cell growing in vitro increasing "MR signal" by 300% compared to scramble peptide-linked Gd. Intravesically delivered ligand- linked Gd successfully bound to the surface tumor and allowed for easy imaging for up to 6 hours after infusion. Similar results were found when the ligand-linked Gd was delivered intravenously and imaged 12-24 hour later.

CONCLUSIONS: Cancer targeted Gd can be delivered intravesically and intravenously to allow for enhanced MR imaging of superficial bladder cancer. This approach may be first step toward MR-based noninvasive surveillance of the bladder for recurrent non-muscle invasive cancer.

THE EFFICACY OF RADIOTHERAPY FOR DUPUYTREN'S CONTRACTURE AND MORBUS LEDDERHOSE
Presenter: M. Leann Smith

M. Leann Smith, M.D., Chance Matthiesen, M.D., Abeer Arain, M,B.B.S.

Purpose: Dupuytren's Contracture (DC), a fibroproliferative disorder of the palmar fascia was first described by Guillaume Dupuytren in 1831. (1) DC and Morbus Ledderhose (ML), a rare, benign fibromatosis affecting the plantar aponeurosis, afflicts mainly Caucasians of northwestern European origin. (2,3)) Prevalence in the U.S. has been estimated at 7.3%. Radiation Therapy (RT) has been shown to improve symptoms and decrease progression of Dupuytren's Contracture (DC) and Morbus Ledderhose (ML). In the United States it is a successful treatment which is underutilized. We examined the experience and outcomes of patients treated at our facility.

Methods: 31 patients (14 males and 17 females) have been treated. All patients were mailed an informed consent and detailed questionnaire to complete and return. 17 patients (55%) responded, of which 40 sites were treated including 28 hands (70%) and 12 feet (30%). Nine pts had bilateral palm involvement, 5 had bilateral feet involvement and 4 had both bilateral palm and either single or bilateral feet involvement. 12% of patients returned 5 months and 21 months after initial treatment for a second treatment. Utilizing the revised Tubiana's Staging System, 18 hands had stage N, 5 hands had stage 1 and 2 hands had stage 2. RT was delivered with 6-12 MeV electron therapy with customized blocking and bolus. Treatment was 3Gy per fraction x 7 fractions in 5 days to a total dose of 21Gy. 100% of the patients received the planned dose. Median post treatment evaluation time was 28 months and the mean was 35 months with a range of 8-67 mos.

Results: No patients had progression of flexion deformity or contracture after RT. There was a decrease or stabilization of DC or ML symptoms in 14 pts (82%) with a treatment failure rate (progression of symptoms) of 18%. None of the treated patients (0%) reported that they have had any additional treatment for their DC or ML since RT at our facility. Nine patients (52%) had symptoms present for 3-9 months prior to diagnosis. 4 pts (23%) reported symptoms for 1-2 yrs and 2 pts (28%) reported symptoms present for 10 yrs or longer. Acute toxicity was experienced by 8 pts (50%) with the majority (7 pts) reporting mild symptoms and 1 reporting moderate symptoms which included skin tenderness, redness, peeling, blistering or mild pain. Chronic side effects experienced were mild tightness of skin, dryness, skin thickening, mild swelling, worsened hand grip or strength, or decreased sensation, and were experienced by 5 patients (31%). Reduction of pretreatment symptoms of poor hand grip, reduced hand strength, or decreased sensation, was experienced by 3 patients. Pretreatment pain was reported by 6 patients with DC and 5 pts with ML. 100%, had reduction or complete disappearance of pain after RT. One pt had complete disappearance of nodules. Seven pts (58%) had decreased size of nodules, 2 pts (17%) had stable nodules after RT. 2 patients (17%) experienced progression of nodules. Five (56%) reported improvement of cords after RT, and 2 (22%) had stabilization of cords. 2 patients (22%) had progression of cords after treatment. 50% of pts reported improvement in flexion deformity with the other 50% reporting stabilization.

Conclusion: RT remains an underutilized treatment method for DC and ML. Our experience has demonstrated success in prevention of disease progression or reduction of symptoms. Our experience demonstrates RT is effective in stopping progression of flexion deformity and eliminating or decreasing the symptom of pain.

MICRORNA PROFILING SHOWS DIFFERENTIAL EXPRESSION PATTERN IN THE TUMOR TISSUES FROM OVARIAN CANCER PATIENTS RECEIVING ANTIANGIOGENIC THERAPY

Presenter: Akhil Srivastava

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Ovarian cancer is the leading cause of death from gynecological cancers. In United States alone about 22,300 women will be diagnosed with ovarian cancer and with approximately 15,000 women dying from the disease. The high mortality and poor prognosis of ovarian cancer is due to its late diagnosis and recurrence of the disease that is often resistant to therapy. Further, the inability to predict which of the patients will respond or fail to therapy thwarts the opportunity to provide the most effective treatment. Studies have shown micro (mi) RNAs, a class of non-coding RNAs of 22-24 nucleotides in length, play a role in tumor growth and metastasis and in drug resistance. Further studies have shown miRNA profiles are altered in cancer cells that are exposed to cancer therapeutics. Based on these reports we hypothesized the presence of unique miRNA profile in ovarian cancer tissues that differ from normal tissue and can be used as a predictor for therapy outcomes.

In the present study we examined the micro (mi) RNA profile in tumor tissues obtained from ovarian cancer patients (n=19) receiving antiangiogenic agents as adjuvant therapy and compared to normal tissues (n=2). The expression levels of 84 mature human miRNAs in the tissues were analyzed by a high throughput RT-PCR based array system. Of the 84 miRNAs, 12 miRNAs were up-regulated by five-fold or higher in the tumor tissues compared to normal. Rank ordering based on fold change in the expression levels showed the top five miRNAs to be miRs hsa-miR-141-3p, hsa-miR-142-3p, hsa-miR-29b-3p, hsa-let-7f-5p and hsa-miR-19a-3p. Validation of the miRNA array result on two of the miRNAs, hsa-miR-141-3p and hsa-miR 142-3p was individually confirmed by qRT-PCR. Further, *in silico* studies were performed to identify the potential mRNA targets and to elucidate the putative role of hsa-miR-141-3p and hsa-miR-142-3p in the pathophysiology of cancer cells in response to the treatment. Web based miRNA-mRNA target prediction tools: TargetScan and miRTarbase were used for identification of mRNA targets. Hsa-miR-141-3p, a member of miRNA 200 family was predicted to target the epithelial-mesenchymal transition (EMT) pathway genes Zeb1 and Zeb 2. mRNA targets for hsa-miR-142-3p included HMGA2, XPO 1 and Rictor. We are currently examining the mRNA and protein expression levels for ZEB1/2; HMGA2 and Rictor in the tumor and normal tissues. Demonstrating that these proteins are regulated by hsa-miR-141-3p and hsa-miR-142-3p will confirm the miRNA/mRNA study results. In conclusion, the present study has identified differentially expressed miRNAs and their putative downstream targets in ovarian cancer tissues receiving antiangiogenic therapy. Our study results provides a basis for conducting large scale studies and the results thus obtained will further our understanding of physiology of ovarian cancer cells in response to the anti-angiogenic therapy. Additionally, we will be able to determine if regulation of the miRNAs and the identified miRNAs can serve as markers for predicting treatment outcomes.

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DISRUPTION OF ZIP4 FROM LIPID RAFTS: A NOVEL THERAPEUTIC STRATEGY FOR PANCREATIC CANCER
Presenter: X. Sun

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Introduction: Recently, the role of lipid rafts in cancer pathogenesis and progression has been well recognized. Lipid rafts is a special membrane micro-domain enriched in cholesterol, in which multiple cancer related signaling transductions take place. Our previous studies have shown that the membrane protein ZIP4 promotes pancreatic cancer growth. In this study, we aim to further determine whether ZIP4 is located in lipid rafts and the potential function in pancreatic cancer.

Methods: Both MIA PaCa-2 and AsPC-1 cells were used. Cells were lysed in 1% Triton X-100 (TX-100) at 4ºC followed by sucrose gradient ultracentrifugation. Western blot and ABE assay were used to determine the lipid rafts association and protein modification of ZIP4. Flotilin-1 and caveolin-1 were used as positive markers for lipid rafts, and CD71 as a negative marker.

Results: We found that ZIP4 was associated with lipid rafts in human pancreatic cancer cells. Zinc deficiency increased the percentage of ZIP4 in low density fractions. Both ZIP4 and rafts proteins became TX-100 soluble when cells were treated with methyl-β-cyclodextrin which depletes cholesterol, or octyl-β-glucoside which destroys lipid rafts. Investigation on the amino acid sequences of ZIP4 indicates that multiple cysteine residues exist in the transmembrane and cytoplasmic domains, which were considered to be potential palimtoylation sites. Multiple site-directed mutagenesis on those sites were performed, which decreased the association of ZIP4 with lipid rafts.

Conclusion: The association of ZIP4 in lipid rafts might be a major molecular event in ZIP4-mediated pancreatic cancer growth and metastasis. Disruption of ZIP4 from lipid rafts may lead to a new therapeutic strategy for pancreatic cancer.

This work was done at Department of Medicine and Surgery, The University of Oklahoma Health Sciences Center.

EXAMINING SMOKING AND VAPING BEHAVIORS OF VAPOR STORE CUSTOMERS

Presenter: Noor N. Tahirkheli

Noor N. Tahirkheli, B.A.(1,2); Alayna Tackett, M.A.(1,3); Ellen Meier, Ph.D. (1,3); Leslie M. Driskill, M.S.(1,2); Theodore L. Wagener, Ph.D(1,2)

Oklahoma Tobacco Research Center 2. The University of Oklahoma Health Sciences Center 3. Oklahoma State University

This study was performed at The University of Oklahoma Health Sciences Center, Department of Pediatrics.

The prevalence of e-cigarette (EC) stores has increased dramatically in recent years, as has the use of tank systems. The available literature explores online vapor forums to profile the EC community, yet there is little research investigating the vaping behaviors and preferences of EC store customers. The purpose of the present study is to begin to address this gap in the literature. A convenience sample of 100 vapor store customers (51% male; 76% White; Mage = 37.6, SD = 15.1) from four Midwestern, metropolitan vapor stores completed a short survey assessing their vaping/smoking history, current vaping/smoking behaviors, and vaping attitudes and preferences. All participants completed exhaled carbon monoxide testing to biochemically confirm self-reported smoking status (CO<11ppm). Participants had been vaping for a little over a year (M_{months}=14.6, SD=9.7), with 63.4% of EC users biochemically-verified smoking abstinent. The majority of customers (91%) reported enjoying vaping more than smoking, with 80% preferring non-tobacco EC flavors. However, 60% reported that they would still vape if the only flavor available was tobacco. On a scale from 1 (not important) to 10 (very important), participants reported that the most important EC features were “battery life” (M=8.5, SD=2.6), “tastes good” (M=8.4, SD=2.6), and “curbs cravings” (M=7.8, SD=3.3); the least important feature was “feels/looks like traditional cigarette” (M=2.9, SD=3.2). A majority ‘agreed’ or ‘strongly agreed’ that they preferred to buy EC supplies at vapor stores because of “access to staff who can help troubleshoot EC problems” (85%), “enjoy the atmosphere” (74%), and “because the e-liquid is fresher” (66%). No significant differences were found between EC-only users and dual (EC & cigarette) users in terms of number cigarettes smoked per day prior or nicotine dependence prior to initiation, length of EC use, and use of tobacco vs. non-tobacco EC flavors. Overall, vapor store customers demonstrated high rate of smoking abstinence and overwhelmingly preferred vaping to smoking; however, no differences were seen between EC-only users and dual users in terms of smoking history or vaping behaviors.

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ASSOCIATION OF MAMMOGRAPHIC IMAGE FEATURE CHANGE AND AN INCREASING RISK TREND OF DEVELOPING BREAST CANCER: AN ASSESSMENT

Presenter: Maxine Tan

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We recently investigated a new mammographic image feature based risk factor to predict near-term breast cancer risk after a woman has a negative mammographic screening. We hypothesized that unlike the conventional epidemiology-based long-term (or lifetime) risk factors, the mammographic image feature based risk factor value will increase as the time lag between the negative and positive mammography screening decreases. The purpose of this study is to test this hypothesis. From a large and diverse full-field digital mammography (FFDM) image database with 1278 cases, we collected all available sequential FFDM examinations for each case including the "current" and 1 to 3 most recently "prior" examinations. All prior examinations were interpreted negative, and current ones were either malignant or recalled negative/benign. We computed 92 global mammographic texture and density based features, and included three clinical risk factors (woman's age, family history and subjective breast density BI-RADS ratings). On this initial feature set, we applied a fast and accurate Sequential Forward Floating Selection (SFFS) feature selection algorithm to reduce feature dimensionality. The features computed on both mammographic views were individually/separately trained using two artificial neural network (ANN) classifiers. The classification scores of the two ANNs were then merged with a sequential ANN. The results show that the maximum adjusted odds ratios were 5.59, 7.98, and 15.77 for using the 3rd, 2nd, and 1st "prior" FFDM examinations, respectively, which demonstrates a higher association of mammographic image feature change and an increasing risk trend of developing breast cancer in the near-term after a negative screening.

A NOVEL MISSENSE MUTATION IN THE EXTRACELLULAR DOMAIN OF THE *PDGFRA* GENE INDUCES FUNCTIONAL CONSEQUENCES *IN VIVO*

Presenter: Amanda K. Templeton

Amanda K. Templeton[1,2], Imelda T. Sandoval[1], Richard Glenn C. Delacruz[1], Christeena Satterfield[1], Braden Miller[1], and David A. Jones[1]

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Platelet-derived growth factor (PDGF) receptor-α (PDGFRA) belongs to the class III receptor tyrosine kinase family, which also includes c-KIT, colony stimulating factor-1 receptor, and FLT3. Members of this family share structural similarity including immunoglobulin-like extracellular domains, a transmembrane domain, and intracellular protein kinase domains. Additionally, mutations in both *PDGFRA* and *c-KIT* have been described in skin and myeloproliferative malignancies as well as in gastrointestinal stromal tumors. Exome sequencing of a patient with basal cell carcinoma revealed a *PDGFRA* E459K missense mutation. This mutation lies within the Ig5 domain of *PDGFRA* that may parallel mutations in *c-KIT* that result in constitutive receptor activation or altered ligand affinity in skin malignancies. Additionally, analysis of the COSMIC database revealed that in *PDGFRA* the most common mutation is the single amino acid change at codon 459. We were, therefore, interested in investigating whether mutations in *PDGFRA* are also implicated in the pathogenesis of skin cancer. Assessment of functions of PDGRA and the novel variants was examined by performing loss-of-function and gain-of function experiments in zebrafish. Analysis of *pdgfra* expression *in vivo* revealed strong staining in the developing retina, pharyngeal arches, and pectoral fins. Morpholino knockdown of z*pdgfra* resulted in blebbing on the head and body, which was rescued by injection of human wild-type *PDGFRA* mRNA. Injection of human *PDGFRA* carrying the E459K mutation alone resulted in defects in structures known to be derived from neural crest cells. These defects included a decrease in epithelial pigmentation, altered migration of melanocytes, neural tube defects, defective jaw formation, and ectopic development of eyes or secondary body axis. Similar developmental defects were observed in embryos injected with human *PDGFRA* carrying a characterized gain-of-function mutation, but not in those injected with only wild-type human mRNA. Collectively, these findings suggest that this novel *PDGFRA* variant carries functional consequences and that this function may contribute to skin tumor development. Therapeutic agents blocking PDGFRA may, therefore, represent novel approaches to treating skin cancer.

EPSIN IS REQUIRED FOR DISHEVELLED STABILITY AND WNT SIGNALING ACTIVATION IN COLON CANCER DEVELOPMENT

Presenter: Kandice L. Tessneer

Baojun Chang[1], Kandice L. Tessneer[1], John McManus[1], Xiaolei Liu[1,2], Scott Hahn[1], Satish Pasula[1], Hao Wu[1], Hoogeun Song[1], Yiyuan Chen[1], Xiaofeng Cai[1], Yunzhou Dong[1], Megan L. Brophy[1,2], Ruby Rahman[1], Jian-Xing Ma[3], Lijun Xia[1,2], and Hong Chen[1,2]

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Uncontrolled canonical Wnt signaling supports colon epithelial tumor expansion and malignant transformation. Understanding the regulatory mechanisms involved is crucial for elucidating the pathogenesis of and will provide new therapeutic targets for colon cancer. Epsins are ubiquitin-binding adaptor proteins upregulated in several human cancers; however, epsins' involvement in colon cancer is unknown. Here we show that loss of intestinal epithelial epsins protects against colon cancer by significantly reducing the stability of the crucial Wnt signaling effector, dishevelled (Dvl2), and impairing Wnt signaling. Consistently, epsins and Dvl2 are correspondingly upregulated in colon cancer. Mechanistically, epsin binds Dvl2 via its epsin N-terminal homology domain and ubiquitin-interacting motifs and prohibits Dvl2 polyubiquitination and degradation. Our findings reveal an unconventional role for epsins in stabilizing Dvl2 and potentiating Wnt signaling in colon cancer cells to ensure robust colon cancer progression. Epsins' pro-carcinogenic role suggests they are potential therapeutic targets to combat colon cancer.

MECHANISM OF SHetA2 SENSITIZATION OF OVARIAN AND KIDNEY CANCER CELL LINES TO DEATH RECEPTOR 5 (DR5) AGONISTS

Presenter: Elangovan Thavathiru

Shylet Chengedza[1], Elangovan Thavathiru[2] and Doris Mangiaracina Benbrook[2,3]

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Resistance of cancers to biological agents that activate death receptors (DRs) is associated with low levels of DR cell surface expression in patient tumors. Several drugs sensitize cancer cells to the cognate DR5 activating ligand TRAIL (tumor necrosis factor (TNF) receptor apoptosis inducing ligand) *in vitro* by inducing DR5 expression through specific DR5 gene promoter elements or an intronic p53 DNA binding site. SHetA2 (NSC 721689) is a Flex-Het (Flexible Heteroarotinoid) compound that circumvents ovarian and lung cancer cell line resistance to DR4 and DR5 mediated apoptosis.[1-4] We hypothesized that SHetA2 sensitizes ovarian and kidney cancer cell lines to TRAIL by inducing transcription of the DR5 gene. In this study, SHetA2 caused transactivation of the DR5 gene promoter and induced DR5 mRNA, protein and cell surface expression in association with induction of CHOP (CAAT/Enhancer Binding Protein Homologous Protein) mRNA and protein in ovarian and kidney cancer cell lines regardless of their p53 status. DR5 promoter deletion and mutation, and CHOP siRNA studies demonstrated the critical role of CHOP in the mechanisms of transactivation and sensitization. Consistent with the known repression of nuclear factor kappa B (NF-κB) by SHetA2[1], mutation of the NF-κB site in the DR5 promoter enhanced SHetA2-induced transactivation. In summary, SHetA2 sensitizes ovarian and kidney cancer cells to TRAIL by inducing CHOP-dependent transactivation of the DR5 gene promoter independent of p53 and Elk-1. NF-κB repression by SHetA2 reduces, but does not prevent, this induction.

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GTSE1 IS A NOVEL REGULATOR OF CHROMOSOME ALIGNMENT DURING MITOSIS
Presenter: Aaron R. 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 mitosis is a major cause of congenital birth defects and major factor in the development of 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 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 does not affect phosphorylation of S7 on 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 chromokinesin levels on mitotic chromosomes. However, we cannot rule out a potential role in regulating microtubule depolymerases and microtubule stabilizers. At anaphase onset, polar ejection forces are switched off facilitating chromatid movement to the poles.

CAFFEINE REDUCES FUTURE TENSION GENERATION BUT HAS LITTLE EFFECT ON PRE-STRESSED COLLAGEN LATTICES

Presenter: Melville B. Vaughan

Melville B. Vaughan, Ph. D.

Center for Interdisciplinary Biomedical Education and Research; and Department of Biology, University of Central Oklahoma

Caffeine can block the progression of reactive tumor stroma fibroblasts into myofibroblasts; this suggests caffeine may have use as a tumor treatment. Our goal was to determine how caffeine treatment affected tension generation by myofibroblasts using a stress-relaxed collagen lattice assay. Fibroblasts were cast into the lattices in the presence of transforming growth factor-beta to stimulate myofibroblast differentiation. Replicate lattices were treated with caffeine for the same time period. Increased force generation was observed in TGF-beta treated lattices, when compared to no-treatment control. Caffeine treatment blocked tension generation in the TGF-beta treated lattices. Interestingly, caffeine had no effect in lattices when tension and myofibroblasts were already present. Caffeine appears to block the tractional force mechanisms relevant to resting dermis rather than contraction activities characteristic of wounds and tumor stroma. This suggests in tissues where tension is already present, tension reduction by other methods may be required prior to caffeine treatment.

PHOTOTHERMAL ABLATION OF BLADDER CANCER USING PHOSPHOTIDYLSERINE TARGETED SINGLE-WALLED CARBON NANOTUBES

Presenter: Needa Virani

Needa Virani[1], Carole Davis[2], Paul Hauser[2], Robert Hurst[2], Joel Slaton[2], Roger Harrison[1]

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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 partially due to the residual tumor which is reported to be present within 27-62% of patients. The high risk of recurrence is also associated with a high risk of tumor progression into more muscle-invasive and metastatic tumors. Phosphatidylserine 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. Single-walled carbon nanotubes (SWNTs) are known to absorb near infrared light (NIRF) at 980 nm and dissipate most of its generated heat into the surrounding substrate, such as cancerous tissue. This study has focused on treating superficial bladder cancer via thermal ablation using annexin V surface modified SWNTs.

In vitro studies confirmed the binding strength of SWNT-AVs to mouse bladder cancer (MB49) as well as human bladder cancer (J82) lines. These results were confirmed with fluorescence microscopy. Quantitative analysis of cell surface bound annexin V was conducted for each cell line. Additional experiments were run using docetaxel and hydrogen peroxide, known to increase phosphatidylserine surface receptors, at subtoxic levels to enhance the number of bound annexin V molecules for a possibly amplified therapeutic effect. Studies were conducted to determine the cytotoxic effect of NIRF heated SWNT-AVs on both bladder cancer lines. Both lines showed significant cell death as compared to control untreated cells.

In vivo studies were conducted to determine the biodistribution of intravesically delivered SWNT-AVs in MB49 orthotropic models. Controls of saline, non-targeted SWNTs, and non-tumor bearing mice with SWNT-AVs were run as well. Raman spectroscopy will be performed on the harvested organs (lungs, liver, kidney, spleen, blood, and bladder) to determine SWNT-AV accumulation. Results will be confirmed with immunofluorescence.

SWNT-AVs have proven to specifically target bladder cancer cells and, in combination with NIRF, to cause significant cytotoxicity via thermal ablation. The results of this study show promise for NIRF thermally heated SWNT-AVs as a viable therapeutic option for residual tumor cells in recurrent superficial bladder cancer.

PANCREATIC CANCER: A SURVIVAL ANALYSIS STUDY

Presenter: Margaret Wahutu

College of Public Health, University of Oklahoma Health Sciences Center

Background: Pancreatic Cancer is ranked highly among deadly cancers in the United States. Risk factors associated with the disease include age, race, sex, smoking status, and diabetes status. Current findings have suggested that the survival rates for this cancer are worse than lung, breast, and prostate cancer combined. In Oklahoma, there have been very few epidemiological studies conducted to examine pancreatic cancer. The purpose of the current study was to identify risk factors that led to decreased survival of Oklahoma pancreatic cancer patients.

Method: We conducted a prospective analysis of risk factors and length of survival among pancreatic cancer patients living in Oklahoma (n= 5545). Patients diagnosed with pancreatic cancer between 1997 and 2010 and followed up through 2011. Data for this study originated from the Oklahoma Central Cancer Registry. We estimated overall and stratified survival curves using the Kaplan Meier Method and differences observed. Cox regression model was also used to examine the strength of association through the estimated hazard ratios.

Results: The median survival time of the cohort was three months. Significant risk factors for reduced survival times include age, gender, and stage at diagnosis. The association between age and survival time differed depending on gender of patient (p=0.0029).

Conclusion: Results are in agreement with previous research findings. There have been little or no improvements in the survival times of pancreatic cancer patients over the past 13years. Pancreatic cancer still remains a killer disease and more resources should be put forward for research purposes. Additionally, future survival analysis studies should look into behavioral risk factors such as smoking and diabetes status.

ELECTROCHEMICAL DRUG SCREENING STRATEGY FOR CARCINOGENIC PROTEIN – PROTEIN INTERACTIONS

Presenter: Charuksha Walgama

Charuksha Walgama*, Mayowa Akinwale*, Anuruddha Pathiranage* and Sadagopan Krishnan*

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Protein-protein interactions are essential biological processes in living organisms and play key roles such as signal transduction and conserving the dynamics of the cellular architecture. Apart from important biological roles, some incongruous protein interactions lead to many diseases including cancer. The interaction between the tumor suppressor p53 and murine double minute 2 protein (MDM2; HDM2 in humans) is one of the classic examples for such inappropriate interactions, which promotes cancer. Our research objective is to develop a label-free, rapid, and inexpensive electrochemical method for straight-forward monitoring of cancer protein-protein interactions, and small molecule drugs that inhibit such undesired interactions. Thus, systematic screening of small molecule drug libraries using such in vitro, fast, simple and robust techniques have immense advantages to reduce the challenge of selecting the most efficient drug candidate to disrupt disease promoting protein-protein interactions.

To develop the described new method, we are utilizing the interaction between p53 and HDM2 as a model system. p53 is self-assembled on miniature screen-printed electrodes as a stable covalent monolayer. The subsequent binding of HDM2 to the surface p53 is monitored by the electrochemical impedance signal changes. Furthermore, the inhibition of such undesired p53-HDM2 interactions, which promote tumor growth, was successfully monitored by using commercially available preclinical Nutlin 3 drug. Our results demonstrate the simplicity of the developed novel, label-free electrochemical method to address important biological problems related to cancer and anticancer drug development in a single assay. Our future objective is to develop a high-throughput array format of the described method integrated with microfluidics for automation of the screening platform to detect cancer protein-protein interactions and potential drugs.

LPA-INDUCED INVASIVE MIGRATION OF OVARIAN CANCER CELLS INVOLVES MIR-141-3P
Presenter: Jeremy D. Ward

Jeremy D. Ward[1,2,3] Ji Hee Ha[1,2] and Danny N. Dhanasekaran[1,2]

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Ovarian cancer is currently the most fatal gynecological cancer with a 5-year survival rate of only 46%. Recent studies have identified a critical role for lysophosphatidic acid (LPA) in the genesis and the progression of ovarian cancer. Furthermore, microRNA (miRNA) has recently been shown to play an important role in preventing or enhancing tumorgenesis of a multitude of cancers, including ovarian cancer, by directly inhibiting the expression of multiple genes simultaneously. To date, very few studies have looked at the effect of LPA stimulation and the change in the levels of miRNA in ovarian cancer cells. Stimulating the ovarian cancer cell line OVCA429 with 20 □M of LPA for and hypoxic conditions, we identified that miR-141-3p, miR-200a-3p, miR-15a-5p, and miR-101-3p were downregulated. Of the identified miRNAs, miR-141-3p was shown to be downregulated the most in both normoxic (14-fold) and hypoxic conditions (15-fold). To date, miR-141-3p has been linked to the inhibition of epithelial-to-mesenchymal transition (EMT). Additionally, several miRNA databases predicted Src as a potential target for miR-141-3p, which our lab previously linked Src with invasive migration of ovarian cancer cells. Therefore, we hypothesized that miR-141-3p may be important for preventing induction of EMT and subsequent invasive migration of ovarian cancer cells. Testing this hypothesis, we found that overexpression of miR-141-3p significantly decreased LPA-mediated invasive migration of two different ovarian cancer cell lines. In addition, we observed that the ectopic expression of miR-141-3p reduced the expression levels of Src in these cells. Furthermore, miR-141-3p decreased the expression of Slug in these cells, supporting previous studies that show it can inhibit Slug expression and prevent EMT. Thus, our findings unravel a novel mechanism in which LPA induces EMT and invasive migration of ovarian cancer cells through the inhibition of miR-141-3p. Overall, this is the first study to show that miR-141-3p can downregulate the expression of Src and directly inhibit invasive migration of ovarian cancer cells in response to LPA, indicating that downregulation of miR-141-3p and potentially other miRNAs identified in this study may represent a novel way in which LPA can induce invasive migration of ovarian cancer cells.

THE ENDS GAME: FACTORS AFFECTING E-CIGARETTE USE IN OKLAHOMA

Presenter: Ashley H. White

Ashley H. White, Laura A. Beebe, Dana S. Mowls, and Theodore L. Wagener,
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The use of electronic nicotine delivery systems (ENDS) is increasing but estimates of prevalence in Oklahoma are lacking, and factors associated with ENDS use are underexplored. We analyzed population-based, cross-sectional data from a statewide evaluation of a health campaign. Telephone surveys were conducted in 2014 with a sample of adults living in households with children. Respondents (n=1030) were asked if they had ever tried ENDS, which included any form of electronic cigarette, tank system, vapor device or other similar device. Current ENDS use was defined as some day or everyday use in the last 30 days. Data were weighted to represent the state's adult population, and multivariable logistic regression was used to explore the relationship between cigarette smoking status and socio-demographic variables with current ENDS use. About 25% (n=274) of respondents had ever tried ENDS and 10% (n=112) were current users. Seventy-six percent (n=129) of everyday smokers, 57% (n=40) of someday smokers and 32% (n=76) of former smokers had tried one. Less than 5% of never smokers had ever tried ENDS. Thirty-one percent (n=53) of everyday smokers, 28% (n=19) of someday smokers and 14% of former smokers (n=35) were current ENDS users. Only five never smokers (1%) reported current use. After controlling for covariates, current smokers were about 8 times more likely to be current ENDS users than non-smokers (former and never smokers combined, OR=8.3, 95% CI 5.1–13.4). Younger age (<35 years) was associated with a 6-fold increase in the odds of current ENDS use, independent of smoking status and other covariates (OR=6.3, 95% CI 1.3-30.9). The most common reason given for using ENDS was to quit smoking cigarettes (52%) and another 12% reported using to reduce the number of cigarettes smoked. Dual use of ENDS and combustible cigarettes was high. From these cross-sectional data it is unclear the extent to which dual use represents a transitory stage toward quitting cigarette smoking, or a pattern of sustained nicotine addiction which might undermine cessation attempts.

THE SWI/SNF ATP-DEPENDENT CHROMATIN-REMODELING ENZYMES, *Brg1* AND *Brm*, ARE DISPENSABLE IN MULTIPLE MODELS OF POSTNATAL ANGIOGENESIS BUT ARE REQUIRED FOR VASCULAR INTEGRITY IN INFANT MICE

Presenter: Mandi M. Wiley

Mandi M. Wiley[1], Vijay Muthukumar[1], Timothy M. Griffin[2], Courtney T. Griffin[1]

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Mammalian SWI/SNF ATP-dependent chromatin-remodeling complexes play important roles in embryonic vascular development by modulating transcription of specific target genes. We sought to determine if SWI/SNF complexes likewise impact postnatal physiological and pathological angiogenesis. BRG1 and BRM are ATPases within mammalian SWI/SNF complexes and are essential for the complexes to function. Using mice with vascular-specific mutations in *Brg1* or with a global mutation in *Brm*, we employed three models to test the role of these ATPases in postnatal angiogenesis. We analyzed neonatal retinal angiogenesis, exercise-induced angiogenesis in adult quadriceps muscles, and tumor angiogenesis in control and mutant animals. We found no evidence of defective angiogenesis in *Brg1* or *Brm* single mutants using these three models. *Brg1/Brm*-double mutants likewise show no evidence of vascular defects in the neonatal retinal angiogenesis or tumor models. Interestingly, using a tamoxifen-inducible endothelial-specific *Cre* to induce *Brg1* deletion beginning at postnatal day three (P3) on a $Brm^{-/-}$ background, we observed 100% death of *Brg1/Brm*-double mutants by weaning age (P19). These animals had massive hemorrhaging in the small intestine and in the heart. *Brg1/Brm*-double mutants also had blood-filled lymphatics in the distal ileum. These data suggest that while neither *Brg1* nor *Brm* appear to be important for postnatal angiogenesis, they are essential for maintaining vascular integrity in specific tissue beds prior to weaning. These findings highlight the temporal and spatial specificity of SWI/SNF activities in the vasculature and may indicate that other chromatin-remodeling complexes play redundant or more essential roles during physiological and pathological postnatal angiogenesis.

THE IMPACT OF LIMITED ACCESS TO HEALTHY FOODS AMONG CANCER SURVIVORS IN OKLAHOMA
Presenter: Mary B. Williams

Mary B. Williams, PhD, Marianna S. Wetherill, PhD, RD/LD, and Laura A. Beebe, PhD

Williams and Beebe: Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, College of Public Health, Wetherill: Department of Health Promotion Sciences, University of Oklahoma Health Sciences Center, College of Public Health – Tulsa

Background: Although progress has been made in reducing cancer incidence, the number of cancer survivors increased to 13.7 million in the U.S in 2012.[1] The American Cancer Society and World Cancer Research Fund recommend cancer survivors eat a healthy diet with an emphasis on plant foods.[2, 3] Although cancer patients and survivors may be highly motivated to follow these guidelines, those without access to healthy foods may find it difficult to achieve healthy eating goals. The aim of this study was to determine what proportion of Oklahoma cancer survivors had limited access to healthy foods, and to assess whether that limited access was related to not meeting recommended guidelines for fruit and vegetable intake.

Methods: The 2011 and 2013 Oklahoma Behavioral Risk Factor Surveillance Survey (BRFSS) included self-reported previous cancer diagnosis, dietary consumption of fruits and vegetables, and state-added questions regarding healthy food access. Weighted proportions were estimated for those who met dietary guidelines and those with limited access to healthy foods by cancer history. The proportion of adequate fruit and vegetable intake was also estimated by healthy food access among cancer survivors. Finally, logistic regression was used to examine the association between fruit and vegetable intake and access to healthy foods. All analyses were conducted in SAS, version 9.3.

Results: Eight percent of Oklahomans reported a previous cancer diagnosis, other than skin cancer. Cancer survivors were more likely to consume fruits and vegetables at least five times daily than participants with no cancer history (12.7% vs 8.8%). However, survivors were also more likely to report limited access to healthy foods (40.6% vs 34.0%), compared to those with no cancer history. Furthermore, cancer survivors with access to healthy foods were two times more likely to meet the recommended intake of fruits and vegetables than survivors with limited access to healthy foods (AOR=2.2; 95% CI: 1.1, 4.6), after controlling for age, gender, race, education, and income. Specifically, having access to a large selection of high quality fresh fruits and vegetables doubled the odds that a cancer survivor's diet met the recommended level of fruit and vegetable consumption (AOR=2.2; 95% CI: 1.1, 4.5).

Conclusions: More than one-third of cancer survivors in Oklahoma do not have easy access to healthy foods, and the majority of survivors do not meet the recommendations for fruit and vegetable intake. Among cancer survivors, limited access to healthy foods was related to an increased odds of not meeting the recommended guidelines for fruit and vegetable intake. Since there is evidence suggesting diet, exercise and weight influence health-related outcomes and quality of life among cancer survivors,[4] these findings pose significant concern that cancer survivors with limited access to healthy foods may have worse health outcomes and lower quality of life.

EXPERIMENTAL VALIDATION OF NOVEL CANCER BIOMARKERS IDENTIFIED VIA TRANSCRIPTIONAL NETWORK ANALYSIS

Presenter: Jonathan D. Wren

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Motivation: Molecular diagnostics, prognostics and therapeutics ("theranostics") relies upon consistent and discernible molecular differences between cancerous and non-cancerous cells, which are frequently referred to as biomarkers. Proteins that exist on the cell surface are attractive as biomarkers because antibodies raised against them could potentially bind to them *in-vivo* and be used for theranostic purposes. For example, molecular targeting of liposomes or nanoparticles to cancerous cells often relies upon biomarkers disproportionately present in tumors. The ability to identify novel biomarkers opens up new theranostic possibilities.

Approach: We have developed an algorithmic approach based upon integrating a Global Microarray Meta-Analysis (GAMMA) of over 420,000 human microarray experiments with literature-derived information about genetic involvement in gliomas. In total, we have been able to experimentally validate GAMMA's phenotype predictions in 46 out of 55 experiments (85%), suggesting it would be effective at biomarker prioritization. GAMMA identified a set of proteins with no documented involvement in gliomas, yet implicated because of their consistent co-transcription with known glioma-related genes. We then narrowed the list to proteins known/predicted to be expressed on the cell surface that had commercial antibodies. Then, we used both *in-vivo* and *in-situ* approaches to assess their suitability as glioma biomarkers.

Results: The first six of these potential biomarkers we tested: ELTD1, SPON1, Plexin-B2, SLIT3, Fibulin-1, and Lingo1, were validated as proteins highly expressed on the surface of human gliomas using immunohistochemistry. Expression of SPON1, Plexin-B2, and SLIT3 was significantly higher ($p<0.01$) in high-grade versus low-grade gliomas. These biomarkers were significant discriminators in Grade IV gliomas compared with either Grade III or II tumors and also distinguished between glioblastoma multiforme subclasses. We validated *in-vivo* expression of ELTD1 in a rat model of glioma using iron-labeled antibodies and found that it preferentially bound to the angiogenic regions of tumors.

Conclusions: GAMMA is an effective way of prioritizing potential cancer biomarkers for further clinical development, six of which we have validated to date in a glioma model.

DQE CHRACTERIZATIN OF A HIGH-ENERGY IN-LINE PHASE CONTRAST PROTOTYPE UNDER DIFFERENT KVP AND BEAM FILTRATION

Presenter: Di Wu

[1]Di Wu, [1]Molly D. Wong, [1]Yuhua Li, [2]Wei R. Chen, [1]Bin Zheng, [3]XizengWu and [1]Hong Liu

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The objectives of this research are to characterize the detective quantum efficiency (DQE) of a high-energy in-line phase contrast prototype operated under the same estimated absorption dose and different x-ray exposure conditions.

First of all, an imaging prototype was demonstrated based on a high-energy in-line phase contrast system prototype. The DQE of this system is calculated through modulation transfer function (MTF), noise power spectrum (NPS) and input signal to noise ratio under same absorption radiation dose. The x-ray exposure conditions were modified by not only using different tube voltage but also different prime beam filtration. Aluminum, Molybdenum, Rhodium, and a combined filter were selected to acquire a variety of x-ray energy compositions with 100, 110 and 120 kVp exposures. The estimated 1.295 mGy absorption dose onto a 4-cm-thick BR12 tissue equivalent phantom was used to regulate the exposure time under different experiment modes. The resultant curves are compared through the modes of different kVp/same filter and different filter/same kVp within the same estimated patient dose.

As a result, the resultant curves, obtained under same absorption radiation dose, indicate that the MTF performs similar behavior under different; the NPS is majorly affected by the composition of x-ray photon energies; and the overall DQE decreases with the increasing portion of high-energy x-ray photons in the exposure.

***Key words*:** High-energy In-line Phase Contrast, MTF, NPS, DQE, Absorption dose, Filter, Spectrum

PHOTO-NANO IMMUNOTHERAPY FOR METASTATIC BREAST CANCER

Presenter: Feifan Zhou

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An immunologically modified nanotube system was developed using an immunoadjuvant, glycated chitosan (GC), as surfactant of single-walled carbon nanotube (SWNTs). This SWNT-GC system not only retained both optical properties of SWNTs and immunological functions of GC, but also could enter cells due to the carrier properties of SWNTs. Cellular SWNTs induced thermal destruction of tumor cells when irradiated by a near-infrared laser and, at the same time, cellular GC could serve both as damage associated molecular pattern molecules (DAMPs) and pathogen associated molecular pattern molecules (PAMPs) to enhance the tumor immunogenicity and enhance the uptake and presentation of tumor antigens, leading to special antitumor response. Using this novel SWNT-GC system with a 980-nm laser, we treated breast tumors, both *in vitro* and *in vivo*, and investigated the induced thermal and immunological effects. Laser+SWNT-GC afforded a remarkable efficacy in suppressing tumor growth in animal cancer models, in many cases resulting in complete tumor regression and long-term survival. This system forms a multifunctional temporal-spatial continuum, which can synergize photothermal and immunological effects. The laser+SWNT-GC could represent a promising photo-nano immunotherapy to induce systemic antitumor immunological responses through a local intervention, while minimizing the adverse side effects.

ELTD1 AND PLEXIN-B2 AS NOVEL ANTIBODY THERAPIES AGAINST GLIOMA BIOMAKERS
Presenter: Jadith Ziegler

Jadith Ziegler[1 2], Richard Pody[1], Landon Rodriguez[1], Nataliya Smith[1], Debra Saunders[1], Patricia Coutinho de Souza[1], Johnathan Wren[1], and Rheal Towner[1 3]

[1]Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States, [2] Pathology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, [3]Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

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. Through bioinformatics and microarray experiments, we have identified ELTD1 and Plexin-B2 as biomarkers for high-grade human gliomas. Here, we report our findings *in vivo* using anti-ELTD1 and anti-Plexin-B2 antibodies on mouse GL261 glioma models. Using MRI we investigate tumor growth and animal survival rate, and as well as report histological findings using mouse tumor tissue.

Mice were implanted with GL261 cells and were either untreated or administered anti-ELTD1, anti-VEGF or anti-c-Met antibodies. MRI experiments were performed on a magnet imaging system. MRI was used to assess tumor growth, calculate tumor volumes and percent survival was obtained from time-points when mice are euthanized. Additionally, representative histology slides (H&E) obtained from GL261 glioma-bearing mice that were either untreated (UT) or treated with anti-ELTD1, anti-c-Met, or mouse anti-VEGF antibodies. Histogram of mitotic index and atypical mitosis were identified. Lastly, representative IHC slides for CD-31 obtained from GL261 glioma-bearing mice that were either untreated (UT), or treated with anti-ELTD1, anti-c-Met, or mouse anti-VEGF antibodies to compare MVD (number of vessels/μm^2) for each group.

There was a significance increase in animal survival for anti-ELTD1 and anti-Plexin-B2 and anti-VEGF antibodies as well as a significance decrease in tumor volumes for anti-ELTD1 and anti-Plexin-B2 anti-VEGF and anti-c-Met (***$p<0.001$) when compared to untreated animals. Significant decreases in the mitotic index were also found for anti-ELTD1 and anti-c-Met treatment groups compared to untreated mice ($p<0.05$ for both). Significant decreases in MVD were found for the anti- ELTD1 treatment group compared to untreated mice ($p<0.01$) and finally, anti-ELTD1 therapy also had a significantly decreased MVD compared to anti-c- Met or anti-VEGF therapies.

ELTD1 is found to be associated with angiogenesis and Plexin-B2 is associated with cell proliferation and angiogenesis. Our *in vivo* studies have found that anti-ELTD1 and anti-Plexin-B2 antibodies to decrease tumor volumes and increase animal survival in mouse GL261 glioma models. Additionally, anti-ELTD1 therapy was found to decrease the mitotic index and MVD in mouse GL261 glioma model. Future studies will investigate anti-ELTD1 and anti-Plexin-B2 antibody therapies in human xenografts. Our results indicate that anti-ELTD1 and anti-Plexin-B2 antibodies could be potential therapies for high-grade gliomas in humans.

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 cytospin 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 Microarray (TMA)
- Digitized Slides and Image Analysis
- Photographic and Imaging Services
- Molecular Biology Services

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-U

Contact Information

For more information please contact:
Muralidharan Jayaraman, PhD
Director of Research Core Operations
Email: muralidharan-jayaraman@ouhsc.edu
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

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

Contact Information

For more information please contact:
Muralidharan Jayaraman, PhD
Director of Research Core Operations
Email: muralidharan-jayaraman@ouhsc.edu
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
- Moleculary Tagged Cancer Cell Lines

Contact Information

For more information please contact:
Rajagopal Ramesh, PhD
Director, Molecular Imaging Core
Email: rajagopal-ramesh@ouhsc.edu

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 Gillaspy, 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. Gillaspy 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
The University of Oklahoma Health Sciences Center
Oklahoma City, OK 73104
405-271-2337
Office hours 8am-5pm (CDT)

DNA sequencing/Genomics information
Email: microgen_support@ouhsc.edu

Flow Cytometry and Imaging information
Email: cytometry-support@ouhsc.edu

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

For additional inquiries:
Dr. Allison Gillaspy, Director
Email: allison-gillaspy@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

Cancer Center
Research Programs

Cancer Biology Research Program

The field of cancer research has made many advances in understanding the genetic, proteomic and molecular mechanisms that lead to tumor formation and metastasis; however, low long-term survival rates for cancer patients highlights the need for an even greater understanding of these mechanisms and how to translate this understanding into novel, innovative approaches to treat cancer.

The goals of the Cancer Biology Program are to increase our understanding of the molecular changes that cause tumor formation and to identify genes, proteins and microRNAs as promising targets to suppress or inhibit tumor growth. Program members investigate the fundamental molecular mechanisms that lead to tumor growth in all cancers, with a particular focus in cancers of the lung, prostate, pancreas and hematopoietic system. The Cancer Center supports program members with resources such as seed grants to promote collaborations with other basic cancer biologists, pharmacologists and clinical scientists with an emphasis on bench-to-beside approaches.

Program Leader
Ralf Janknecht, PhD

Gynecologic Cancer Research Program

The focus of the Gynecologic Cancers Research Program is bridging basic science and clinical research in order to translate laboratory insight into new diagnostics and therapeutics. As a national leader in clinical research, our program has developed multiple investigator-initiated clinical trials that provide our patients with access to the newest drugs.

These trials provide the infrastructure for our large gynecologic biospecimen repository and translational studies of biomarkers as tests that can predict patient outcome and response to treatment. In addition to identifying prognostic biomarkers for gynecologic cancers, our translational research studies have resulted in a cancer prevention agent about to enter Phase I clinical trial. Basic science research in our program has developed experimental models used to increase our understanding of cancer and identify molecular targets and signatures for biomarker and drug development. The goals of the program are to decrease the suffering and death to cancer of the female organs. The Cancer Center supports the program by providing seed funding, mentoring, seminar speakers and regular meetings of the entire program and focus groups.

Program Leader
Scott McMeekin, MD

Experimental Therapeutics Research Program

The goal of the Experimental Therapeutics Program is to integrate novel therapies and technologies developed in the laboratory with clinical applications for treating human cancers. The scientific aims of the program are 1) to develop and test novel, molecularly-targeted drugs, gene and drug delivery systems; 2) to develop and utilize in vitro and in vivo screening models; and to 3) identify molecular targets for new investigational drugs. Program members have expertise with the following:

- Small molecule inhibitors
- Gene therapy (tumor suppressor genes, siRNA, mircro RNA, ncRNA, interleukins)
- Drug delivery systems (polymers, dendrimers, nanomaterials, liposomes, viral vectors)
- Chemistry (organic, medicinal, synthetic)
- Animal models
- Photodynamic therapy
- Natural products
- Molecular imaging techniques and novel contrast agents
- Novel pharmacodynamic and pharmacokinetics analysis tools
- Cell signaling and cell death mechanisms

The Program is developing a preclinical drug development and testing platform for streamlining a product development pipeline to help achieve the aims above. Program members have the opportunity to develop and test novel concepts via seed-grant funding mechanisms that enable them to generate data to compete for federal funding. Additionally, exchange of scientific information and opportunities to collaborate for team science approach occurs via monthly meetings, seminars and invited guest lectures, and an annual retreat.

Program Leader
Rajagopal Ramesh, PhD

Cancer Health Disparities Program

The goal of this program is to foster the generation of high-quality cancer prevention and control research that addresses cancer health disparities and that is responsive to the needs of tribal and other high-risk, underserved communities in Oklahoma. The Scientific Aims of the program are to:

- Develop and test new strategies to measure and improve quality of life, quality of cancer care, and access to care for patients, survivors, and family members/caregivers
- Conduct high-quality and innovative epidemiological, communications, behavioral, and surveillance research that explores the unequal cancer burden among populations in Oklahoma
- Develop and test novel interventions to foster the adoption and improve the delivery of effective cancer prevention and detection services among under served populations in the state
- Engage under served tribal and other communities in collaborative cancer prevention and control research and strategies to reduce cancer-related health disparities

Program Leader
Mark Doescher, MD, MSPH

Cancer Center Researchers & Research Interests

Carl J. Ade, PhD

RESEARCH SUMMARY
The research efforts of the Integrative Cardiorespiratory Physiology Laboratory at the University of Oklahoma are directed at understanding the:

- important changes in physiological function with cancer and the cancer-associated treatments (i.e, chemotherapy, immunotherapy, hormone deprivation, and radiation) and lifestyles (i.e., changes physical activity and exercise capacity);

- the integrative (systemic to cellular) biological mechanisms that mediate these changes;

- the efficacy of interventions, both lifestyle and pharmacologic, for mitigating or reversing these changes in physiological function.

Currently, we focus our efforts on the areas of i) vascular function, specifically arterial stiffness and endothelial dysfunction, ii) the matching of oxygen delivery via the cardiovascular system to oxygen utilization within the metabolically active tissue, and iii) exercise tolerance.

We utilizes a variety of experimental techniques to study these issues in human subjects, including breath-by-breath pulmonary gas exchange, near infrared spectroscopy, vascular ultrasound, arterial pulse wave analysis, and blood-borne endothelial biomarkers.

Our research is performed in the University of Oklahoma-Norman's Department of Health and Exercise Science and the University of Oklahoma Health Sciences Center Stephenson Cancer Center. In addition, the laboratory provides scientific training from the undergraduate to doctoral levels.

Integrative Cardiorespiratory Physiology Laboratory
***Carl** J. Ade, Ph.D. (PI, Laboratory Director)*
PHONE: 405.325.7335
E-MAIL: cade@ou.edu

Naushad Ali, Ph.D.

RESEARCH SUMMARY

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. HCC often occurs in the setting of underlying chronic viral hepatitis, inflammation, steatosis, and cirrhosis. Hepatitis C virus (HCV) infection is considered a major risk factor for the development of HCC. HCV causes chronic hepatitis in most patients (>80%), accounts for 50-76% of all primary liver cancer cases and reduces overall life expectancy by 8-12 years. Chemotherapy, surgical resection, radiation, and local ablation are ineffective in a large group of patients with HCC. Replacement of normal liver tissues with excessive extracellular matrix (ECM) during hepatitis, steatosis and inflammation results in pre-neoplastic conditions such as cirrhosis (e.g. portal-central fibrotic septa and nodules formation in chronic hepatitis C). The molecular mechanism(s) of HCV-induced inflammation, fibrosis/cirrhosis and HCC are poorly understood.

It is widely accepted that majority of HCC arise from a distinct subpopulation of cancer cells referred to as tumor/cancer stem cells (TSCs). An intestinal TSC marker, doublecortin-like kinase (DCLK1), has been shown to promote growth of polyps in $Apc^{Min/+}$ mice and neuronal migration. It also polymerizes microtubules, and regulates microtubule dynamics and epithelial-mesenchymal transition (EMT). We have demonstrated that HCV replication positively correlates with several TSC-related proteins such as DCLK1, CD133, Lgr5, Lin28 and c-Myc. We have also established a positive association of DCLK1 overexpression with the activation of inflammatory pathway via S100A9/NFκB, tumor-associated SW1/SNF1 chromatin remodeling complexes and HCC-like tumor growth. We are currently deciphering a putative DCLK1-controlled signaling network and its role in tumorigenesis. Our final goal is to develop anti-DCLK1 drugs as novel therapeutic agents for the treatment of gastro-intestinal cancers including HCC.

James D. Battiste, MD, PhD

RESEARCH SUMMARY

Diffuse single cell infiltration into normal surrounding brain is a pathological hallmark of Glioblastoma (GBM), the most common and most lethal of all primary brain tumors. Infiltrating GBM cells pose the single greatest challenge to patients. Therapies which effectively block cell migration could transform this fatal tumor into a local disease, one that could be effectively treated by surgery and/or high dose focal radiation. There is little information on how GBM cells gain traction and generate sufficient contractile forces to overcome the mechanical challenge of migrating through tightly confined spaces through a highly compliant organ, the brain. For the past three decades, mechanisms of GBM migration and invasion have relied on *in vitro* modeling on 2D, flat petri dish based assays that did little to recapitulate the 3D environment of the brain. My interest is to develop novel mechanisms to study glioma cell migration and to characterize unique features of cell migration that could translate to novel therapeutics for gliomas.

As a fellow in the lab of Dr. Robert Bachoo, I participated in the development of an *ex vivo/in vitro* 3D microfluidic device that is designed to study how GBM cells migrate through the confined interstitial space of the brain parenchyma. Our preliminary studies provided unprecedented insights into cellular adaptations that GBM cells are capable of as they migrate through confined spaces. My preliminary results show that as GBM cells are confined physically, they switch from an adhesion-dependent (mesenchymal) mode of migration to an adhesion-independent mode (amoeboid) that is associated with intense 'blebbing'. The field has also begun to develop orthotopic xenograft models where tumor cells are injected into mouse brain tissue. These models better reproduce the brain environment, but they remain cumbersome when screening for molecular mechanisms of cell grown and migration. These orthotopic xenograft models will serve as way to validate discoveries found *in vitro*.

The only way to improve patient care is to engage in clinical research. Therefore, I am actively engaged in clinical trials to evaluate new treatments with the potential to improve the overall survival and quality of life of patient's with brain tumors.

My hope is that we can develop scientific practices that allow research and medical practice to communicate from the bench to the bedside and back to the bench for the benefit of our patients.

Laura Beebe, PhD

RESEARCH SUMMARY

As the Deputy Director for Tobacco Research at the Stephenson Cancer Center and Co-Director for Research within the Oklahoma Tobacco Research Center (OTRC), I have more than 17 years of experience conducting research and evaluation with tobacco control programs, with a focus on measuring addiction, tobacco cessation and prevention. I have a record of NIH and state-funded research, serving as Principal Investigator for NCI-funded studies investigating tobacco industry tactics aimed at American Indian communities, a culturally tailored smoking cessation program for American Indian smokers, and smoking cessation messaging aimed at nonsmokers. I have been the Principal Investigator for the evaluation of TSET-funded programs for more than 13 years, and for the past 15 years, I have worked with American Indian communities to address disparities related to tobacco abuse and other cancer risk factors. I am currently directing three internally funded e-cigarette studies. They include a feasibility study comparing e-cigarettes and traditional NRT effects on combustible cigarette behaviors among women with cervical dysplasia; a follow-up study of e-cigarette users calling the Oklahoma Tobacco HeIpline; and an analysis of 2013 Oklahoma BRFSS data which included 5 state-added questions related to e-cigarette use.

Resham Bhattacharya, PhD

RESEARCH SUMMARY

Polycomb signaling. Bmi-1, a member of the polycomb repressor complex 1, has multiple functions in ovarian cancer or otherwise that are only now being discovered. Bmi-1 maintains self-renewal of normal and cancer stem cells. Isolated ovarian cancer stem cells exhibit much higher Bmi-1 levels compared with the differentiated or parental bulk tumor cells, and they have increased resistance to cisplatin and paclitaxel when compared with the tumor cells. Dr. Bhattacharya and her team are investigating the role of Bmi-1 in promoting ovarian cancer stemness, metastasis, chemotherapy resistance and angiogenesis, all of which present a significant barrier to effective therapy.

Nanotherapeutic conjugates. Dr. Bhattacharya is also interested in targeted delivery of nanotherapeutic conjugates to ovarian tumors. As such, her team has functionalized gold nanoconjugates to effectively target and kill ovarian cancer cells by simultaneous conjugation with folic acid and cisplatin.

Angiogenesis. Another area of interest for Dr. Bhattacharya is elucidating the importance of the metabolic enzyme cystathionine beta synthase in physiological, developmental as well as ovarian tumor angiogenesis.

Anthony Burgett, PhD

RESEARCH SUMMARY

The Burgett Research Group uses organic synthesis and biological research to define and discover the cellular mechanisms of action through which novel compounds affect biological systems, and then to apply these research advancements to unlock new understandings in cellular biology and to launch new approaches in the therapeutic intervention of human disease. This research focus is intensely cross-disciplinary, requiring an interwoven union of organic chemistry, cellular biology, protein biochemistry, molecular biology and analytical chemistry. A major research project in the Burgett laboratory is focused on the drug development of new anti-cancer compounds that inhibit cancer cell proliferation through targeting the oxysterol-binding proteins (OSBP/ORPs). The OSBP/ORPs are a family of cytosolic proteins conserved in all eukaryotes with a yet undefined cellular function, although recent evidence suggests the OSBP/ORPs serve as a master cellular sensors for lipids and/or sterols. The OSBPs were shown to be important for cancer cell proliferation when a class of potent anti-cancer natural product compounds were shown to function through targeting this class of proteins. One of these OSBP-targeting compound is the cholestane glycoside OSW-1. OSW-1 (Average NCI-60 GI_{50} = 0.8 nM) was shown to bind two members of the OSBP/ORP family of proteins: OSBP and ORP4L. OSBP is ubiquitously expressed in all human tissue, but ORP4L is normally only expressed in a few tissue types. However, ORP4L was found to be overexpressed in several cancer cells, especially some leukemias, and a recent publication indicates that ORP4L is an important driver of cancer cell proliferation. The Burgett Group has launched a multi-disciplinary research program to verify ORP4L is a cancer-specific target and to develop small molecule lead compounds that selectively bind ORP4L. Currently, we have established methods to quantitate ORP4L expression levels, both at the mRNA and protein level, in cancer cell lines. With these methods in place, we are now verifying that ORP4L levels are important for cancer cell viability and proliferation. In addition to this biological research, we are completing a total synthesis of the OSW-1 compound that will allow for a robust program of new analog synthesis to identify ORP4L-specific lead compounds.

Hong Chen, PhD

RESEARCH SUMMARY

Dr. Hong Chen's research program has centered on unveiling the endocytic regulation of vascular development and remodeling, and cancer development and progression. Our entry point was the endocytic adaptor protein, epsin, which Dr. Chen discovered during her PhD at Yale University (*Chen et al., Nature, 1998*). We have systematically characterized the function of epsin in clathrin and ubiquitin-dependent endocytosis, created genetically modified knockout mice, and revealed the role of epsin in the regulation of Notch signaling (*Chen et al., Proc. Natl. Acad. Sci. USA, 2003, 2005 and 2009*). Mammals express two epsins, epsin 1 and 2, in all tissues. The redundancy of epsins 1 and 2 is exemplified by the normal life span of epsin 1 or 2 single knockout mice (KO) but embryonic lethality in epsins 1 and 2 double KO mice (DKO). At OMRF, we have developed an animal model comprising of two epsin 1 conditional alleles *($Epn1^{fl/fl}$)* and two epsin 2 null alleles (*$Epn2^{-/-}$*); using them to dissect the spatiotemporal and tissue-specific requirement of epsins in the developing embryos and adult physiology. Although epsins are universally expressed, they play a selective role in the endocytosis of specific cell surface ubiquitinated cargos. Despite a well-defined role *in vitro*, the functions of epsins *in vivo*, especially in the adult blood and lymphatic vascular systems were poorly understood. At OMRF, we have characterized an important regulatory role of epsins in vascular remodeling (*Pasula et al., JCI 2012; Tessneer et al. ATVB 2014*) and lymphatic development (*Liu et al. Sci Signal 2014*) through the selective modulation of VEGFR signaling. More recently, we have uncovered a positive correlation between cancer severity and elevated epsins expression within tumor samples from human cancer patients. Importantly, elevated epsin expression is specific to the tumor cells thus implicating a tumor intrinsic role for epsins in the development and/or progression of cancer. We have embarked on studies to identify and characterize the mechanistic roles of tumor cell-specific epsins in regulating cancer development and progression through the creation of epsin-depleted genetically manipulated mouse cancer models and human xenograft models. Methodical *in vivo* and *in vitro* analyses of these epsin deficient models allowed us to clearly identify oncogenic roles for epsins in cancer development and progression. Furthermore, we have successfully identified a novel regulatory role for epsins that is completely independent of its classically defined endocytic adaptor function. The details of these novel and unique intrinsic regulatory roles for epsin in cancer cells are the topic of this presentation (*Chang et al. Nature Comm in press, Cai et al. submitted, Dong et al. JCI revision*).

Marshall Cheney, PhD

RESEARCH SUMMARY

Dr. Marshall Cheney is working to identify the influences of culture, individual beliefs, and the environment on smoking in young adults. Young adults (ages 18-29) are heavily targeted by the tobacco industry and now have one of the highest smoking rates of any age group in the United States. Dr. Cheney is also interested in studying the impact of ethnicity and education on tobacco use, which can create or perpetuate health disparities in adulthood.

Dr. Cheney primarily uses qualitative methods (focus groups and interviews) to understand why young adults begin to smoke and why they continue to smoke once they start.
Dr. Cheney is also studying how electronic cigarettes are influencing tobacco use in non-college educated young adults. In addition, Dr. Cheney has conducted interviews with vapor store owners to understand e-cigarette use and how e-cigarettes are marketed to users.

To complement her risk factor research, Dr. Cheney is studying assets or protective factors (such as family communication and individual aspirations) that prevent the initiation of smoking in young adulthood using longitudinal data from the Youth Asset Study (Roy Oman, PI, Sara Vesely, Co-PI).

The findings from these studies can be directly applied to community-level tobacco use prevention efforts and used to generate further research focused on young adults. The goal of Dr. Cheney's research is to help reduce smoking initiation rates in young adults, which may lead to reductions in health disparities.

Melissa Craft PhD APRN-CNS AOCN

College of Nursing, University of Oklahoma Health Sciences Center

- Dr. Craft is certified Oncology Clinical Nurse Specialist
- Her research interests include storytelling, expressive writing as a mechanism for dealing with distress associated with breast cancer
- Cancer survivorship, psychosocial aspects of survivorship

Wei-Qun Ding, PhD

RESEARCH SUMMARY

This laboratory investigates the cellular and molecular mechanisms of action of anti-cancer compounds, and the potential application of primary exosomes for cancer diagnosis and therapy. In particular, we are interested in the mechanisms of n-3 polyunsaturated fatty acids' anticancer action when used alone and in combination with other therapeutic agents. We are focusing our recent efforts on the use of primary breast cancer exosomes for breast cancer diagnosis and their potential as therapeutic targets in breast cancer management.

A combination of cellular, molecular, and biochemical approaches are applied to address critical questions using *in vitro* and *in vivo* model systems and primary patient samples. Our long-term goal is to develop novel diagnostic and therapeutic strategies against cancer.

Mark Doescher, MD, MSPH

Mark Doescher is the Leader of the Cancer Health Disparities (CHD) research program and Interim Director of Cancer Prevention and Control at the Stephenson Cancer Center and Professor of Family Medicine in the Department of Family and Preventive Medicine at the University of Oklahoma Health Sciences Center. Dr. Doescher is developing a program of research to reduce the burden of cancer in high need populations in Oklahoma with a special focus on the state's American Indian and rural populations. Current activities include the development of research that: promotes physical activity and healthy eating; reduces tobacco and nicotine use; and increases the uptake of recommended cancer screenings. The CHD program also is developing a program of research to improve the quality of cancer care delivery in rural and tribal communities.

From 2007 to 2012, Dr. Doescher served as the Director and Principal Investigator of the University of Washington WWAMI Rural Health Research Center funded by the Federal Office of Rural Health Policy. In this role, he conducted research on the quality of care in rural setting and research on the ability of the health care workforce to meet the needs of rural populations. Dr. Doescher recently completed an NHLBI-funded RO1 study examining "built environment" correlates of walking in rural towns located in the Northeast region, Washington State, and Texas. He has published over 100 articles, federal and state reports, and policy briefs on rural health care delivery, workforce development, and preventive care. He serves as an advisor to for the Association of American Medical Colleges annual workforce research conference, the Oklahoma Health Improvement Plan Finance Workgroup, and the Oklahoma Central Cancer Registry Steering Committee.

Kathleen Dwyer PhD RN

College of Nursing, University of Oklahoma Health Sciences Center

- Dr. Dwyer is a psychiatric mental health nurse by training
- Her research interests include factors influencing cancer screening, the psychosocial impact of cancer on the individual and family and intervention development to enhance QOL in cancer survivors
- Community- based participatory research – engagement of cancer survivors for intervention development

Blas Espinoza-Varas, PhD

RESEARCH SUMMARY

My undergraduate, doctoral, and postdoctoral research training was on the cognitive processing of auditory and speech signals by humans and animals. My PhD degree is from Washington University, St, Louis, and my postdoctoral training is from McGill University, Montreal, Canada.

Current Research Lines:

- Auditory training and CNS neuroplasticity
- Executive-function and emotion-processing deficits in adolescents at risk for alcohol use disorder
- Executive function deficits induced by chemotherapy, treatment adherence, improving cancer treatment outcomes.
- Fetal hormone exposure and gender differences in physiological indices of auditory processing
- Effects of aging on cognitive and executive functions

I have two fully-automated, state-of-the-art laboratories, one for research on cognitive processing of auditory and speech signals, and the other for research on auditory evoked potentials and otoacoustic emissions. For the past 10 years, I have investigated effects of conflicting auditory information in adolescents, young, and older adults, and reported the research results in numerous articles and conference presentations. I am Associate Member Peggy & Charles Stephenson Cancer, Oklahoma City.

J. Kimble Frazer, MD, PhD

RESEARCH SUMMARY

The Frazer laboratory studies genetic features of T cell acute lymphoblastic leukemia (T-ALL) and T cell lymphoblastic lymphoma (T-LBL) using zebrafish *in vivo* models and human T cell cancer lines. They investigate inherited and acquired mutations to learn: (1) what molecular mechanisms drive T-ALL and T-LBL oncogenesis, (2) why some cases show different clinical progression than others, and (3) how some cases become resistant to therapies used against them. Their prior work has discovered candidate genes involved in these processes, and current projects are underway to build novel lines to investigate these candidate genes' biologic roles.

Bio: Dr. Frazer was a trainee in the University of Texas Southwestern's MST Program, moved to OMRF in 1997 with his graduate school mentor, Don Capra, and finished his medical studies at the OU College of Medicine, receiving his PhD in 1998 and MD in 2000. He completed residency in Pediatrics and fellowship in Pediatric Hematology-Oncology at the University of Utah from 2000-2005. He was an Instructor and Assistant Professor at the University of Utah's Huntsman Cancer Institute from 2006-2012. He accepted the E.L. & Thelma Gaylord Chair in Pediatric Oncology in fall 2012 and moved to OUHSC to start an independent laboratory. He holds faculty appointments in the Departments of Pediatrics, Cell Biology, and Microbiology and Immunology at OUHSC and is a Stephenson Cancer Center member.

Jack Friedman PhD

Center for Applied Social Research, University of Oklahoma

- Dr. Friedman is a cultural anthropologist who has been involved in medical anthropology research in Romania, California, and Oklahoma
- Expertise in psychiatric and public mental health
- Dr. Friedman is particularly interested in understanding how cancer experiences are situated within broader social, political, economic, and cultural contexts in addition to the ways in which the particularities of life history experiences can both shape and be shaped by the experiences of cancer.

Stephen R. Gillaspy, PhD

A licensed psychologist and Associate Professor of Pediatrics at the University of Oklahoma Health Sciences Center since 2005. He is a Clinical Associate Professor in the Department of Psychiatry and Behavioral Sciences and serves as the Pediatric Psychology Emphasis Director for the Clinical Psychology Internship Program and Post-doctoral Fellowship Program. He completed his graduate training in Clinical Psychology at Oklahoma State University and completed his Clinical Internship at the University of Oklahoma Health Sciences Center in the Department of Psychiatry and Behavioral Sciences. Following internship Dr. Gillaspy completed a post-doctoral fellowship in Primary Care and Health Psychology at the University of Oklahoma Health Sciences Center in the Department of Psychiatry and Behavioral Sciences.

Dr. Gillaspy is one of the Co-Directors for the Oklahoma Tobacco Research Center (OTCR). In this position he directs the Tobacco Dependence Treatment Program (TDTP) which provides tobacco cessation services to patients and families. In this position, Dr. Gillaspy also provides oversight for the Oklahoma Tobacco Helpline.

Dr. Gillaspy is the Director of Research for the Section of General & Community Pediatrics within the Department of Pediatrics at the University of Oklahoma Health Sciences Center. His research focuses on intervening with caregivers to improve pediatric health outcomes. Specifically, his research focuses on parental tobacco use, pediatric obesity, and postpartum depression. Additionally, he has both clinical and research interests with respect to the accessibility of medical and mental health care to children.

Dr. Gillaspy is the Associate Director of the General Academic Fellowship Program within the Department of Pediatrics at the University of Oklahoma Health Sciences Center. He is actively engaged in training medical students and pediatric residents and is the PI on a five year HRSA residency training grant to train pediatric residents in behavioral health issues.
Dr. Gillaspy is a member of APA Divisions 54, 53, 37, 38, and 12. He is a Division 54 Representative to the Interdivisional Health Committee, serves as a member of Division 38 Integrated Primary Care Committee, and the Division 54 Integrated Care Task Force. At the state level, he has served as a board member for the Oklahoma Psychological Association in several capacities: Director of the Division of Research, Academics, and Training; and President of the State Association.

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Gary Gorbsky, PhD

RESEARCH SUMMARY

Chromosome instability, the mis-segregation of chromosomes during meiosis and mitosis, is a major cause of congenital birth defects and an important contributing element in cancer malignancy. We have characterized some of the components of the cell cycle checkpoints that regulate the timing of chromosome segregation to ensure the genetic material is equally distributed to the newly formed cells during division. Our laboratory uses a combination of molecular biology and advanced imaging of living cells by microscopy to study the mechanisms of chromosome movement and how these movements influence checkpoint signaling.

The kinetochore is an organelle that forms during meiosis and mitosis at the centromeric chromatin and serves to move chromosomes and to integrate cell cycle progression. Previously, our laboratory showed that translocation of the kinetochores along microtubules is the prime mediator of chromosome movement in mitosis. We later discovered that individual kinetochores within a mitotic cell were biochemically distinct and developed the model of kinetochores as the sites where cell cycle progression through mitosis is regulated.

Currently, we are addressing the mechanochemistry of the motors that move chromosomes in mitosis and how these mechanical forces act to modulate kinase and phosphatase activities at the kinetochores of mitotic chromosomes. We have identified functions for several of the biochemical components of kinetochores including the Ndc80 protein complex and the Aurora B kinase. Recently, we discovered that the activity of another regulator, polo-like kinase-1, at mitotic kinetochores is regulated by the mechanical tension imparted by the attachment of the spindle microtubules.

In other studies we are investigating whether the defective cell cycle checkpoints of cancer cells may provide a target for the development of therapeutics that are specifically effective against tumors. Overall, we seek to understand how progression through cell division is regulated, how this regulation becomes defective in cancer cells and how these defects might be exploited to develop novel approaches in cancer therapy.

Mary Gowin, MPH

Mary Gowin is a second year doctoral student from the University of Oklahoma Health and Exercise Science Department. She has her Master of Public Health from the College of Public Health at the University of Oklahoma Health Sciences Center. Her research interests include technology in health promotion, health communication, social marketing, and the social determinants of health. She has a particular interest in adolescents and young adults as this time in the lifespan is particularly important to the development of positive health habits.

Roger Harrison, PhD

RESEARCH SUMMARY

The focus of my research is on the development of targeted therapies for treating cancer. In one approach, an enzyme prodrug treatment is targeted to the tumor vasculature. In this method, an enzyme converts a nontoxic prodrug to a cytotoxic drug in the tumor. We have developed several enzyme prodrug systems that all target phosphatidylserine that is expressed on vascular endothelial cells in the tumor vasculature but not on normal endothelial cells. We have developed one of these systems so that it does not give a harmful immune response. We are studying the combination of this therapy with (1) immunostimulation to increase the immune response to the tumor and (2) blocking the tumor's response to the hypoxia created by the vascular targeting.

In another approach, we are targeting single-walled carbon nanotubes (SWNTs) to tumors. SWNTs are unique in that they strongly absorb near-infrared light, while biological systems have very low levels of absorption of NIR light. The targeting of SNWTs to tumors and subsequent application of NIR light has the potential to selectively eliminate tumors. In one published study, we showed that 4T1 primary breast tumors implanted in BALB/c mice were eliminated with a 3 minute irradiation with NIR light that was performed 1 day after i.v. administration of SWNTs. Currently, we are collaborating with Dr. Joel Slaton and Dr. Robert Hurst in the Department of Urology at the OU HSC on the testing of a variation of this approach to treat non-muscle invasive bladder cancer (NMIBC) in a mouse model. In another project in collaboration with Dr. Rajagopal Ramesh of the Department of Pathology at the OU HSC, we are evaluating this approach combined with two immunostimulants to treat cutaneous malignant melanoma in a mouse model.

Tim Hubin, PhD

RESEARCH SUMMARY

1. CXCR4 Chemokine Receptor Antagonists: Activation of cellular migration 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, including cancer cell metastasis. In many forms of cancer, receptor over-expression is observed, and it is hypothesized that metastasis can be mediated by small molecule receptor antagonists. Chemokine receptor CXCR4, which is overexpressed in a large number of cancer types, is exclusively activated by chemokine CXCL12. We have designed, synthesized, and screened a large library of highly efficient (sub-nanomolar IC_{50}'s) CXCR4 antagonists based on configurationally constrained tetraazamacrocyles and their transition metal complexes. Recently, we have begun to collaborate with Dr. Rajagopal Ramesh of OUHSC toward the synergistic inhibition of cancer metastasis by his IL-24 gene and our small molecule CXCR4 antagonists, with improved results in combination of both therapies.

2. Dual CXCR4/CCR5 Chemokine Receptor Antagonists: As 20 chemokine receptors and 46 chemokines are known, with few of these participants exclusive to their partners, a huge number of targets for antagonists are possible. Indeed, progress towards the development of a number of single-chemokine receptor antagonists has been steady. However, the promiscuity native to chemokines provides for the possibility of the defeat of a single-receptor antagonist, as alternate chemokine/receptor interactions can circumvent the blocked signal. The two most studied chemokine receptors, due to their function as required co-receptors for HIV infection, are CXCR4 and CCR5. However, CXCR4 and CCR5 are linked through a number of other diseases, including a growing number of cancers. Specific calls for dual CXCR4/CCR5 antagonists have appeared recently in the literature in the context of the study and treatment of cancer, and the general study of chemokine receptors. For these reasons, we have chosen to design, synthesize, and screen the biological activity of dual CXCR4/CCR5 antagonists. These antagonists are based on topologically constrained tetraazamacrocycle transition metal complexes. We have produced multiple compounds demonstrating sub-micromolar IC_{50}'s for antagonism of both of the CXCR4 and CCR5 chemokine receptors.

3. PET Imaging of Cancer Targeting the CXCR4 Receptor: A growing list of cancer types have been found to overexpress the CXCR4 chemokine receptor. Based on our highly efficient CXCR4 chemokine receptor antagonists, we have the ability to bind transition metal complexes strongly to this cell surface receptor. Positron Emission Tomography (PET) Imaging is a growing medical imaging modality that requires specific radionuclides. ^{64}Cu is one such radionuclide that can be seamlessly incorporated into our CXCR4 chemokine receptor antagonists. We are beginning to use PET imaging, after introducing our antagonists, to image tumors *in vivo* in a mouse model.

Michael A. Ihnat, PhD

RESEARCH SUMMARY

The focus of our laboratory is on preclinical small molecule anticancer drug development. In this regard, we have developed microplate cellular bioassays for screening synthesized chemicals and chemical libraries against particular biochemical endpoints. We also work to determine the mechanism of action of compounds using a combination of biochemical and genetic techniques combined with chemical probes. Finally, we test compounds for preclinical efficacy using several mouse tumor models and examine the toxicology and pharmacokinetics of these compounds using rat models. Some specific projects ongoing in our laboratory are: 1) with Dr. Robert Hurst in the Department of Urology to discover molecules capable of targeting suppressed breast and bladder cancer cells before they reactivate; 2) with Dr. Shelley Lawrence in the Department of Pediatrics to identify immune cells capable of reactivating dormant tumor cells; 3) with Dr. Aleem Gangjee at Duquesne University to find novel small molecules capable of triggering rapid and selective tumor cell death in drug resistant metastatic breast cancer; 4) with Dr. Gangjee and Dr. Rheal Towner at the Oklahoma Medical Research Foundation (OMRF) to find novel small molecule dual acting antimicrotubule/antiangiogenic agents for the treatment of glioblastoma multiforme; and 5) with Dr. Hariprasad Gali in the Department of Pharmaceutical Sciences to develop novel small molecule APN inhibitor anti-angiogenic agents.

Kenneth W. Jackson PhD

Associate Professor of Research, Department of Medicine, received his doctorate from the Department of Biochemistry, OUHSC, doing his graduate work and post-doctoral studies with Dr. Jordan Tang, OMRF. An accomplished protein chemist, Dr. Jackson joined the OUHSC faculty in 1986 where he initiated, built and led the Molecular Biology Proteomics Core Facility for some 24 years, during which time the laboratory offered, amino acid compositions, protein/peptide sequencing, customized peptide and DNA synthesis, LC/MS analyses, and proteomic analyses as they became progressively defined. His collaborative studies led to 55 publications in first-line journals. Subsequently some of his interactions with investigators using the core laboratory led to long-term collaborations in cancer drug design and immunotherapeutic agents, both areas in which he remains currently very active.

Shirley James

Shirley James is a PhD graduate student at the University of Oklahoma Health Sciences Center with an interest in tobacco cessation/nicotine reduction. She has recently been studying electronic cigarette use in Oklahoma. She also recently completed a pilot project studying electronic cigarette use for patients with cervical dysplasia and associated diagnoses who must reduce/quit smoking immediately to prevent recurrence and regression. Shirley works under the direction of Dr. Laura Beebe from the Oklahoma Tobacco Research Center.

Ralf Janknecht, PhD

RESEARCH SUMMARY

Precise control of gene expression is a prerequisite for cellular homeostasis and safeguards against tumor development. Our long-term objective is to understand how dysregulation of DNA-binding transcription factors and epigenetic regulators contributes to carcinogenesis, which may help to develop novel strategies of cancer treatment and detection. In particular, we focus on the oncogenic transcription factor ETV1 and a novel class of epigenetic regulators, the JMJD proteins. Using a great variety of in vitro and in vivo technologies, we endeavor to elucidate how these proteins modulate normal cell function and to determine their roles in the development of cancer and other diseases.

The ETV1 transcription factor

ETV1 (also called ER81) belongs to the ETS class of DNA-binding transcription factors. Its activity is greatly stimulated by the Raf, Ras and HER2/Neu oncoproteins through the induction of posttranslational modifications in ETV1. Moreover, chromosomal translocations involving ETV1 are found in prostate carcinomas and Ewing sarcomas, and mouse models overexpressing ETV1 develop prostatic intraepithelial neoplasia. Altogether, these data indicate that aberrant activation of ETV1 and its target genes is an underlying cause of cancer. Indeed, we have identified several ETV1 target genes, whose dysregulation is involved in cancer formation. These include MMP7, a metalloproteinase involved in tumor invasion and metastasis, and RCL, a hitherto scarcely characterized putative proto-oncogene.

In the future, we would like to unravel the consequences of various posttranslational modifications on ETV1 function, study how other transcription factors interfere with ETV1 activity and analyze the physiological functions of its target gene, RCL.

JMJD proteins

JMJD proteins are implicated in chromatin regulation and often possess the ability to demethylate lysine residues on histones. Also, they are involved in developmental processes, and several JMJD proteins are suspected to be oncoproteins or tumor suppressors. We have cloned the majority of the 30 known human JMJD proteins and started searches for interaction partners. For instance, we found that JMJD2 proteins are pivotal cofactors of androgen and estrogen receptors. Since JMJD2 expression is upregulated in prostate and breast tumors, this suggests one mechanism by which JMJD2 proteins contribute to carcinogenesis through aberrantly stimulating androgen and estrogen receptors, the key villains in prostate or breast tumors.

Our future goals are to analyze how JMJD proteins modulate chromatin structure, how they impact on cell physiology, how their knock-out or overexpression in mice will affect development and tumor formation, and screen for small molecule JMJD inhibitors to combat cancer.

David A, Jones, PhD

RESEARCH SUMMARY

Colorectal cancer is a common malignancy in terms of new cases and deaths among men and women in the United States. Our long-term goal is to facilitate the development of new preventive measures for colon adenoma and carcinoma formation by understanding the earliest cellular perturbations leading to disease development.

APC and Retinoic Acid Biosynthesis in Cancer and Development - One type of inherited colon cancer predisposition, familial adenomatous polyposis (FAP), results from mutations in a single gene known as adenomatous polyposis coli (APC). Recent studies from our laboratory indicate that APC may promote colonocyte differentiation by stimulating the production of retinoic acid. Retinoic acid is a lipid mediator with important roles in controlling cell patterning, fate, and differentiation. Central to the ability of a cell to respond to retinoic acid is the requirement of first converting dietary retinol (vitamin A) into retinoic acid, a process that occurs via two enzymatic steps. The first step of this process converts retinol into retinal and is mediated by alcohol dehydrogenases (ADH) and short chain dehydrogenases (SDR). The second step involves conversion of retinal into retinoic acid via aldehyde dehydrogenases (ALDH). Given the required conversion of vitamin A, retinoic acid production is limited to cells harboring the necessary biosynthetic enzymes. We have demonstrated that loss of retinoic acid production is an early event following mutation of APC and that this contributes to the mis-fating of intestinal epithelial cells.

DNA Methylation in Cancer and Development - Much of our understanding of gene dysfunction in disease comes from the concept of gene mutation or gene deletion. Epigenetic mechanisms, however, can also lead to a functional “knockout” of key disease genes. Among these epigenetic mechanisms is silencing of genes by DNA methylation. DNA methylation in mammalian cells occurs at cytosines residing within CpG dinucleotides. Alterations in developmentally established methylation patterns may alter the gene expression patterns within tissues and cause or promote disease. We are currently studying how methylation patterns are established and the potential for targeting enzymes that establish and interpret methylation patterns with therapeutics.

Zebrafish as a Model for Studying Intestinal Development and Differentiation - Zebrafish have emerged as a powerful genetic model system for identifying and mapping signaling pathways critical to embryological development. Since the zebrafish gastrointestinal tract displays many features similar to that of higher vertebrates, we utilize zebrafish as a model system to study the role of APC, retinoic acid, and DNA methylation in directing development and differentiation of the gastrointestinal tract. For example, using this system we have recently confirmed a genetic relationship between APC and retinoic acid in controlling zebrafish gut development and differentiation. Our data show that knock down of either APC or retinoic acid biosynthesis in zebrafish results in the development of intestines that lack differentiated epithelial cells. Treatment of either APC mutant embryos with retinoic acid rescued the defective phenotypes, thus placing retinoic acid downstream of the APC tumor suppressor.

Rashmi Kaul, PhD

RESEARCH SUMMARY

Our laboratory investigates the role of estrogen and estrogen receptors in regulation of immunity and inflammation during development of chronic infection-related cancer development. To evade innate immunity, virulent pathogens utilize host cell receptors that are involved in innate immunity for their colonization, and thus, modulate the development of inflammation. We are studying host-pathogen interactions at the cellular receptor level to understand the role of hormones and their receptors in regulating innate immunity and inflammation.

We are studying the estrogen related etiology of liver cirrhosis and cancer development due to chronic Hepatitis C virus (HCV) infection. HCV infection is the primary cause of the rising incidence of hepatocellular carcinoma (HCC) in the United States. The chronic sequel of HCV infection includes progressive hepatic fibrosis, cirrhosis and HCC. Recent reports suggest that estrogen levels and estrogen receptor status play an important role in HCV disease pathogenesis. We have experimental data from our lab supporting the estrogen related etiology of HCV pathogenesis and are conducting further experiments to elucidate the mechanisms by which estrogen may modulate the molecular pathways involving HCV viral proteins in mediating hepatocarcinogenesis. We have established *in vitro* (HCV replicon cells, liver cancer cell lines) and *in vivo* disease models to understand estrogen and estrogen receptor-regulated modulation of liver carcinogenesis by HCV.

Sadagopan Krishnan, PhD

RESEARCH SUMMARY

The research objectives of the Krishnan group at Oklahoma State University are focused on Clinical Biosensors/Arrays, Point-of-care methods, Biocatalysis, Biomarker validation, Novel Anticancer drug screening arrays, Bioelectrochemistry, and Electrochemical investigation of meat color.

Joy L. Leuthard, MS, LSWA

Joy L Leuthard, MS, LSWA, is currently the Manager of Health Improvement Initiatives at the Oklahoma Hospital Association.

Ms. Leuthard has 35 years of experience working in community-based, non-profit, state agency and medical associations providing direct health care services and managing many local, regional and state programs and initiatives with specialty in program development and implementation. She has fifteen years of experience working in the area of tobacco treatment and cessation. The past six years she has managed a TSET grant to assist health systems and hospitals in developing a tobacco free culture through policy development and permanent systems changes for tobacco treatment of inpatients, outpatients and employees.

Ms. Leuthard coordinated a five-year Robert Wood Johnson grant, Smoke Free Beginnings, in partnership with the OU Department of Family Medicine and College of Public Health, assisting physicians in private practice and residency programs to implement smoking cessation clinical guidelines with their pregnant patients. That model has been adopted by the Oklahoma Health Care Authority in working with their contract physicians who provide health services for Medicaid eligible pregnant women.

Ms. Leuthard has five years of experience advancing statewide tobacco control policy and legislative efforts including clean indoor air, reducing youth access to tobacco, and passage of the Oklahoma tobacco tax. She served on the Governor's Task Force on Tobacco and Youth in 2002 and received the 2003 Dr. Edward R. Munnell Award from the Oklahoma Chapter of the American Lung Association.

Min Li, PhD

RESEARCH SUMMARY

The major goal of my research is to study the pancreatic cancer (PC) pathogenesis and develop new therapies. Current projects include the role of zinc transporter ZIP4 in PC, the therapeutic potential for ZIP4 shRNA-based treatment, the function of microRNAs in ZIP4-mediated PC growth, signaling transduction and metabolism in PC, and cancer genomic sequencing. Our group is the first to identify a key zinc transporter ZIP4, which is aberrantly expressed in PC, and promotes cancer growth and metastasis. My group has published more than 120 papers in the above mentioned research area. I have a track record of mentoring junior faculties, postdoctoral fellows, students, surgical fellows, residents, and visiting scholars nationally and internationally. We have obtained both federal (NIH R01 and R21) and private foundation grants to support our research. I am a permanent member of NIH study section, and many other funding agencies, and I serve as Associate Editor, Editor-in-Chief, and editorial board member for many journals.

David H. Lum, PhD

RESEARCH SUMMARY

The OMRF Patient-Derived Xenograft and Pre-Clinical Therapeutics (PDX-PCT) Core was developed in July 2014 with the arrival of two researchers at the forefront of patient-derived xenograft (PDX) cancer research, Dr. Alana Welm and Dr. Bryan Welm. The goal of the core is to enable clinicians and researchers to utilize PDX models in their cancer research. We will provide the expertise and reagents, such as a growing PDX bank, necessary to perform a wide variety of experiments related to tumor biology.

Dr. Alana Welm developed the first collection of patient-derived orthotopic breast xenografts (PDX). PDX models recapitulate the molecular and phenotypic features of their corresponding patient tumors. In contrast, cancer cell lines do not have a reference patient tumor for comparison. This advantage provided by PDX makes them a more relevant model for studying tumor biology in vivo. Indeed, granting agencies, scientific journals and reviewers often request the use of PDXs because of the evidence that they better represent various aspects of patient tumors than established cell lines. In addition, PDX growth and metastasis mirror these clinical outcomes in the corresponding patients and therefore may have prognostic value. PDX models are also uniquely suited to address the increasing demand for research regarding the benefits of personalized medicine. Thus, PDX are quickly becoming the 'gold standard' model for cancer research.

My research focuses on the development of in vivo models of cancer that more closely represent the disease observed in patients. To this end we have developed tumor models derived from fragments of patient tumor samples implanted directly into the relevant organ in mice. These 'patient-derived' xenografts (PDX) are remarkably similar to the tumor of origin and represent not only important tools for cancer research and discovery but an exciting step in the path to personalized medicine. We have had success generating PDXs from breast, colon and skin tumors and are continuing to expand our banks of patient samples and tumor grafts models. My current research include: 1) validating the PDX models as predictors of therapeutic response in patients; 2) testing the ability of PDXs to recapitulate tumor evolution observed during the development of chemo-resistance and 3) developing the next advancement in human cancer: immuno-competent PDX models.

Sydney Martinez, MPH

Sydney Martinez, MPH, is a doctoral candidate in the Epidemiology program at the University of Oklahoma Health Sciences Center. Her research efforts focus on understanding health disparities, particularly among populations with low socioeconomic status, to hopefully identify strategies to begin reducing the health disparities in tobacco-related morbidity and mortality. She also works as a Research Project Coordinator/Evaluator at the University of Oklahoma Health Sciences Center, College of Public Health. In the Biostatistics and Epidemiology Department, she is currently evaluating multiple public health prevention programs focusing on tobacco, physical activity, and nutrition. Recent research has included cancer disparities among American Indians in Oklahoma. Ms. Martinez received her Masters of Public Health in Epidemiology from the University of Oklahoma Health Sciences Center and a Bachelor's of Science Degree from the University of Oklahoma in Health and Exercise Science.

Chance Matthiesen, MD

RESEARCH SUMMARY

The principal investigators major areas of research interest include benign conditions treated effectively with radiation therapy, evaluation of effective treatment of head and neck cancer, breast cancer treatment with radiation therapy, dosimetric comparisons of alternative treatment modalities, Stereotactic body radiotherapy, hyperfractionation and accelerated fractionation.

D. Robert McCaffree, MD, MSHA

D. Robert McCaffree, MD, MSHA, is Regents' Professor of Medicine in the Pulmonary Disease and Critical Care Section in the OU College of Medicine. He is also the Director of the Oklahoma Tobacco Research Center of the Stephenson Cancer Center. He was a founder member and original Chair of Board of Directors of the Oklahoma Tobacco Settlement Endowment Trust Fund. He has been the Chair of the Oklahoma Alliance for Tobacco or Health. He is Past-President of the American College of Chest Physicians, in which position he testified before Congress on tobacco issues. He is Past-President both of the Oklahoma County Medical Society and the Oklahoma State Medical Association.

Blaine Mooers, PhD

RESARCH SUMMARY

My lab is interested in the structure of RNA as a target for the development of drugs to treat cancer and infections. RNA structure-based drug design is a new field and uses the lessons learned from the structure-based design of drugs that target proteins. We use X-ray crystallography to obtain atomic resolution models of RNA that are required for successful drug design. RNA crystallography is a small field compared to protein crystallography, so we are developing methods to accelerate its progress. We use small angle X-ray scattering to obtain the low-resolution information about the shape and flexibility of the RNA molecule in solution, often before we can obtain the high-resolution crystal structure.

We have expertise in crystallizing double-stranded RNAs that form the substrates of the mRNA editing system found in trypanosomes that threaten the lives of 600 million people worldwide and that infect 300,000 Latin American immigrants and dozens of wild and domesticated mammal species in the southern half of the United States. We have found that these RNAs adopt two distinct conformations with X-ray diffraction data going to atomic resolution (better than 1.2 Å). We are relating RNA structure to RNA editing efficiency, and we are engaged in ligand docking trials to find potential inhibitors of the editing reactions.

We also have expertise in protein crystallography. We crystallized and determined the 1.67-Å crystal structure of human gamma glutamyltranspeptidase (hGGT), the first crystal structure of a eukaryotic GGT. hGGT has many differences from known bacterial homologs, including seven glycosylation sites and tethering on the exterior of the cell by a transmembrane domain. This high-resolution crystal structure was published last year and is being used in Marie Hanigan's lab at OUHSC to design new inhibitors of GGT to make chemotherapy more effective.

Our current protein crystallography project is the structure determination of human JMJD4. This oxygenase hydroxylates a lysine side chain on eukaryotic Release Factor I, which mimics tRNA and controls the termination of translation in the ribosome. This hydroxyl group is thought to hydrogen bond with a uracil in the stop codon of mRNA. The introduced hydroxyl group is essential for the correct termination of protein synthesis. The improper termination of translation is linked to several cancers and to the inherited diseases myotonic dystrophy and cystic fibrosis.

I supervise the OUHSC Macromolecular Crystallography Lab, one of the three core labs of the Oklahoma CoBRE in Structural Biology (PI: Ann West, OU-Norman).

Dana Mowls, MPH

Dana Mowls is currently pursuing a doctorate in epidemiology at the University of Oklahoma Health Sciences Center. As a research assistant with the Department of Biostatistics and Epidemiology, Dana works on an array of projects, such as mapping electronic cigarette shops and creating health indicator reports, all of which allow her to pursue her research interests in the field of epidemiology with regards to understanding and eliminating disparities in tobacco-related morbidity and mortality.

Dana grew up in Ohio where she obtained a BS at The Ohio State University and a MPH at Kent State University. Currently, Dana is exploring gender and race-specific trends in lung cancer incidence rates to understand the impact of anti-tobacco efforts and to identify at-risk populations. Dana also has a position with a bench science lab, where she studies molecular alterations in head and neck tumors with special attention on the implications of nicotine and tobacco exposure. Dana's overarching career goal is to contribute to research and practice that works to eliminate disparities in tobacco-related morbidity and mortality. In the future, Dana hopes to hold a position in academia so that she can engage in research, teaching, and mentoring opportunities.

Ikuko Mukai, PhD

RESEARCH SUMMARY

Dr. Mukai's research at the LIBR seeks to understand the neurophysiological underpinnings of the exaggerated smoking/nicotine dependence seen in individuals with Major Depressive Disorder (MDD). She uses functional Magnetic Resonance Imaging technique to investigate the short and long term interaction effects of smoking/nicotine on cognition and emotion processes in MDD patients with the long term goal of providing knowledge of more effective treatment options for alleviating depressive symptoms in MDD patients.

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Beverly Patchell PhD APRN-CNS

College of Nursing, University of Utah

- Dr. Patchell is an enrolled member of the Cherokee Nation of Oklahoma and has been a Clinical Nurse Specialist in Psychiatric Mental Health Nursing for more than 20 years
- Her research interests focus on how the confluence of cultural history, education, and belief systems interact and effect identity formation in American Indian children and youth and influence illness and disease

Lurdes Queimado, MD, PhD

RESEARCH SUMMARY

My research focuses on the molecular mechanisms that lead to oncogenesis and determine cancer risk and outcome. Our long term goals are to develop personalized preventive and therapeutic strategies. Our major areas of research are:

1. DNA Damage and Repair in Cancer Risk and Response to Therapy: DNA damage causes more than 80% of all human cancers. Strikingly, chemo- and radio-therapy rely precisely on the induction of DNA damage to kill cancer cells. The *in vivo* levels of DNA damage reflect inherent variations in DNA repair capacity and the unique individual genotoxic exposures. The inclusion of DNA damage parameters in cancer prediction models is expected to improve the accuracy of cancer risk and outcome estimation. Recently, we filled a major methodological gap in the field of DNA damage detection by developing a novel and highly sensitive assay (PADDA) to map and quantify *in vivo* DNA damage. We are exploring the utility of this assay for cancer risk stratification, and the prediction of head and neck cancer risk and response to chemotherapy.

2. Cell Signaling and Stem Cells: Cancer stem cells drive tumor growth, metastasis, resistance to therapy, and tumor recurrence. Therefore, treatments targeting cancer stem cells have major potential to impact patient's prognosis. We are characterizing the role of secreted WNT proteins in stem cell self-renewal and multi-potency. We are studying the specific mechanism of action of Wnt proteins and determining whether Wnt inhibitors are potential cancer therapeutic agents. We are also determining the effects of smoking, as well as electronic nicotine delivery systems, in normal and cancer stem cells. Our studies offer new insights into the regulation of the Wnt pathway, and have the potential for development of novel prognostic markers and drugs to treat head and neck cancer.

Select Publications:

1. Ganapathy V, Ramachandran I, Rubenstein D, Queimado L. Detection of *in vivo* DNA damage induced by very low doses of mainstream and sidestream smoke extracts using a novel assay. Amer J Prev Med. In Press.
2. Ramachandran I, Gillies E, Fonseca I, Kaufman KM, Sureban SM, Houchen CW, Reis A, Queimado L. Wnt inhibitory factor 1 suppresses cancer stemness and induces cellular senescence. Cell Death Dis. 22;5:e1246, 2014.
3. Ramachandran I, Thavathiru E, Ramalingam S, Natarajan G, Mills W, Benbrook D, Zuna R, Lightfoot S, Reis AMC, Anant S and Queimado L. Wnt inhibitory factor 1 induces apoptosis and inhibits cervical cancer growth, invasion and angiogenesis *in vivo*. Oncogene, 31:2725–2737, 2012. Awarded Best Paper of Year at OUHSC.
4. Reis AMC, Mills W, Ramachandran I, Friedberg EC, Thompson DM, Queimado L. Targeted detection of in vivo endogenous DNA base damage reveals preferential base excision repair in the transcribed strand. Nucleic Acids Res. 40(1):206-219, 2012.

Yuchen Qui, PhD

RESEARCH SUMMARY

This study was supported in part by TSET Cancer Center Program from Oklahoma Tobacco Settlement Endowment Trust. The title of the subcontract of the program to College of Engineering, University of Oklahoma Norman Campus is “Developing an Advanced Medical Imaging Core Facility” and the Principal Investigators in Norman are Drs. Hong Liu and Bin Zheng. The purpose of this study is to develop a new quantitative image feature analysis scheme and investigate whether using such a new scheme enable to more accurately and reliably predict efficacy of clinical trials for testing new chemotherapeutic drugs to treat ovarian cancer patients.

The major areas of the research interest of the PI and his team focus on developing new cancer imaging detection and diagnosis modalities, computer-aided detection and diagnosis (CAD) schemes of cancer images (including mammograms and MRI for breast cancer, CT images for lung and ovarian cancers, cytogenetic images for leukemia). Using CAD schemes we work to identify new quantitative image biomarkers and develop/optimize the statistical machine learning classifiers or assessment models to improve prediction of cancer risk, cancer prognosis and treatment efficacy.

Rajagopal Ramesh, PhD

RESEARCH SUMMARY

Major research focus of the laboratory is to develop effective treatments for lung cancer. At present the five-year survival rate for patients diagnosed with lung cancer is dismal (14%) and has not significantly improved over past four decades. Therefore, development and testing of novel therapeutic strategies are needed.

Studies in my laboratory are focused in developing and testing various nanoformulations as gene and drug delivery vehicles for systemic treatment of cancer with emphasis on translational cancer research. Nanoformulations using lipids, biodegradable polymers and gold are being developed and tested for gene and drug delivery. Another area of research in the laboratory is in investigating the antitumor activities of novel tumor suppressor genes and small molecule inhibitors for lung cancer therapy. Some of our laboratory studies have successfully been translated into clinical testing for treatment of solid tumors including lung cancer.

Ashish Ranjan, B.V.Sc., PhD

RESARCH SUMMARY

Image Guided Therapy: Cancer chemotherapy employs systemic delivery of antitumor drugs with limited specificity, causing toxic side effects in normal tissues and insufficient drug delivery to tumor cells. To address these problems, stealth drug delivery systems have been developed to enhance intratumoral drug delivery while reducing drug exposure and toxicity to normal tissue. However, available clinically-approved nanocarriers release their payload only within the perivascular space of tumors, preventing distribution to poorly-perfused remote cells in the tumor core that contribute to drug resistance and tumor recurrence. The long-term goal of our research is to optimize and provide uniform intratumoral delivery of antitumor drugs with real-time control, thereby providing clinicians more precise dosing control. The concept builds upon our expertise in biodegradable Low Temperature-Sensitive Liposomes (LTSL) synthesis, a technology that permits induction of drug release using mild local elevations in tissue temperature, and their application in combination with Magnetic Resonance-High Intensity Focused Ultrasound (MRI-HIFU), Laser applicators, ultrasound and Proton Beam Radiotherapy.

Radiation guided drug delivery: Concurrent chemo and radiotherapy is an established treatment modality for malignancies in which loco-regional control is necessary. Despite heavy reliance in clinics for this approach, concurrent chemoradiation presents multiple challenges regardless of cancer type. Clinically, due to sub-optimal delivery methods, a significant portion of systemically injected chemotherapeutics end up in healthy organs, causing severe side effects and limiting therapeutic dosages. Similarly, traditional radiotherapy (X-ray based) is not target specific and can damage normal cells adjacent to the tumor. Thus, the overall outcomes are life threatening acute toxicities and in most cases only modest patient survival. To meet the critical need of precise targeting and delivery of both chemo and radiotherapies, our research program is focusing on combining targeted Proton Beam Radiotherapy with drug encapsulated nanoparticles to achieve radiation triggered delivery of anticancer agent at the targeted site.

Chinthalapally V. Rao, PhD

RESEARCH SUMMARY

Molecular and Preclinical Approaches to Clinical Prevention of Colorectal and other Aero-digestive Tract Cancers: Research in my lab is focused on cancer prevention with major goal to design and develop efficacious strategies for clinical prevention of colorectal cancer and other aero-digestive tract cancers. Current efforts focus on identifying optimal molecular targets for chemopreventive drug development and understanding the molecular mechanisms involved in the pathology of colorectal, pancreas and lung cancers.

Dr. Dr. Rao earned B.S. degree in Biology and Chemistry; M.S. (1983) and Ph.D. (1987) degrees in Microbiology from the Osmania University, Hyderabad, India. Dr. Rao joined University of Oklahoma Health Sciences Center in Oct 2004. Previously he held the position of Chief, Division of Nutritional Carcinogenesis and Leader of Chemoprevention Program at the American Health Foundation (AHF)-Cancer Center, an NCI-designated Cancer Center, Valhalla, New York. Dr. Rao joined AHF-Cancer Center in 1988 as a Senior Research Fellow and appointed in 1992 as a Member of American Health Foundation Cancer Center (AHF-CC) and Section Head of the Division of Nutritional Carcinogenesis; and by 2001, he came up through the ranks to become Division Chief, and Cancer Center Program Leader of Chemoprevention and Nutritional Carcinogenesis.

Dr. Rao is currently the principal investigator or the co-principal investigator on the NIH/NCI grants. Since joining the OUHSC Dr. Rao has been brought >$24.5 million the NCI funding. Also, he significantly contributed to the Cancer CoBRE program resulting over $10 million. Also, he has been PI and Co-PI on previously awarded NIH/NCI peer-reviewed funding totaling over $43.5 million before joining the OUHSC at the American Health Foundation Cancer Center.

Dr. Rao is a member of the Board of Scientific Counselors/Reviewer of the National Cancer Institute. He was a member of Chemo/Dietary Prevention Study Section (CDP), Cancer Biomarkers Study Section (CBSS) and Metabolic Pathology Study Section (MP) at the National Institutes of Health. Currently, he is member of Molecular Targets for Cancer Intervention (MTCI) study section. Dr. Rao served /active member of the NCI's Cancer Drug Discovery, Biomarkers & Prevention, and Molecular Oncology (P01) program reviewer. He is part of Nutrient-Gene interaction and Cancer Chemoprevention Think Tank and the Review Panel for Prevent Cancer Program, Division of Cancer Prevention at the National Cancer Institute. He has mentored a large number of graduate students and post doctoral fellows and has a large laboratory, including a number of research and research track Assistant Professors.

Dr. Rao has been awarded young scientist award from the Council of Scientific and Industrial Research. In 2007 Dr. Rao has been Awarded Outstanding Achievement in Cancer Research from AACR-Society of American Asian Scientists in Cancer Research. In 2008, the Board of Regents of the University of Oklahoma awarded the Regents Award for "Superior Research and Creative Activity. In 2011, he has been awarded "George Lynn Cross Research Professorship" form University of Oklahoma.

Dorothy A. Rhoades, MD, MPH

Dr. Dorothy A. Rhoades, MD, MPH joined the Stephenson Cancer Center in 2012 as Director of American Indian Cancer Research Initiatives at the Stephenson Cancer Center, where she is also a 2014 Tobacco Settlement Endowment Trust Cancer Research Scholar. She is also a hospitalist, having worked for 15 years in Seattle, WA, before joining the Department of Medicine at the University of Oklahoma Health Sciences Center. She has more than 15 years of experience investigating the epidemiology of chronic diseases and their risk factors among American Indians and Alaska Natives. She is the current Chair of the Cancer Working Group for the Strong Heart Study, a longitudinal cohort study of American Indians in Arizona, North Dakota, South Dakota, and Oklahoma. Her current research interests focus on cancer and its risk factors among American Indians, including the burgeoning phenomenon of electronic cigarettes and its role in nicotine addiction, lung cancer screening, and cancer risk reduction among youth.

Alicia L. Salvatore, DrPH, MPH

RESEARCH SUMMARY

Dr. Salvatore is a social scientist with expertise in community-based participatory research (CBPR), mixed-method research, the design and implementation of community-based interventions and community-engaged research translation. Her work spans the areas of environmental and occupational health promotion and chronic disease prevention. She uses mixed-methods research and behavior and environmental change strategies to examine and address health and social disparities faced by underserved and marginalized populations such as low-wage workers, immigrants, American Indian/Alaska Native communities, and poor families in the U.S. and internationally.

New to Oklahoma, some of Dr. Salvatore's current projects include a study of food and activity environments with Dr. Valarie Jernigan and the Chickasaw and Choctaw Nations of Oklahoma. She is also conducting research on working conditions and health among low-wage workers in Oklahoma. In the near future, Dr. Salvatore is interested in developing interventions to reduce exposures to carcinogens and other toxin to workers and their children (i.e., nail salon workers, agricultural workers) and translating evidence-based chronic disease self-management interventions for AI/AN and Latino cancer survivors in Oklahoma.

Dr. Salvatore's public health training includes a two-year NHLBI-funded Postdoctoral Fellowship at the Stanford Prevention Research Center, a doctorate from the University of California Berkeley School of Public Health, and a master's degree in Health Education and Health Behavior from the University of North Carolina Gillings School of Global Public Health. Three years spent "on the ground" in Burkina Faso, West Africa as a Peace Corps Volunteer were also influential in shaping her research and practice.

Susan Schroeder, MD

RESEARCH SUMMARY

Schroeder lab focuses on predicting RNA structure, function, and drug targets from sequence. Thermodynamic parameters for RNA motifs provide the foundation for accurate predictions of RNA structure. Our lab has developed new rules for predicting the thermodynamic stabilities of consecutive terminal mismatches, a motif that commonly occurs in microRNA-mRNA interactions in cancer gene regulation. These motifs are more stable than previously predicted, and the new accurate predictions improve the correlation between thermodynamic stabilities and effective gene silencing by an siRNA for chemokine receptor 4 (CXCR4) gene. Our research has provided benchmarks for RNA duplex stabilities in different salt concentrations and molecular crowding conditions, which makes RNA predictions more applicable to common experimental conditions. We have probed the enthalpic and entropic contributions to consecutive terminal mismatch motifs using substitutions with locked nucleic acid adenosines and different polytheylene glycol conditions. Consecutive terminal GU pairs show the most sequence-dependent stabilities. NMR, crystallography, and molecular modelling studies show cross-strand G stacking that explains the sequence dependence of this motif. The crystallography studies were done in collaboration with Dr. Blaine Mooers, a member of the Stephenson Cancer Center.

We are currently exploring ways in which RNA thermodynamic stabilities and RNA structure prediction tools can test the competing endogenous RNA (ceRNA) hypothesis. The competing endogenous RNA (ceRNA) hypothesis presents a systems view of small RNA-mRNA networks where multiple RNA effectors, such as mRNA, long noncoding RNA and pseudogenes, present multiple binding sites for small RNA regulators. The accessibility of small RNA binding sites are a crucial feature of this model. Thus, improvements in RNA thermodynamics and structure prediction can facilitate experimental tests of this model and the development of RNA therapeutics to regulate gene expression in cancer biology. We are seeking productive collaborations at the Stephenson Cancer Center to further pursue this research.

Relevant Publications

"The Effects of Salt, Polyethylene Glycol, and Locked Nucleic Acids on the Thermodynamic Stabilities of Consecutive Terminal Adenosine Mismatches in RNA Duplexes." X. Gu, M.-T. Nguyen, A. Overacre, S. Seaton, **S.J. Schroeder*.** *J. Phys. Chem. B.* 117, 3531-3540 (2013).

"Consecutive Terminal GU Pairs Stabilize RNA Helices." M.-T. Nguyen, **S.J. Schroeder*** *Biochemistry*. 49, 10574-10581 (2010).

"3' Terminal Nucleotides Determine Thermodynamic Stabilities at the Ends of RNA Helices," K. Clanton-Arrowood, J. McGurk(co-frst author), **S.J. Schroeder*,** *Biochemistry*, 47, 13418-13427 (2008).

"Structural Basis for Consecutive Terminal G·U Pairs Stabilizing RNA Helices" X. Gu, L. Thomas, J. Malone, S. Harris, B. Mooers*, S.J. Schroeder*, in preparation.

W. Kyle Simmons, PhD

RESEARCH SUMMARY

My principal research interest lies in understanding the neural systems underlying the conceptual representation of primary rewards in humans. Currently, my lab has active studies examining the neural systems supporting food taste and reward inferences, both in healthy adults and in psychiatric populations, including patients with Major Depressive Disorder and Eating Disorders. Along these same lines, my lab is performing a study of interoception and nicotine reward processing in cigarette smokers in order to clarify the role of interoceptive regions in the insula in the neural basis of nicotine craving.

In an associated area of research, my lab is examining the functional organization of the insular cortex, with particular attention to the insula's role in interoceptive awareness. This line of research seeks to detail how the insula integrates interoceptive signals about the body's homeostatic state with emotional and hedonic information represented in brain regions to which the insula is strongly connected, such as the cingulate, amygdala, striatum, and orbitofrontal cortex. As with my studies of food reward representation, this area of research also seeks to bring cognitive neuroscience into the clinical domain, with ongoing studies of insula functional organization in both depressed and eating disordered populations. Additionally, my lab is undertaking studies of the neural interactions between nicotine craving and interoception with the aim of elucidating central nervous system mechanisms influencing tobacco-use and the success of smoking cessation interventions. The common goal of these lines of research is to reveal how the body's homeostatic state influences reward-related decision-making, both normatively as well as in psychiatric illness and substance abuse disorders.

Susan Sisson, PhD, RDN, CHES, FACSM

Dr. Sisson earned a MS in Health and Exercise Science at the University of Oklahoma and a PhD in Exercise and Wellness at Arizona State University. She completed a post-doctoral fellowship at the University of South Carolina in Health Psychology and Pennington Biomedical Research Center in Physical Activity Epidemiology.

Dr. Sisson conducts her research in the Behavioral Nutrition and Physical Activity Laboratory in the Department of Nutritional Sciences at the University of Oklahoma Health Sciences Center. Research in the lab focuses on physical activity and sedentary behavior epidemiology and related risk behaviors such as the consumption of poor quality food. Other research interests include the influence of the physical and social environment on food consumption and physical activity behaviors and the impact of sedentary lifestyle on chronic diseases such as obesity as well as intervention development and evaluation to combat sedentary lifestyle and poor food choices. Children and disadvantaged populations are of particular interest.

Grant H. Skrepnek, PhD

RESEARCH SUMMARY

Dr. Skrepnek's research activities within health economics, outcomes, and policy focus upon investigations involving nationally-representative and large-scale health-system databases, decision-analytic modeling and mathematical simulations, prospective observational and randomized clinical trials, and survey research. He has worked extensively to study outcomes associated with acute, chronic, and rare diseases in oncologic, cardiovascular, pulmonary, endocrine, mental health, and infectious disease. Particularly relating to cancer, he was involved in early studies on the cost-effectiveness of tyrosine kinase inhibitors and has since investigated numerous issues relating to clinical, humanistic, and economic outcomes and broader health policy concerns across several types of cancers and other disease states. Dr. Skrepnek's research involves advancing methodological and statistical approaches used health technology assessments, including both frequentist and Bayesian methods, modeling, econometrics, and biostatistics. His interests extend to policy issues concerning health disparities, Medicare and Medicaid, industrial organization economics of the pharmaceutical research and development, and financial econometrics. Dr. Skrepnek also studies practice-related aspects of healthcare which include reimbursement, academia, safety, patient compliance and adherence, treatment guideline implementation, disease management, and the use of technology by clinicians.

Joel Slaton, MD

Dr. Slaton is a clinician scientist with a laboratory located in the Adult Urology Laboratory in the BSMB. His research is primarily focused on use of rodent models of urologic neoplasms (bladder, prostate, kidney) as targets for imaging and therapy. We have autologous murine and rat tumors as well as human cell lines that are fluorescently labelled. Our lab is collaborating with Rheal Towner, PhD (Oklahoma Medical Research medical Foundation) on translation of the antioxidant compound OKN-007 for the treatment of prostate cancer as well as use of a targeting ligand against urothelial cancer bound to gandolinium to image superficial bladder cancer. We are working with Daqing Paio (Oklahoma State University) on use of single-fiber reflectance spectroscopy to image superficial bladder cancer. In conjunction with Dr. Paio and Robert Hurst, we are exploring the ability of infrared-deoxyglucose dyes to image bladder cancer and bladder healing.

William E. Sonntag, PhD

RESEARCH SUMMARY

The Sonntag laboratory is focused on understanding how the interactions between the endocrine, vascular, and the central nervous system lead to cognitive impairment. Specifically, we have two main areas of study: 1) Examine the effects of IGF-1 signaling in the brain throughout the lifespan and 2) Understand the effects of brain radiation on microvasculature and cognition. Our studies on the effects of radiation result from studies in humans demonstrating that approximately 50% of individuals that undergo the clinical series of whole brain radiation for brain metastases undergo mild cognitive impairment. The etiology of cognitive impairment after radiation in humans is poorly understood but we have been successful in modeling the condition in rodent models. Our results indicate that there is a profound cerebrovasculature rarefaction in response to the clinical series of radiation and that activation of bone marrow cells can be used to reverse both the decline in vascular density after radiation and the mild cognitive impairment.

Lancer Stephens, PhD

College of Public Health, University of Oklahoma Health Sciences Center

- Dr. Stephens is a member of the Wichita & Affiliated Tribes of Oklahoma and specializes in brokering research agreements between the University and Tribal Nations within the state of Oklahoma.
- Expertise in tribal health policy, tribal and Indian Health Service Institutional Review Boards, and building community coalitions.
- His research interest lie in disease prevention programs for youth, health literacy for all ages and promotion of health equity.

Michael E. Sughrue, MD

Michael E. Sughrue, MD is an assistant professor in the OU Department of Neurosurgery, specializing in neuro-oncology and minimally-invasive/skull base surgery. He is also Director of the Oklahoma Comprehensive Brain Tumor Center. His research interests are broad and include many aspects of neuro-oncology, including the genomics and proteomics of glial tumors as well as other CNS neoplasms. He has published extensively on all aspects of neurosurgery, with a focus on neuro-oncologic research. He has a long-standing interest in the role of complement in the regulation of tissue repair/regeneration, and has extensively investigated the role of complement in neoplastic proliferation. Other translational research goals include identifying molecular and genetic targets and evaluating chemotherapeutics directed at these targets, including the identification and evaluation of potential agents to inhibit cell migration in gliomas. His clinical research focus includes evaluating the use of minimally-invasive “keyhole” techniques to approach a variety of complex intracranial pathology.

Heather Summers, MS, RN

Heather Summers is the Undersecretary of Operations, Hospital and Clinics for the Chickasaw Nation. She graduated from East Central University in Ada with a bachelor's degree in Nursing in 1994 and from the Oklahoma University Health Science Center College of Nursing in May 2012 where she received a Master of Science in Nursing Administration.

Her career began as an Indian Health Service employee in July 1994 at the Carl Albert Indian Health Facility, just months before Compact in October of 1994. She continued working at Carl Albert for two and a half years on the Medical Surgical Unit & Obstetrics Unit. In 1997 she left Carl Albert to return home to the Chickasaw Nation as a tribal employee in 1999 where she was hired as an Outpatient Registered Nurse. Over the next 16 years she has held a variety of roles within the Chickasaw Nation Department of Health. Her positions include: Outpatient Nursing Manager, Deputy Director of Outpatient Services, Director of Nursing, and the Executive Officer of Clinical Services. Most recently she was appointed the Undersecretary of Operations, Hospital and Clinics.

Ms. Summers has provided leadership and direction at the hospital the past 18 months, working in partnership with the Oklahoma Hospital Association, the OSDH Tribal Affairs Office and the Oklahoma Tobacco Helpline to implement an evidence-based, tobacco treatment system for inpatients that is imbedded within their existing electronic medical record, RPMS. Led by Ms. Summers, the internal clinical and information technology team developed and successfully launched this protocol in November 2014 which includes a bi-directional, encrypted electronic referral directly to the Helpline through the electronic medical record, the first of its kind in Oklahoma.

As Ms. Summers has advanced into leadership roles within the Chickasaw Nation she has seen great and dynamic changes. This has allowed her to understand that change doesn't lead to a destination but that it is a state of being, a perspective that helps to guide decisions that improve the lives of those she serves further illuminating the Mission of the Chickasaw Nation- To Enhance the overall quality of life of the Chickasaw People.

Eleni Tolma, PhD

RESEARCH SUMMARY

Dr. Tolma has a deep interest in women's health issues and particularly on cancer prevention. As a result of that, her dissertation work at the University of South Carolina focused on breast cancer prevention. In 2002, the University of Oklahoma Health Sciences Center (OUHSC) hired Dr. Tolma as an assistant professor in the Health Promotion Sciences (HPS) Department where she continued pursuing her interest in the early detection of breast cancer and the Theory of Planned Behavior.

In 2005 Dr. Tolma earned a seed grant to start her research with the AI women who live in the Shawnee area. The project was a prospective study, which entailed both qualitative and quantitative research. Through qualitative research she developed a survey that measured AI women's beliefs about mammography. Although the funding for the pilot study ended in 2006, with the help of collaborators from the OUHSC, they established the psychometric properties of the survey and conducted preliminary quantitative data analysis. The results indicated that social norms and social modeling toward mammography screening seemed to be the most important predictors of the decision-making process in getting future mammograms. The research team built a culturally sensitive intervention through a community-based participatory research (CBPR) approach that will promote mammography screening. Dr. Tolma secured external funding from the Suzan G. Komen® to implement and evaluate the proposed intervention.

This 3-year project started in December 2011. In January of 2011 Dr. Tolma also earned another seed grant from the Peggy and Charles Stephenson Cancer Center at the OUHSC to collect additional data via the same survey that would enable us to conduct higher level statistical analysis. The results were used to refine the current Logic Model, the education materials, and alliances built with other grassroots initiatives in the region. The intervention includes four main strategies: a) Structured communication between medical practitioner and patient; b) Receipt of a breast cancer brochure and subsequent follow-up letter from the medical provider; c) Participation in a discussion group modeled after the Freire methodology of raising consciousness; and d) Congratulatory bracelet upon receipt of a mammogram. The intervention pilot testing is completed, and the project's full implementation and evaluation is underway.

Dr. Toma's plans for the future include continue working with the AI tribes on cancer prevention and the implementation of theory-based interventions via CBPR.

Rheal Towner, PhD

RESEARCH SUMMARY

The research in our laboratory centers on developing new ways to diagnose and predict the outcome of human diseases using non-invasive imaging and spectroscopic methods. These methods also allow us to evaluate new and existing drugs and determine optimal treatment protocols for the specific disease. In our laboratory we use the techniques of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) to identify and study specific conditions of injured or diseased tissues in small animal models of disease. The experimental approach of using MRI and MRS technology with small animal models of disease has many advantages, including the ability to investigate disease processes both in vivo, and in real time. Currently, interests focus regarding the understanding of molecular events that lead to the formation and development of cancers, such as adult and pediatric gliomas, hepatocellular carcinomas; and oxidative metabolic processes associated with diabetes, neurological diseases, cancer and sepsis.

Both a fundamental and key issue in the early detection of disease is to identify and understand characteristic molecular or metabolic events that occur in altered cells but do not occur in normal cells. One way that we study this issue in my laboratory is to investigate specific components of metabolic reactions (metabolites), or molecular indicators, in altered cells that are different from those in normal cells. These molecular indicators of altered tissues can then be used to predict and understand the development of disease pathology. Over the past few years, we used this strategy in rodent (mice and rat) models of liver and brain cancer to investigate tumor morphology, new blood vessel formation, and fatty acid metabolism. The MRI techniques that we use can even detect certain changes in metabolites inside the cells of the nodules or tumors and then correlate these changes with stages of tumor progression (also called tumor grading). One metabolic change that we have detected in cancer cells is an alteration in lipid unsaturated fatty acids. Additionally, they have found that certain enzymes involved in the metabolism or breakdown of fatty acids by cells are altered during tumor formation and thus, these findings may explain the metabolic changes that we observed by MRI. In similar studies, we used the same MRI strategies and techniques to measure structural and metabolic changes in brain tumors called gliomas. We have used various MRI methods to assess tumor morphology, vasculature and metabolism in several rodent models of gliomas.

Another focus in our laboratory is on the discovery of “MRI molecular targeting agents”, or agents that selectively target or pinpoint tumor antigens in cancer or other diseased cells or tissues, and then allow these cells or tissues to be visualized by MRI in live animals. By using in vivo MRI techniques to study tumors in the liver and brain of rodent models of cancer, or other disease models such as diabetes, amyotrophic lateral sclerosis (ALS) or septic encephalopathy, Dr. Towner’s lab was the first to detect tumor markers such as c-Met, VEGFR2 and iNOS, found in many human cancers, as well as macromolecular free radicals in diabetes, ALS and septic encephalopathy using the in vivo MRI molecular-targeting approach.

Melville B. Vaughan, PhD

RESEARCH SUMMARY

My primary research interest is to identify and modulate microenvironmental factors that stimulate cell differentiation and/or proliferation. The primary cell of interest is the myofibroblast, a contractile cell found in wound healing, tissue fibroses, and tumor stroma. The myofibroblast responds to tension in the matrix by expressing unique proteins, responding differentially to chemical treatments, proliferating, or undergoing apoptosis. I use synthetic tissue models to study the myofibroblast and epithelial cells as well.

Theodore Wagener, PhD

Theodore Wagener, PhD, is an Assistant Professor in General and Community Pediatrics, with a joint appointment as an Oklahoma TSET Tobacco Research Scholar at the Peggy and Charles Stephenson Cancer Center and the Oklahoma Tobacco Research Center. He is also serving as the Director of Policy and Program Development at the Oklahoma Tobacco Research Center. His research focuses on parental and caregiver smoking, modified risk tobacco products (e.g., dissolvable tobacco, electronic cigarettes), effective tobacco harm reduction strategies, risk perception of smoking, and Motivational Interviewing (MI). Dr. Wagener is currently PI of a NIH/NCI grant investigating the use of dissolvable tobacco products by caregivers who smoke as a means to reduce their children's secondhand smoke exposure. He also serves as a Co-I on an OCAST grant investigating an online smoking cessation intervention. Dr. Wagener is also a licensed psychologist and directs the Behavioral Sleep Medicine Clinic at OU Children's Physicians where he treats children and adults with sleep disorders and supervises interns, residents, and postdoctoral fellows in sleep medicine.

Alana Welm, PhD

The research in my laboratory is focused on the mechanisms of breast tumorigenesis and metastasis, where we have developed new, complementary in vitro and in vivo approaches to gain a better understanding of this process. Using these methods, we discovered that the Ron signaling pathway is an important facilitator of breast cancer metastasis. Our current areas of research include:

1. Mechanisms by which Ron and short-form Ron promote metastasis, including the role of Ron in anti-tumor immunity
2. Mechanisms by which Ron signaling preferentially induces breast cancer metastasis to bone
3. Pre-clinical studies of Ron inhibitors for treatment of metastatic breast cancer
4. Development of innovative mouse models for improved prediction of drug response in breast cancer, including our published patient-derived breast tumor graft models.

Bryan Welm, PhD

RESEARCH SUMMARY

My research interest is to develop personalized therapeutic strategies for the treatment of breast cancer. We use primary cancer cells from patients to identify mutations that predict sensitivity to targeted therapies; with functional studies of therapeutic response performed in patient-derived xenografts (PDX). In addition, we use small molecules and forward-chemical genetics to understand biologically relevant pathways in both cancer and normal mammary tissue.

Ashley White, MPH

Ashley White received her Master of Public Health degree in Epidemiology and Biostatistics from the University of Oklahoma Health Sciences Center. She is currently a staff member in the Department of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center. Ms. White serves as a Research Project Coordinator for tobacco control and prevention, primarily on projects funded by the Tobacco Settlement Endowment Trust. Her research interest centers on the epidemiology of tobacco use and program evaluation research. Previous evaluation and epidemiologic work includes worker cohort mortality, cancer epidemiology research, and substance abuse prevention and treatment among American Indian/Alaska Natives.

Mary B. Williams, PhD

My research interests include chronic disease epidemiology and factors associated with the risk or prevention of chronic diseases, especially the behavioral and social aspects of chronic disease. Most of my recent work has been in tobacco use. I was drawn to tobacco use because it remains the most preventable cause of most chronic diseases. Although the risks of tobacco use are commonly known, tobacco use remains high especially in vulnerable populations and certain locations, such as Oklahoma. Although the addictive nature of nicotine and other biologic factors contribute to the continued use of tobacco use when risks are known; recent research has found policies and social factors of tobacco use are associated with cessation or tobacco use.[1-9] In my dissertation I investigated how unassisted smoking quit attempts and cessation were related to policies and social factors at the state and individual levels. I am interested in continuing to examine how policies and social factors at various levels are related to tobacco use and cessation, as well as how these factors may be related to disease risk.

Lijun Xia, MD, PhD

PERSONAL STATEMENT

Glycosylation is increasingly appreciated as having a wide and yet largely unexplored spectrum of biological functions. Our research focuses on biological functions of O-glycans/O-glycoproteins. Our published studies have identified new roles for O-glycans in blood cell trafficking, vascular integrity, and intestinal inflammation/cancer development. We discovered that O-glycosylation of E-selectin ligands on leukocytes, the mucins-type O-glycoprotein podoplanin, or mucins in intestinal epithelial cells are responsible for these functions. Current research focuses primarily on roles of O-glycans/specific O-glycoproteins in platelet function, vascular permeability, and intestinal inflammation/tumorigenesis.

Selected Peer-reviewed Publications, since 2007

1. An G, Wei B, Xia B, McDaniel JM, Ju T, Cummings RD, Braun J, **Xia L***. Increased susceptibility to colitis and colorectal tumors in mice lacking core 3-derived O-glycans. *J Exp Med*. 2007 Jun 11;204(6):1417-29. PMCID: PMC2118614. *Corresponding author.
2. An G, Wang H, Tang R, Yago T, McDaniel JM, McGee S, Huo Y, **Xia L***. P-selectin glycoprotein ligand-1 is highly expressed on Ly-6Chi monocytes and a major determinant for Ly-6Chi monocyte recruitment to sites of atherosclerosis in mice. *Circulation.* 2008 Jun 24;117(25):3227-37. PMCID: PMC2596619. *Corresponding author.
3. Miner JJ, **Xia L***, Yago T, Kappelmayer J, Liu Z, Klopocki AG, Shao B, McDaniel JM, Setiadi H, Schmidtke DW, McEver RP. Separable requirements for cytoplasmic domain of PSGL-1 in leukocyte rolling and signaling under flow. *Blood.* 2008 Sep 1;112(5):2035-45. PMCID: PMC2518905. *Co-First author.
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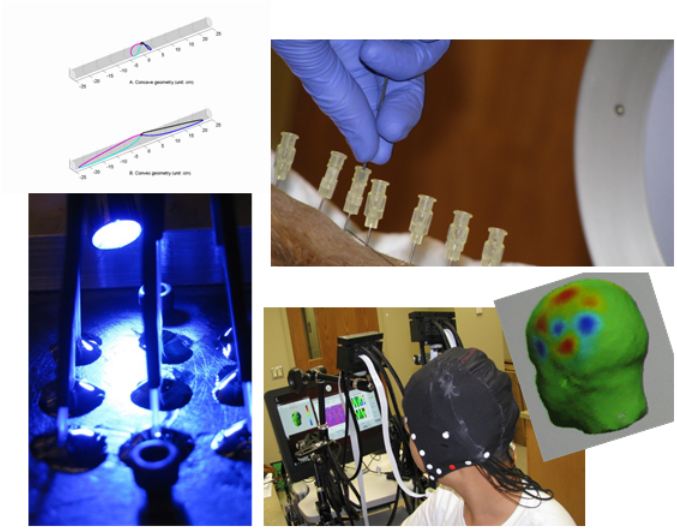
Youngjae You, PhD

RESEARCH SUMMARY:



- We focus on understanding how light can be used to measure the normal and detect the abnormal conditions of human organ systems and tissues.
- Examples of the conditions being investigated include urinary bladder cancer, mineral degeneration causing herniation of the intervertebral disc, and fatty liver that affects the suitability of the organ for transplant.
- These understanding are translated to developing non-invasive or minimally-invasive technologies that are deployable with existing clinical practices including surgical protocols.
- These clinical technologies aim to make the diagnosis, therapy monitoring, and treatment of the applicable disease conditions more precise and evidence-based.

Wei Yue, PhD

Wei Yue, PhD, received her PhD after completing a joint PhD program in the Department of Immunology at the Peking Union Medical College and the Department of Developmental Biology at Shandong University in China. For her postdoctoral training, she joined the Lineberger Comprehensive Cancer Center at the University of North Caroline at Chapel Hill. At the LCCC, she focused on studying tumor virology and the post-translational regulation of virus-host interactions by phosphorylation and ubiquitination. While working in the field of cancer research, Dr. Yue became interested in drug transport proteins, particularly in how post-translational modifications may regulate drug transport protein function and affect transport-mediated drug-drug interactions and drug efficacy. Dr. Yue joined the Division of Pharmacotherapy and Experimental Therapeutics at the UNC Eshelman School of Pharmacy in 2007 as a postdoc and was appointed as a research assistant professor in 2008. In 2011, Dr. Wei Yue received her first R01 award entitled “Function and Regulation of organic anion transporting polypeptides (OATP) 1B1 and OATP1B3”. She is currently an assistant professor in the Department of Pharmaceutical Sciences in the College of Pharmacy at OUHSC.

OATP1B1 and OATP1B3 are major hepatic transport proteins that mediate uptake of a diverse array of endogenous compounds and drugs, including statins and many anti-cancer drugs, from the blood into the liver. While under normal circumstances OATP1B3 is primarily expressed in the liver, the protein is aberrantly expressed in various cancers. Dr. Yue's primary areas of interest include investigating the role of OATPs in healthy and disease states, including cancers, establishing a mechanistic model to predict OATP-mediated drug-drug interactions and toxicities, and identifying novel therapeutic targets for cancer therapy.

Bin Zheng, PhD

RESEARCH SUMMARY

This study was supported in part by Grant R01 CA160205 from the National Cancer Institute, National Institutes of Health, to University of Oklahoma Norman Campus. The title of the project is “Mammographic Density and Tissue Asymmetry Based Breast Cancer Risk Stratification” and the Principal Investigator is Bin Zheng. The purpose of this project is to develop a new quantitative image feature analysis scheme and investigate whether the quantitatively computed bilateral mammographic density asymmetry is highly associated with near-term risk of women developing breast cancer in the near-term and thus develop a new near-term breast cancer risk assessment model (predictor). The success of this project will help to establish the optimal personalized breast cancer prevention and screening programs in the future clinical practice.

The major areas of the research interest of the PI and his team focus on developing computer-aided detection and diagnosis (CAD) schemes of cancer images (including mammograms and MRI for breast cancer, CT images for lung and ovarian cancers, cytogenetic images for leukemia). Using CAD schemes we work to identify quantitative image biomarkers and develop/optimize the statistical machine learning classifiers or assessment models to improve prediction of cancer risk, cancer prognosis and treatment efficacy.

Jadith Ziegler

I am a first year PhD graduate student at the University of Oklahoma Health Sciences Center. As a direct admit to the Pathology graduate program, I am a great interest in becoming a research scientist in the medical field. I am currently working with my mentor, Dr. Rheal Towner at the Oklahoma Medical Research Foundation. We are currently researching glioma tumor biomarkers and effective antibody treatments against those biomarkers in the hopes that it may reduce tumor size and prolong survival time using MRI techniques. My research interests as a Pathology student is to understand disease mechanisms in order to find effective treatments for humans by using mice as models. My interests are currently specific to high grade glioma brain tumors. Additionally, my interests include using MRI techniques to detect tumor volumes in mice and conduct other profusion and diffusion assays with mice implanted with brain tumors.